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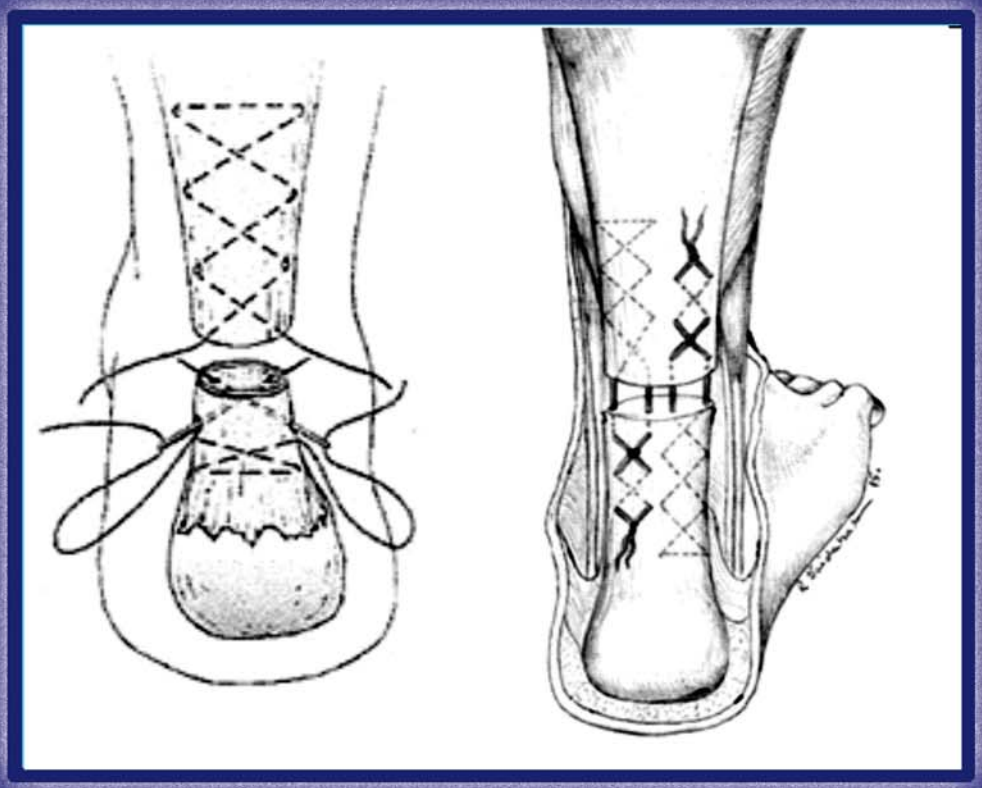

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Comments: Original Bunnell suture (left). Author's technique - detail (right)

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ORIGINAL PAPER

EFFECT OF THE DISTANCE BETWEEN THE FRACTURE LINE AND FIRST SCREW OF MINI-PLATE ON BONE RESORPTION

Teodora Silagieva Pituru[1], C. Gudaș[2], S.M. Pituru[3], O. Dincă[4], C. Vlădan[5], Al. Bucur[6]

[1]DMD DDS Medical Department of Oro-Maxillo-Facial Surgery,
University of Medicine and Pharmacy "Carol Davila" , Bucharest, Romania
[2]Dipl Eng Senior Stress Analyst, C&D Gudas, Sydney, Australia
[3]MD DMD, Professional Organization in Medical and Dental Legislation
University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
[4]Phd MD DDS Medical Department of Oro-Maxillo-Facial Surgery
University of Medicine and Pharmacy" Carol Davila" , Bucharest, Romania
[5]Phd MD DDS Medical Department of Oro-Maxillo-Facial Surgery
University of Medicine and Pharmacy" Carol Davila" , Bucharest, Romania
[6]Prof. Phd MD DDS Medical Department of Oro-Maxillo-Facial Surgery
University of Medicine and Pharmacy" Carol Davila" , Bucharest, Romania

Summary

The study presents how the maximum strains developed during biting near the fracture line affect the balance of bone resorption /remodeling. 2D models were used to evaluate the distribution of the reaction forces among the screws when a mini-plate is used for the fixation of mandibular angle fractures. Using a biting force of 100N, the results indicate that for distances smaller than approximately 1.7 screw-diameters, the strains exceed a resorption threshold of 1500 μ-strains for all the cortical tissue. The distance between the first screw and fracture line should be 2.0-2.5 screw-diameters to limit the high strain values.
Key words: fixation of mandible fracture, single mini-plate, resorption, strains, screw reaction forces

Résumé

L'effet de la distance entre la ligne de fracture et la première vis de la mini-plaque sur la résorption osseuse

L'étude présente la façon dont les tensions maximales développées pendant la morsure près de la ligne de fracture affectent l'équilibre de la résorption osseuse / du remodelage. Des modèles 2D ont été utilisés pour évaluer la répartition des forces de réaction entre les vis lorsque la mini-plaque est utilisée pour fixer les fractures de l'angle mandibulaire. En utilisant une force de morsure de 100N, les résultats ont indiqué que pour les distances inférieures à 1,7 diamètre de vis, les tensions dépassent un seuil de résorption de 1500μ - les tensions pour tout le tissu cortical. La distance entre la première vis et la ligne de fracture devrait être de 2,0-2,5 diamètres de vis pour limiter les valeurs élevées de la tension.
Mots-clés: fixation de la fracture de mandibule, mini-plaque unique, résorption, tensions, les forces de réaction des vis

Introduction

Given the diversity of clinical situations of the mandible fractures under the influence of anatomical and biomechanical factors, many authors have tried classification of these fractures after various criteria. Of these, clinical criteria are the most used. According to the classification by anatomic location of the fracture line there are fractures of the mandibular body (median, paramedian and lateral), mandibular angle fractures

Correspondence address: *Teodora Silagieva Pituru, MD*
DMD DDS Medical Department of Oro-Maxillo-Facial Surgery, Bucharest, Romania
e-mail: tedysil@yahoo.com

(fractures located before muscle insertions or in full muscle), fractures of the mandibular ramus (vertical, oblique, horizontal) fractures of the mandibular condyle (subcondylar, low subcondylar, tall intracapsular) fractures of the coronoid process [1].

There are enough studies that describe the use of osteosynthesis systems for the treatment of jaw fractures [2,3,4,5]. Each anatomoclinical form of mandibular fracture receives individualized treatment, the choice of the method of treatment being conditioned by the following factors: traumatic lesion location, the existence of single fracture lines /multiple jaw fractures, associated maxillary fractures, displacement of bone fragments, the line fracture, the presence of teeth. Based on the criteria we will choose the most appropriate method of surgical treatment, according to the type and location of site of the fracture.The titanium mini plates show considerable advantages over other forms of fixation being small, malleable and easy to insert [6]. The results of investigations on the maximum strains, developed during mastication near the fracture line and close to the first screw, are presented in order to illustrate how the distance between them affects the balance between bone resorption and remodeling. Examples using the same bite force show that for distances smaller than 1.7 screw diameters the strains exceed the maximum resorption threshold, despite the reduction of the reaction force developed by the first screw. Several models using the 2D finite element method were used to evaluate the distribution of reaction forces of the screws when a mini plate with six holes is used for fixing fractures at different inclination angles. The reaction forces were applied to a second set of models to visualize the displacements and extract the local maximum strains. Using a clinically relevant biting force of 100N the results indicate that for a distance to the fracture line smaller than about 1.7 screw diameters, the maximum principal strains peak above a resorption threshold of 1500 micro-strains in the cortical tissue for the entire area, regardless of the orientation of the fracture. We conclude that the distance between the first screw and the fracture line should be around 2.0-2.5 screw diameters to limit the high strain values to the cortical bone around the loaded screws, and thus to minimize the likelihood of bone resorption near the fracture line.

In the treatment of mandibular angle fractures, the open reduction and internal fixation using single mini-plates installed along Champy's line of osteosynthesis at the upper border [6], above or just below the superior oblique ridge, is a very popular technique.

Often the mini-plates used in these situations are 2.0 mm straight plates with four or six holes and 2.0 mm diameter screws of various types, generically called fasteners from now on can be with or without bars.

The fixation hardware used during the healing stage is required to transfer across the fracture line the forces and the moments generated during biting and mastication. To avoid postoperative mechanical loosening of fasteners caused by excessive loading it is important to evaluate the load distribution among the fasteners each side of the fracture and the effect their loads have on the natural response of the healing bone. From a mechanical perspective, these reactions are dependent on parameters like the magnitude and position of the biting force, the type of fracture (favorable, unfavorable), the angle between the fracture line and the direction of the biting force, the structural properties of the mandibular bone, the distance between the fasteners and, maybe less intuitive, on the distance between the fracture line and the first fastener. For convenience of notation this distance will be referred as the edge distance in these investigations.

For thin, shell like structures made from materials with isotropic and homogeneous properties or composites with anisotropic properties, the magnitude and distribution of stresses (and strains)around a discontinuity introduced by a fastener hole is significantly different from the ones present further away. Thus the value of the peak stress/strain near the edge of the hole is amplified by a factor of approx. 2.0 when there is no load transfer between the two constituents and from there it increases in direct relationship with increase in the load transferred. These effects are very much localized and they dissipate into a relatively uniform pattern over a distance equivalent to about 2 -2.5 hole diameters. When a free edge (like a fracture line) is located closer than that, the stress field in the space between the two intensifies and the stresses and strains around the hole and near the free edge increase accordingly. For cyclic loading situations, the increase in the local stresses degrades the fatigue strength of the shell and reduces its life.

Considering that thickness of the cortical layer in relation to the dimensions of the mandible, the cortical bone can be approximated with a shell like structure for which the biting and/or the masticatory processes represent sources of cyclic loading. In this context the fixation hardware used during the healing stage is required to transfer across the fracture line the forces and the moments generated during biting and mastication.

Studies on bone degradation due to mechanical loading have demonstrated the fatigue damage accumulation in living bone and postulated it as a stimulus to the bone modeling and remodeling response [7]. Often in a structural stress analysis context, effects of mechanical loading are measured in strains or, for very small numbers, in micro-strains. C.E. Misch shows that between 1500 and 3000 micro-strains there is the "mild overload zone which corresponds to bone modelling stimulation and remodeling inhibition. As a result, the bone strength and density eventually may decrease. The histologic description of the bone in this range is usually woven or repair bone"[8].

In this study it was considered that in order to avoid post-operative mechanical loosening of fasteners it is important to evaluate the load distribution among the fasteners each side of the fracture and the effect these loads have on the natural response of the healing bone. From a mechanical perspective, these reactions will be dependent on parameters like the magnitude and position of the biting force, the type of fracture (favorable, unfavorable), the angle between the fracture line and the direction of the biting force, the structural properties of the mandibular bone, the distance

between the fasteners and, maybe less intuitive, on the distance between the fracture line and the first fastener. At the cortical level, these reactions can generate zones of high stress and local deformations (strains).

Materials and Methods

By using the finite elements analysis (FEA) software MSC NASTRAN 2010, a sample of bone was taken and analyzed and the data were extrapolated to a mandibular angle fracture immobilized with a plate with six holes. With the help of an Excel spread sheet the FEA data was used to investigate the correlation between the distance of first screw to the fracture line and bone resorption for a bite force of 100N applied to the incisors. [9].

Loads

The evaluation of the loads acting on the mini-plate was done considering a clinically relevant incisal edge loading of B = 100N, applied as shown in fig. 1 [9]. For an angle α, between the horizontal and the direction of the fracture, the components of B along the axis of the mini-plate, perpendicularly and the moment generated by B about a middle point of the mini-plate were taken as:

Hpl=B*cos (α),

Vpl= B*sin (α),

M = B x l (oriented clockwise)

The moment M was considered to be transferred across the fracture line by a couple of equal and opposite forces: one through the mini-plate (tension) and the other one (compression) acting at the centroid of the triangularly shaped distribution of compressive loads developed between the fractured parts of the mandible, as shown in fig. 1b. The distance between the two forces was identified as h. With the above notations, the total load on the plate was:

$$P = \sqrt{(H_{pl} + H_{pl}')^2 + V_{pl}^{\ 2}}$$ acting at an angle of

$$\beta = \tan^{-1}\left(\frac{V_{pl}}{(H_{pl} + H_{pl}')}\right)$$ from the plate axis.

Fastener reactions

Several linear elastic 2D finite elements models, solved with MSC Nastran, were prepared in order to extract the fastener reactions in response to a 100N unitary force applied to the mini-plate at angles between 0 and 90 degrees.These results of the unitary model were next combined, scaled appropriately, for angles of the fracture at every 10 degrees between 0 and 90 plus a 45 degrees case. The material properties for these models were assumed to be linear elastic, isotropic for the mini-plate and orthotropic for the cortical strip.Values for moduli of elasticity and Poisson's ratios for the cortical were extracted from data available in [11]. The direction of the larger modulus of elasticity (E1) was oriented to be aligned parallel with Champy's lines. The values used are shown in table 1. The cortical thickness used was 2.5 mm. For the mini-plate the thickness was chosen as 1.0 mm.

Considering the installation of mini-plates to be approximatively perpendicular to the fracture lines, the situations, where the main axis was non-parallel with Champy's lines, were addressed by using models with direction of E1 at multiple angles between 0 and 90 degrees (in steps of 10 degrees and the 45 degrees). The investigations were conducted using as main parameter the diameter of the fastener (numerical application on d=2.0 mm).The other dimensional variables expressed as function of d were:

- The edge distance (ED), of1.5d, 2.0d, 2.5d and 3.0d;
- Cortical strip width (WD), having values of 4d, 6d and 10d;

For the fasteners connections, two joint flexibility values were used. The first one was calculated using an experimental formula [10], for joints with one metallic adherent (Ti), the other a unidirectional composite laminate and the metal fastener (Ti). The lateral stiffness of the joint resulted from calculations was k1 = 15500 N/mm.The second value was deliberately selected as very large k2 = $1.5*10^8$ N/mm to assess the effect of joint flexibility on fastener load transfer. The fasteners were modelled with elastic elements (CBUSH)

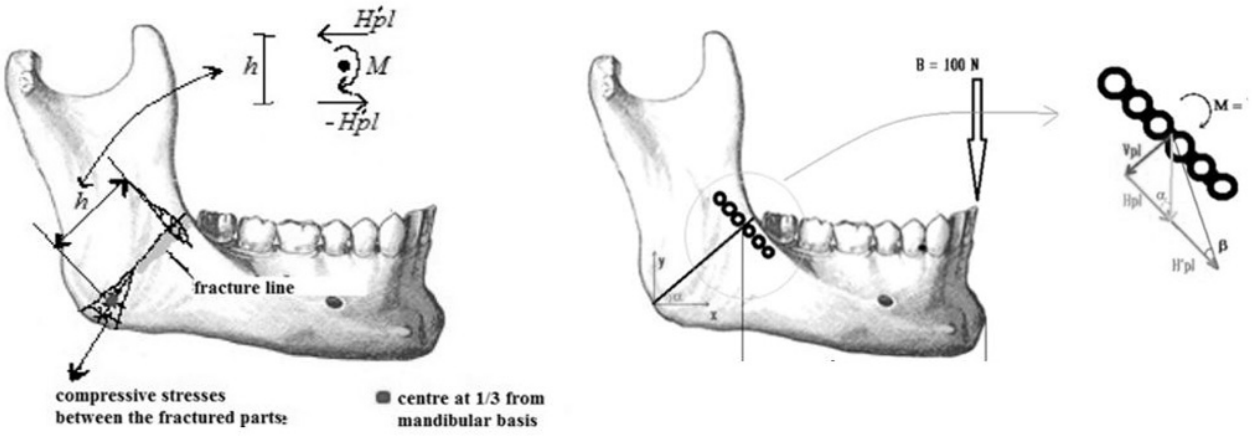


Figure 1 - Loading Diagrams

Table 1 - Material propreties

Materials	E1	E2	V12	G12	G13	G23
	(MPa)	(MPa)		(MPa)	(MPa)	(MPa)
Titanium	120000	-	0.32	45454.6	-	-
Cortical	28500	19800	0.21	7900	5800	5200
E1 in plane, parallel with Haversian channels						
E2in plane, perpendicular to E1						
E3 through thickness						

located at the center of each fastener hole. Their loads were transferred along the circumference of the holes in cortical and mini-plates using rod type elements (CROD) - these elements are able of transferring only axial loads - see (fig. 2).

Strains evaluation

Evaluation of the strains at first fastener hole and along the edge of the fracture line was conducted using a set of models similar to those used for the derivation of fastener loads.These set of models did not incorporate the second and third holes.

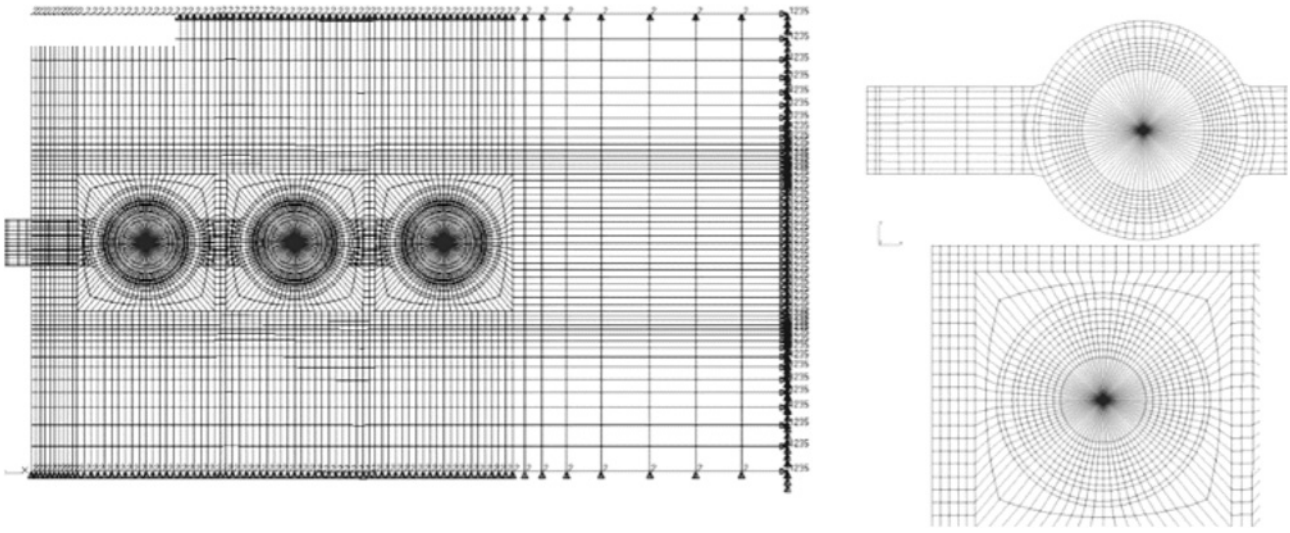
For these models, the bearing contact between the cortical and the fastener was simulated by including "linear gap elements" between the nodes at the end of the rods and the nodes on the circumference of the hole. As these "elements" are formulated to release the connection when they are loaded in tension, the edge of the hole was loaded only by a non-uniform (parabolic) distribution of compressive forces acting along an arc of circle oriented in the direction of transfer of forces between the screw and bone and spanning for approximately 180 degrees.

RESULTS

Fastener Loads

For the two far apart values for joint flexibility selected (k1 and k2), the variation in fastener reactions was found to be 27% for first fastener, 20% and 27% for the second and third ones regardless of the fracture orientation. The reaction at the first fastener increased with the increase in joint stiffness (stiffness = flexibility-1) while, for the second and third fasteners the variation was in the opposite direction. (fig. 3)

The distribution of the reactions for the three fasteners is influenced by orientation of the fracture in the angle of the mandible, the edge distance (principles of a lever of first order), distance between fastener holes and the cortical density which, among other things, affects directly the joint flexibility. Taking for example a fracture at 45 degrees for an incisive bite with 100N, the fastener reactions in the direction parallel with the miniplate for a flexible joint are 246N at the first fastener with 166N and 151N at the second and third fasteners. This represents 44%, 29% and 27% of the total axial load of 563N. (fig. 4)



Left: Cortical bone WD10_ED10 and mini-plate showing
Right Detail of fastener connection for mini-plate (top) and cortical (bottom)
Figure 2 - Sample 2-D FEA for Extraction of Fastener Loads

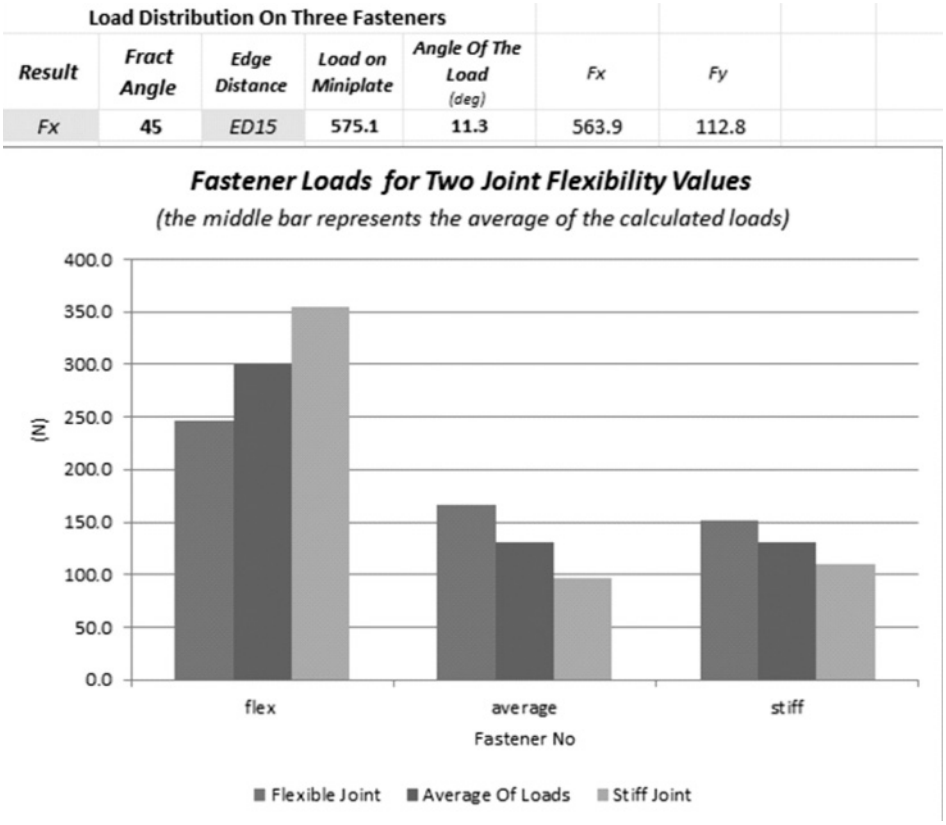


Figure 3 - The force applied on the flexibility joint (in N) for a mandible angle fracture at 45 deg

For a stiff joint the ratios are 63, 17 and 20%. For the first fastener the difference between the two flexibility extremes taken is around 110N. There is little effect of the distance between the fracture line and first fastener for the reactions in a direction parallel with the mini-plate. For the plate forces in the other direction (in this case a value

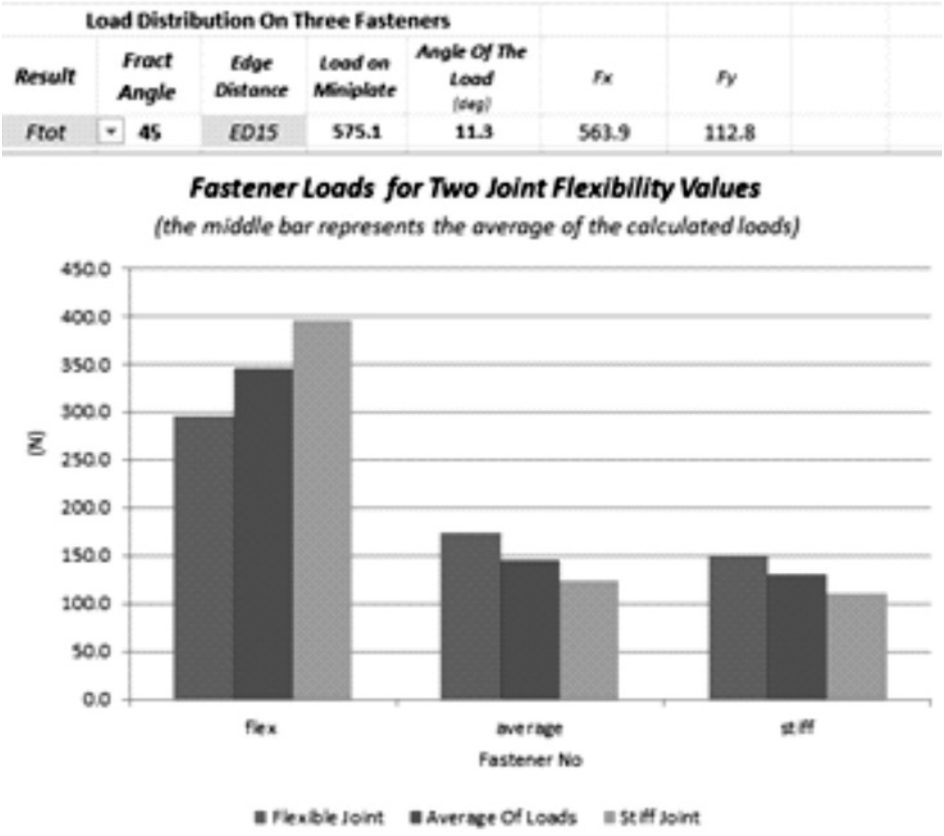


Figure 4 - The reprezentation of the horizontal component alongthe mini plate for a mandible angle fracture at 45 deg

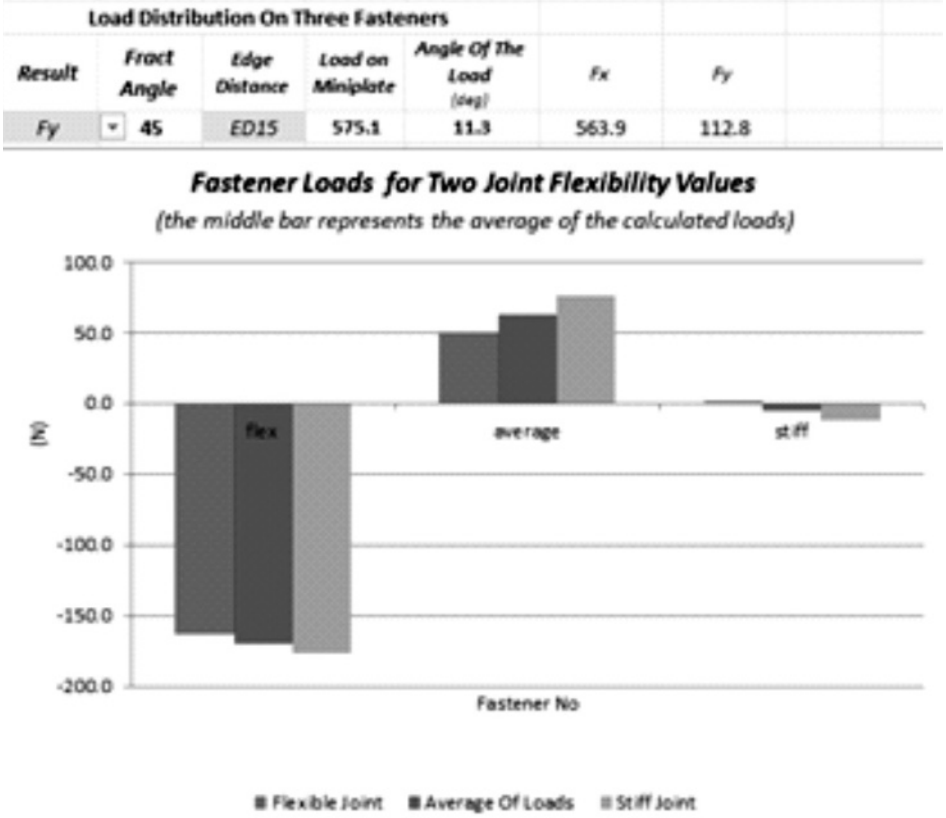


Figure 5 - The representation of the perpendicular component along the mini plate for a mandible angle fracture at 45

of 113N and an edge distance of 1.5d) the reaction on first fastener is (-165N) for flexible joint (-177N for stiff). If the first hole is at 3.0d, these values are -174N and -192N respectively. (fig. 5)

The combined effect shows that in the distribution of fastener reactions, mainly at the first fastener, the axial load induced by the moment of incisive bite has the primary effect. The direct contribution of the transversal load (shear), depending on fracture orientation and the edge distance, can change the orientation of the reaction by a maximum of 40 degrees. Fig. 6 shows the variation of loads on first fastener as an average of the two flexibility values used for edge distances from 1.5 d to 3.0d and several angle for the fracture orientation. (additional data in table 2)

3.2 Strains:

The maximum strains were extracted for the fastener reaction results in Table 2 only in the zones immediately adjacent to the interface between cortical and the fastener and near the fracture line. Maximum principal strain

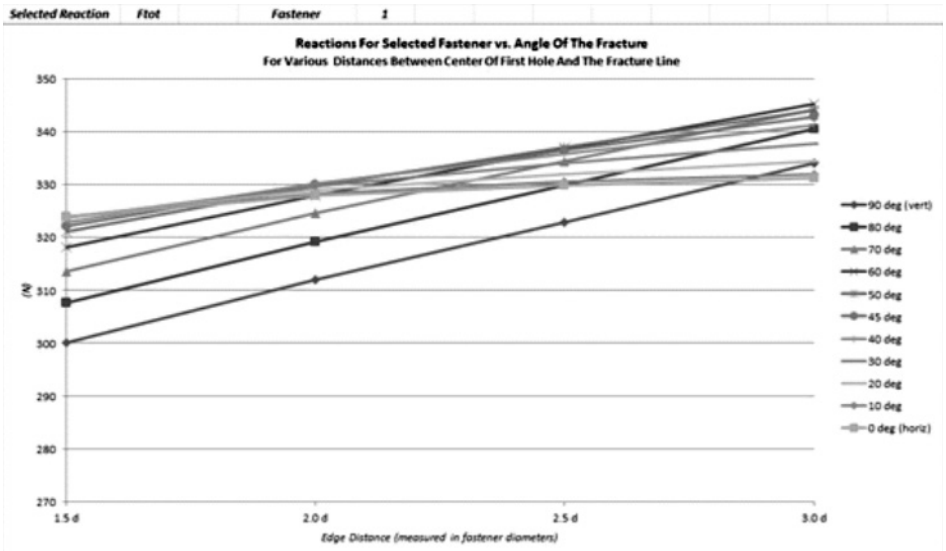


Figure 6 - Averaged Reactions on First Fasteners for Various Orientations of Fractures in Mandible Angle

Table 2. Average Reaction Values and Orientations at First Fastener

Fast ID			**1**				**Fastener reactions for various fracture angles**							
Joint flexibility			averaged											
Cortical band width			Wd_10											
Cortical proprieties			orthotropic											
Fiber angle (for ortho prop)			0											
Result required for fastener load			F tot											
Biting force								**100**						**(N)**
Dist. Biting teeth – fracture line (l)			50	50	50	50	50	50	50	50	50	50	50	(mm)
Angle of fracture line (α)			90	80	70	60	50	45	40	30	20	10	0	(deg)
Dist. For reacting the induced moment (h)			10	10	10	10	10	10	10	10	10	10	10	(mm)
Moment and resultant force & direction at midpoint of miniplate		M	5000.0	5000.0	5000.0	5000.0	5000.0	5000.0	5000.0	5000.0	5000.0	5000.0	5000.0	(N*mm)
	Hpl	0.0	17.4	34.2	50.0	64.3	70.7	76.6	86.6	94.0	98.5	100.0	(N)	
	Vpl	100.0	98.5	94.0	86.6	76.6	70.7	64.3	50.0	34.2	17.4	0.0	(N)	
	Hpl +H`pl	500.0	517.4	534.2	550.0	564.3	570.7	576.6	586.6	594.0	598.5	600.0	(N)	
	P	500.0	517.7	535.3	552.3	567.9	575.1	581.7	593.0	601.4	606.4	608.3	(N)	
	β	11.3	10.8	10.0	8.9	7.7	7.1	6.4	4.9	3.3	1.7	0.0	(deg)	
Fastener loads	ED15	1.5d	300	308	314	318	321	322	323	324	324	324	324	(N)
	ED20	2.0d	312	319	325	328	330	330	330	330	329	328	328	(N)
	ED25	2.5d	323	330	334	337	337	337	336	334	332	330	330	(N)
	ED30	3.0d	334	341	344	345	344	343	341	338	334	332	331	(N)
Angle for resultant of fastener reactions	ED15	1.5d	29.5	28.3	26.5	24.0	21.0	19.3	17.5	13.6	9.3	4.7	0.0	(deg)
	ED20	2.0d	32.1	30.8	28.8	26.2	23.0	21.2	19.2	14.9	10.2	5.2	0.0	(deg)
	ED25	2.5d	34.6	33.3	31.2	28.5	25.1	23.1	21.0	16.4	11.2	5.7	0.0	(deg)
	ED30	3.0d	37.0	35.6	33.5	30.6	27.1	25.0	22.8	17.8	12.2	6.2	0.0	(deg)

values were used to identify the areas in the mild overload zone for the cortical tissue. The findings are shown in chart format in fig. 7 and fig. 8. Note that the first row of elements around the hole, where the loads are transferred from the fastener into the bone has not been considered (St Venant's principle).

During biting, when the entire area between the edge of the fracture and the first fastener is mechanically strained into the mild overload zone it is most likely to result in an increased duration of the healing process. This negative effect can be mitigated reasonably easy, at no extra cost by using larger edge distances 2.0d to 2.5d.

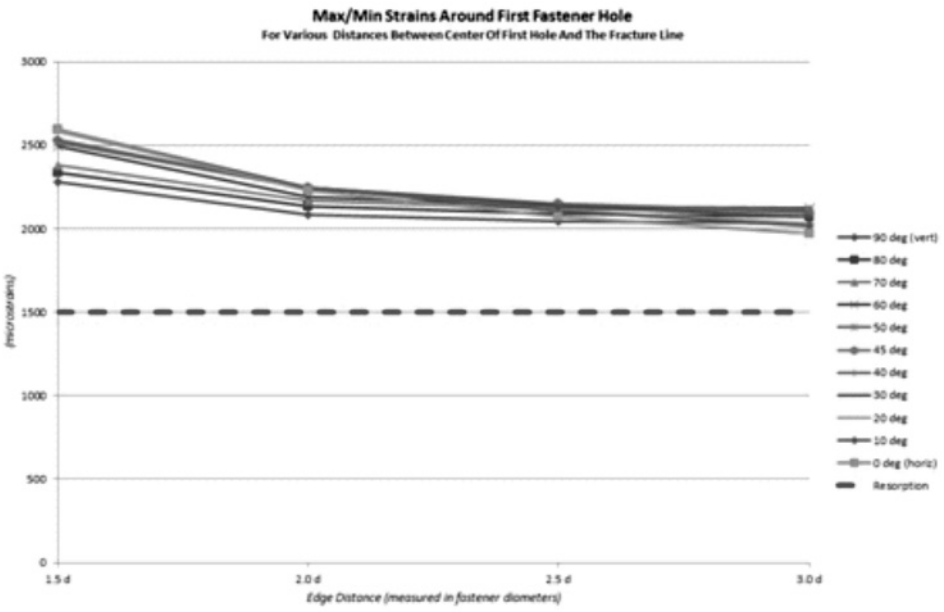


Figure 7 - Variation of Maximum Principal Stresses in the Cortical Near the Fracture Line

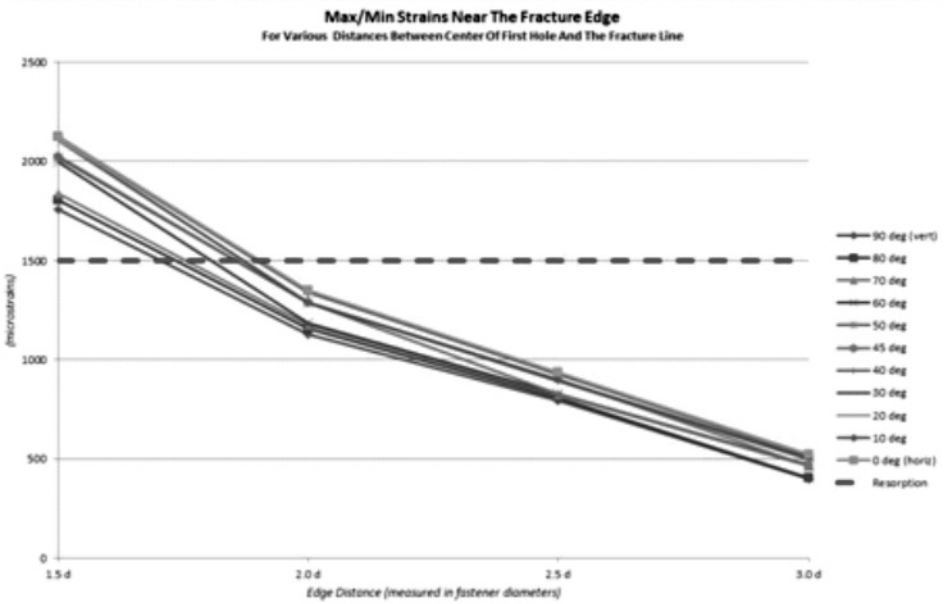


Figure 8 - Variation of Maximum Principal Stresses in the Cortical Near the Fracture Line

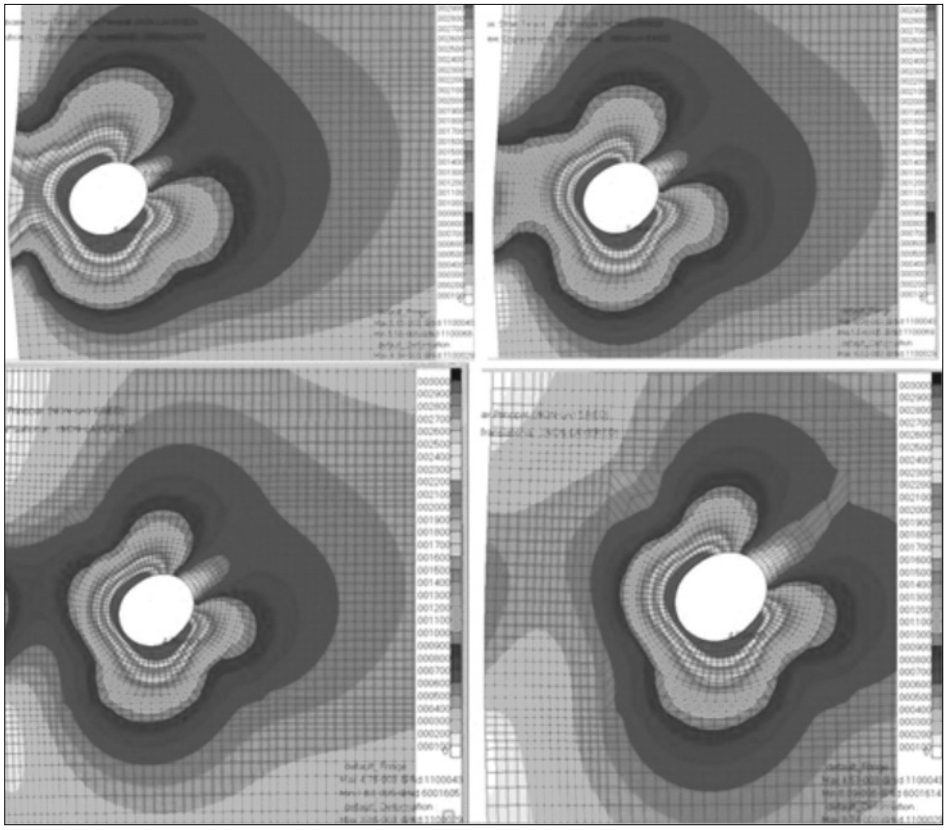


Figure 9 - Distributions of Maximum Principal Strains for 45 Degrees Facture with Various Edge Distances

While the relative position between the plate and Champy's lines has minimal effect on the fastener reactions (having used uniform properties on the entire bone span), for an angle of 45 degrees between the two, the peak max principal strains around the hole have increased by 10%. They decreased marginally near the fracture line. Plot of the distribution for maximum principal strains for edge distances considered for a fracture oriented at 45 degrees is shown in fig. 9.

Discussions and Conclusions

Material properties and their variations in individual bone organs are important for understanding bone adaptation and quality at a tissue level, and are essential for accurate mechanical models [11]. Our investigation based on a simple 2D case in which the biting force was projected on to the "plane of analysis" and took into consideration the bending moment M=B x l generated by the projection

of the bite force showed that the area where the balance between bone modelling and remodeling is affected by the fixation hardware can be significantly influenced by the position of the first screw. While a small edge distance is beneficial in the reduction of the reactions on first fastener and also in reducing the pull-out forces developed on this fastener during lateral movements of the mandible, the extent of the strained area in the cortical is increased. For the later type of loading, the strains outside the immediate vicinity of the fastener threads are mainly due to the Poisson effects and they are likely to be of small magnitude. In our analysis the cortical around the screw which is pressed-in by the self-tapping or self-drilling screws was not accounted for. During the fixation operations the pressing-in of the cortical by the fastener threads will create a residual strain (analogous to cold working of holes in metallic components) that will compound with the strains caused by the masticatory forces increasing or decreasing their magnitude depending on location.

For the situations where the bone density is different for the three screws considered, the fastener reactions will migrate towards the screws installed in denser bone thus increasing or decreasing accordingly the state of strain immediately near the fracture line.

For cortical- titanium interfaces the effect of joint flexibility on the local state of stress and strain seems to play a role more relevant that it would be the case with other materials (metal, plastics, composite).

It is probably relevant to mention that the cortical quality used in this evaluation corresponds to a high bone density (D1) which is suggested by the high value of E1 in table 1. For lower bone densities the fastener loads will see minimal changes (as they transfer the same loads across the fracture lines) but the corresponding strain values will increase in inverse relation with the reduction of the elastic moduli (E and G).

For an entire mandible, because of its arch shaped form, an incisive bite will also produce a moment trying to rotate the forward fragment of the mandible inwards and down about the plate midpoint (Mx in the coordinate system of fig. 2). Using normal mandibular geometrical dimensions, the value of this moment is similar to the one used previously.

The components of this new moment in a rectangular coordinate system in which the mini-plate is aligned with one axis, the fracture line is the second axis and the third axis will be through cortical thickness, will represent a torsional load in the plane of the fracture (like a coronal plane) and secondary bending that will tend to further open the vestibular side of the fracture when the facial segment of the fracture are supported on each other.

For single plate fixation, the torsional load is mostly reacted by bone to bone friction. The secondary bending though will have to be reacted by a couple of equal and opposite loads with additional tension components in the mini-plate and compression between the cortical fragments on the facial side. The magnitude of the additional tension loads induced by the secondary bending was not included in this investigation but its effects are worth considering as they have the potential to double the strain values obtained in this study.

During biting, when the entire area between the edge of the fracture and the first fastener is mechanically strained into the mild overload zone it is most likely to result in an increased duration of the healing process. This negative effect can be solved easy, by using larger edge distances 2.0d to 2.5d. Development of a bar type fixation system which reduces the load on first fastener (take out the shear or part of it to the second fastener or, better takes only shear in the first fastener and only tension in the second) will be beneficial in decreasing the strains near the fracture line and first screw to small values.

For favorable fracture orientation a good reduction of the fracture will assist in transferring the direct and induced loads produced by mastication through direct contact and/or friction between the two mandible fragments and reduce the demand on the fixation hardware. The effect of joint flexibility on maximum principal strains is around 30% near the fastener hole and larger on the fracture edge.

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ORIGINAL PAPER

CHARACTERIZATION OF CERTAIN CELL SUBPOPULATIONS PRESENTING POSSIBLE PROPERTIES OF TUMOR STEM CELLS

S. Marinescu[1], Rodica Anghel[1], I. Gruia[2], Lorelei Irina Brașoveanu[3], D.N. Păduraru[5], Maria Iuliana Gruia[1], M. Beuran[4]

[1]*"Prof. Dr. Al. Trestioreanu" Institute of Oncology, Bucharest, Romania*
[2]*Faculty of Physics, University of Bucharest, Romania*
[3]*Center of Immunology, Institute of Virusology „Ștefan S. Nicolau" Bucharest*
[4]*General Surgery Clinic, Clinical Emergency Hospital Bucharest*
[5]*Emergency General Surgery Clinic III - University Emergency Hospital*

Summary

Recent evidence demonstrate the fact that cancers may be regarded as an abnormal organ where the tumor growth is conducted by a population of cancer stem cells (CSC) that may give birth to several CSCs as well as to non-tumorigenic cancer cells. Tumor stem cells exist inside the tumor as a distinct population, which determines the occurrence of relapses and metastasizing. These observations have implications upon the biology of tumor formation as well as upon the diagnosis and cancer treatment. The aim of this paper is to identify a subpopulation of tumor cells having stem cell properties (stem-like) resulting from transplantable experimental tumors and which may serve as departure point in determining some possible mechanisms involved in the resistance to radiotherapy. The goal of this paper is therefore to characterize these cell subpopulations by determining the expression of certain antigens existing on their surface. Thus, we have devised and achieved an experimental model in which these stem-like cells responsible for the resistance to radiotherapy are involved, by monitoring their antigenic expression in parallel with cells, this experimental model involving cell irradiation and the selected markers being measured on irradiated samples and compared to the samples not subject to irradiation. The characterization by flow cytometry of the antigenic profile associated to cancer stem cells was achieved by connecting the antibodies specific to the studied antigens by using the indirect immunofluorescence technique followed by data acquisition by flow cytometry and analysis of the data thus obtained. Pursuant to experimental irradiations a dose-viability relationship was recorded, tested cells are radiosensitive and when subject to a de 5Gy their viability diminishes by 50%. The results obtained demonstrate

Résumé

Caractérisation de certaines sous-populations de cellules présentant d'éventuels traits de cellules souches cancéreuses

Des données récentes démontrent le fait que les cancers peuvent être considérés comme un organe anormal où la croissance de la tumeur est effectuée par une population de cellules souches cancéreuses (CSC) qui peuvent donner naissance à plusieurs CSC, ainsi qu'à des cellules cancéreuses non-tumorigènes. Des cellules souches existent à l'intérieur de la tumeur comme une population distincte, qui détermine l'apparition de rechutes et de métastases. Ces observations ont des implications sur la biologie de la formation de tumeurs, ainsi que sur le diagnostic et le traitement du cancer. Le but de ce document est d'identifier une sous-population de cellules tumorales ayant des propriétés similaires aux cellules souches, résultant de tumeurs expérimentales transplantables et qui peuvent servir de point de départ dans la détermination de certains mécanismes possibles impliqués dans la résistance à la radiothérapie. Le but de cet article est donc de caractériser ces sous-populations de cellules en déterminant l'expression de certains antigènes existants sur leur surface. Ainsi, nous avons conçu et réalisé un modèle expérimental dans lequel ces CSC responsables de la résistance à la radiothérapie sont impliqués, en surveillant leur expression antigénique en parallèle avec celle des cellules normales; ce modèle expérimental impliquant l'irradiation des cellules et les marqueurs sélectionnés étant mesurés sur échantillons irradiés et par rapport aux échantillons non soumis à une irradiation. La caractérisation par cytométrie en flux du profil antigénique, associé à des cellules souches cancéreuses, a été obtenue en reliant les anticorps spécifiques aux antigènes étudiés en utilisant la technique d'immunofluorescence

Correspondence address: *Șerban Marinescu, MD*
"Prof. Dr. Al. Trestioreanu" Institute of Oncology, Bucharest, Romania
e-mail: serban.marinescu@yahoo.com

an increasing apoptosis in the cells cultivated in a stem-cell environment and significant differences between reference cells and the ones collected from the experimental tumor, which suggests that in the tumoral tissue there are subpopulations having stem cell properties which may induce a resistance to treatment.
Key words: stem cells, experimental cancer, resistance to radiotherapy, surface antigens

indirecte, suivie d'acquisition de données par cytométrie en flux et l'analyse des données ainsi obtenues. Conformément aux irradiations expérimentales, une relation dose-viabilité a été enregistrée, les cellules testées sont radiosensibles et quand elles font l'objet d'une irradiation de 5Gy leur viabilité diminue de 50%. Les résultats obtenus démontrent une apoptose croissante dans les cellules cultivées dans un milieu de cellules souches, et des différences significatives entre les cellules de référence et celles collectées à partir de la tumeur expérimentale, ce qui révèle que dans le tissu tumoral il existe des sous-populations ayant des propriétés de cellules souches qui peuvent induire une résistance au traitement.
Mots-clés: cellules souches, cancer expérimental, résistance à la radiothérapie, antigènes de surface

INTRODUCTION

Solid tumors grow inside organs that contain stem cells. Tumors in these tissues consist of heterogeneous populations of cancer cells which are different in terms of their capacity to proliferate and form new tumors. Both in mammary cancer and in central nervous system tumors cancer cells differ by their capacity to form new tumors. While most cancer cells have a limited capacity to divide, a stem cell population that has the exclusive capacity to proliferate extensively and form new tumors may be identified based on markers expression. Recent data suggest that the ways regulating normal stem cells renewal are disordered in cancer stem cells (CSCs) leading to a continuous growth of the number of cancer cells which renew themselves and to tumor formation. This fact suggests that therapeutic agents that aim at deficient ways of self-renewal in cancer cells might lead to an improvement of the treatment of these diseases.(1)

Tumor stem cells exist in the tumor as a distinct population, which determines the appearance of relapses and metastasization. These stem cells have the capacity to renew themselves but, in case of neoplasias, the renewal mechanism is deranged. As stem cells have a long life, they can accumulate the necessary number of sequential mutations able to turn them from a normal cell into a malignant one.(2)

The ways that regulate normal stem cells renewal are deranged in case of tumoral stem cells thus leading to a continuous expansion of neoplasic cells self renewal and to tumor formation. This suggests that the agents targeted upon tumor cells self-renewal may lead to an improved response to the treatment of neoplasias.

In the 1990s, clinical observations as well as genetic studies made for different types of neoplasms lead towards the hypothesis that it takes six genetic mutations to transform normal stem cells into neoplasic stem cells. (3) The balance between inhibitory signals and proliferation promoting signals is the key to the homeostatic regulation of stem cells maintenance versus tissue regeneration. The loss of the niche may lead to the loss of stem cells. Molecular mechanisms meant to host or mobilize normal stem cells in/of niches, may be embezzled and used by tumor stem cells for invasion and metastasization. (4)

In order to prove that a phenotypically distinct cancer cell population was the only responsible for the perpetuation of the disease it is necessary to isolate different cancer cell populations and to demonstrate that one or several groups have the capacity to initiate the disease, while other populations lack this capacity. (5)

Cancer Stem Cells (CSC) have a number of cellular and genetic adaptations that confer them resistance to classic treatment methods. These include kinetics of the dormant/slow cellular cycle, efficient repair of the DNA, the expression membrane transporters of multidrug resistance and resistance to apoptosis. Tumors become chemo- and radio-resistant after non lethal exposures. This process represents the natural selection of CSCs. Radiotherapy and different types of chemical therapy perform an antineoplasic function by interrupting the integrity of the cancer cell. It is therefore possible that the oncogenic resistance of CSCs may result from the growth of the expression of DNA integrity maintenance systems. Thus, DNA-repairing proteins become fundamental objectives for the improvement of the treatment of malignant tumors.

CD133 is a cancer stem cells (CSC) marker associated to radioresistance and chemoresistance in different types of cancer. According to a study made by Piao LS (6), pursuant to the exposure to radiations, hepatocarcinoma cells that express the CD133 present a bigger activation of MAPK/PI3K signaling way and a reduction of the level of oxygen reactive species, compared to cancer cells that do not express CD133. The in vivo study run on a xenograft model revealed a tumoral growth in nude mice injected with CD133+ irradiated cells compared to the group injected with CD133-, thus suggesting that CD133 contributes to radioresistance in carcinomas.

Epithelial cancers such as colon, mammary, lung and prostate cancers are the most common cancers in adults. It is believed that in all of these tissues, the mature cells of the tissue are constantly substituted by a minority population of tissular stem cells. (7) Recent evidence demonstrate the fact that cancers may be regarded as an abnormal organ in which tumoral growth is conducted by a CSC population which may give birth to several CSCs as well as to nontumorigenic cancer cells. These observations have implications upon tumor formation biology as well as upon cancer diagnosis and treatment. In order to have an efficient treatment,

CSC must be eliminated. Otherwise the tumor will grow back rapidly even if the therapy eliminates nontumorigenic cancer cells but it keeps a significant population of CSCs. (8,9).

Studies that have been made these past years focused upon different classes of proliferating cells and especially upon stem cells from different animal tissues. Stem cells have an important role in the regeneration of the tissues that they come from but also in tumorigenesis.

This paper aims at characterizing these cell subpopulations by monitoring the antigenic expression on their surface. Thus, an experimental model was designed and set in place in which stem-like cells responsible for the resistance to oncologic treatment are involved, determining the antigenic expression on their surface in parallel with witness cells, and the markers chosen were measured in irradiated samples in comparison with non-irradiated witness samples.

Materials and Methods

Isolation of tumor cells

Isolated cells from tumor RS-1, obtained by experimental means and which is transplantable were collected in a sterile way from a donor, a Wistar rat provided by the Bucharest Oncologic Institute Biobasis. 28 days after the inoculation, the cells were processed and cultivated in culture mediums of various concentrations of fetal serum, as well as in a special culture medium for stem cells.

Experimental irradiation

Irradiation was performed by using a simple technique, by means of two opposite beams with a 90° and respectively 270° orientation, coordinated IEC 61217, with an energy of 6 MeV photons, in a field of 10 x 10 cm, SAD=100 cm, SSD=95 cm in case of the beam with a 90° orientation and SSD=95.5 cm in case of the beam with a 270° orientation.

The samples were set in a Berzelius glass beaker having a diameter of 8 cm, full of water. The doses prescribed for these samples were of 1,5 Gy, 2,5 Gy, 3,5 Gy, 5 Gy. Calculated monitor units were at a dose rate of 200, and a constant debit of 0.786 cGy/UM. The value of the ambient temperature was 23°C, the humidity level was 42% and the recorded pressure was 1009 hPa. Before exposure, dosimetric measurements were made in compliance with the IAEA TRS 398 protocol.

Characterization of cell subpopulations

Characterization by flow cytometry of the antigenic profile associated to cancer stem cells was made by connecting the antibodies of the studied antigens by using the indirect immunofluorescence technique, followed by data acquisition by flow cytometry and analysis of the data thus obtained.

Tumor cells with stem-cell features were characterized based on some stem cell characteristic surface markers. Evaluation of surface markers was made using as experimental model the cultivated RS-1 tumor cell line: a) under the conditions recommended by ECACC (DMEM: F12 with 2% FCS); b) in the presence of a high concentration of fetal serum (10% FCS); c) in a medium specific to the formation of stem cells characteristic spheres (DMEM: F12 with 20% serum substitute and growth factors). The cells were maintained in the respective cultures for 5 passages.

For antigenic profile evaluation experiments, RS-1 cells attached in FCS mediums (2%, respectively 10%) were detached by means of a PBS/EDTA non-enzymatic solution washed with HBSS by centrifugation at 300xg, and then resuspended in PBS/0,1% BSA. The cells cultivated in suspension in the sphere formation medium were centrifugated, washed with HBSS by centrifugation at 300xg, and then resuspended in PBS/0,1% BSA. After cellular suspensions had been distributed in tubes surface anti-markers primary antibodies were added and the tubes were incubated for 30 min/ 4°C. After having been washed, the cells were incubated with anti-rat secondary antibodies marked by fluorescent staining. After the intubation was over, the cells were washed again with buffer, they were resuspended in 200 μl PBS, and cell fluorescence was evaluated by means of flow cytometry. The data were acquired by flow cytometry by using a FACScan or FACS Canto II flow cytometer, and then they were analyzed using the WinMDI software application, which makes it possible to superpose histograms and to make a statistic analysis.

Characterization of RS-1 tumor cells by determining apoptosis

There are currently a large number of methods used to measure cell apoptotic death. The most used of the biochemical methods is the one consisting in the measurement of DNA inter-nucleosomal fragmentation associated to apoptosis. Induction of apoptosis also determines the activation of endonucleases that cleave the nuclear DNA. DNA fragmentation is acknowledged as a biochemical marker of apoptosis, allowing selection and quantification of apoptotic cells by measuring the amount of cell DNA by means of flow cytometry. As a result of this fragmentation, cells that suffer apoptosis lose a part of the DNA pursuant to their permeabilization with detergents or fixing by alcohol or acetone. By PI coloring (fluorochrome that passes through the plasmatic membrane and intercalates stoichiometrically between the pairs of bases of double catenary nucleic acids and which gives out a red fluorescence when excitated by a laser beam) apoptotic cells are detected based on their lesser content of DNA – hypoploid (subdiploid) which corresponds to a sub-G1 peak on the DNA quantity distribution histogram. Apoptotic cells were identified and quantified by means of flow cytometry. The samples were processed in order to obtain cellular suspension and the nuclei were colored with propidium iodide in hypotonic buffer in order to assess the apoptotic status. Sample reading was performed by using a FACSCalibur flow cytometer (CellQUEST program), and data analysis to determine the percentages of cell numbers in apoptosis was achieved by means of the

WinMDI program. 10,000 events were acquired for the analysis. The resulting histogram-type charts represent the distribution of DNA amount and are expressed depending on the fluorescence given by the FL2-H detector and the number of cells. The existence of a diploid DNA peak indicates the presence of a population of apoptotic cells.

RESULTS

We obtained primary cultures resulting from RS-1 experimental tumor tissue, the cells being incubated in the aforementioned culture mediums. The images in figure 1 here in below present the cells obtained in primary culture.

After irradiation we measured cell viability by means of a Countess Invitrogen and we recorded a dose-viability relationship (fig. 2). Cells of this type are radiosensitive and when exposed to a dose of 5Gy their viability diminishes by 50%.

Based on the determination of surface antigens of the cells taken from RS-1 tumor and cultivated in different mediums, we have obtained the expressions of studied antigens calculated as percentages presented in the table 1.

Apoptosis of RS-1 cells cultivated in various concentrations of fetal serum or in the absence of it

The analysis of apoptotic events associated to RS-1 cells cultivated in culture mediums of different concentrations of fetal serum (2% - normal conditions or 10%) or with SR 20% did not reveal major differences depending on cultivation conditions. The recorded percentages of early apoptosis events ("early apoptosis") were situated between 3,7% for RS-1/FCS 2% cells and 5,24% for RS-1/ FCS 10% cells.

The results obtained suggest that the optimum moment for the study of this experimental tumor is the period between the 21st and 42nd days after it has been inoculated, when metabolic processes associated to the presence of the tumor have grown significantly. After this period, a series of mechanisms connected with cell necroses and apoptosis occur. (fig. 3-8)

The results of the entire experiment are presented in the table 2 and demonstrate apoptosis growth in cells cultivated in a stem-cell medium and significant differences between reference cells and the ones taken from the primary tumor, which suggests that in human tumor tissue there are subpopulations with stem cell properties which may induce resistance to treatment.

Obtained results indicate once more the resistance to irradiation of cells cultivated in cell stem medium coming from the tumor, suggesting the existence of a subpopulation with stem cell properties and which are resistant to irradiation.

DISCUSSIONS

Improvement of tumor control may be achieved by identifying molecular targets and resistance mechanisms

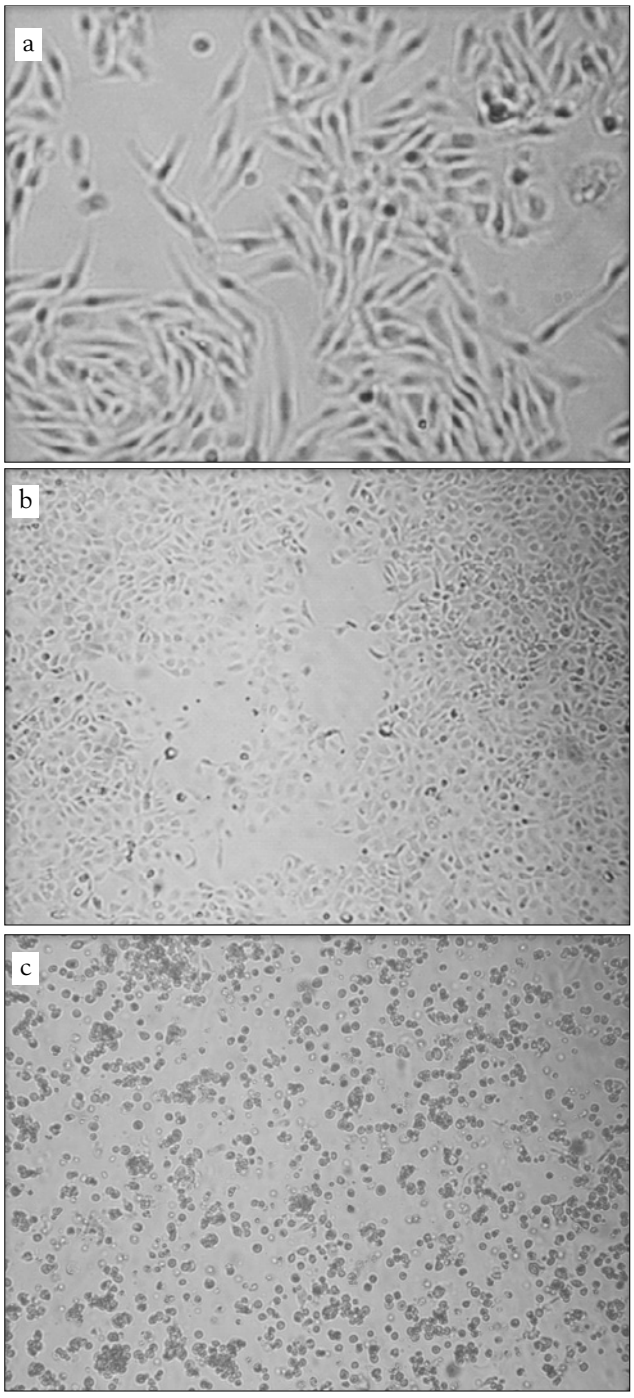

Figure 1 (a.b.c.) - RS-1 cells cultivated in culture mediums of different FCS concentration or in stem cell medium a. RS-1/ FCS 2%; b.RS-1/ FCS 10%; c. RS-1/ SR 20%

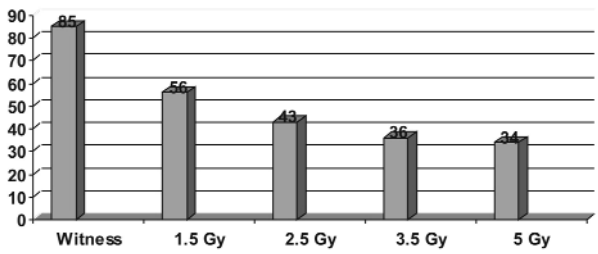

Figure 2 - Cell viability diminution in the dynamic of irradiations

Table 1 - Cell membrane antigen expression of RS-1 cells cultivated in various culture mediums (%)

Antigen/Cell line	RS-1 /FCS 2%	RS-1 /FCS 10%	RS-1 /SR 20%
Ep-CAM	88,2	75,6	92,6
CD24	34	24,3	50,7
CD44	99,8	96,8	95,4
CD71	98,6	88,8	91,4
CD105	8,7	6,9	5,4
CD117	5,5	3,4	8
CD133	21	18,2	3,1
CD166	99,3	97,7	78,4
CD200	3,3	2,4	3

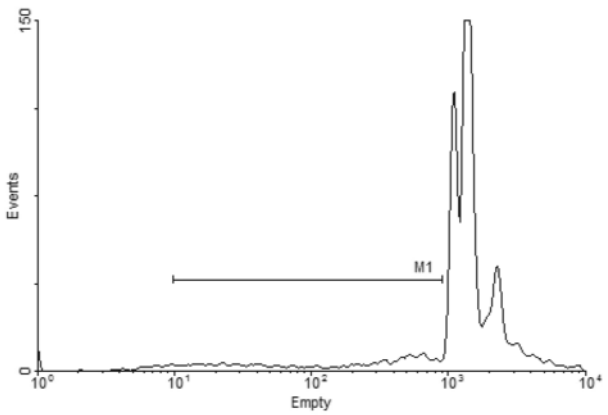

Figure 3 - RS-1FCS2%_Witness

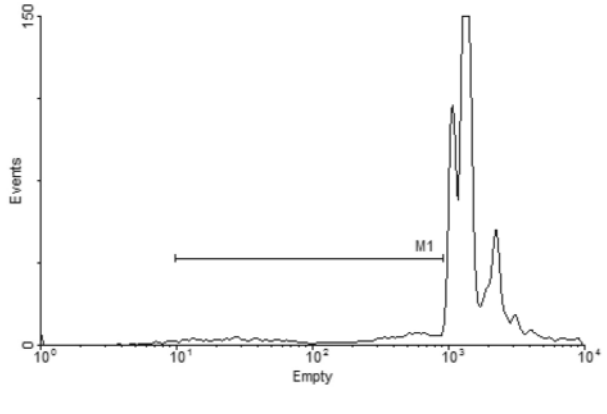

Figure 4 - RS-1FCS2%_Irradiated sample

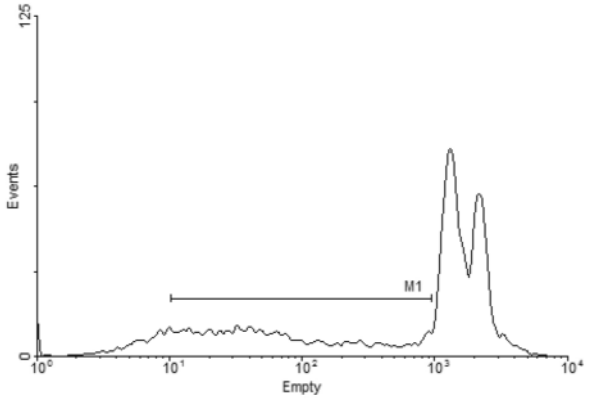

Figure 5 - RS-1 / FCS2%_Stem Witness

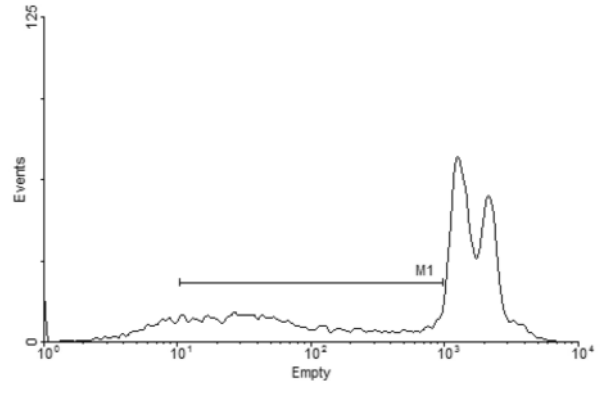

Figure 6 - RS-1FCS2%_Stem Sample

of tumor stem cells. (10)

The existence of these cells has several implications in future cancer therapy. (11) Normal stem cells have a natural resistance to chemotherapeutic agents, as they have various antigens associated with the resistance to medication, DNA-repair proteins, etc. (12)

Cancer stem cells deriving from normal stem cells by mutations may also express proteins that might increase the resistance to cytostatics. These surviving cells then repopulate the tumor, causing the relapse. Targeting them selectively may lead to the possibility to treat patients with non-resectable as well as to prevent tumor metastasization. (13)

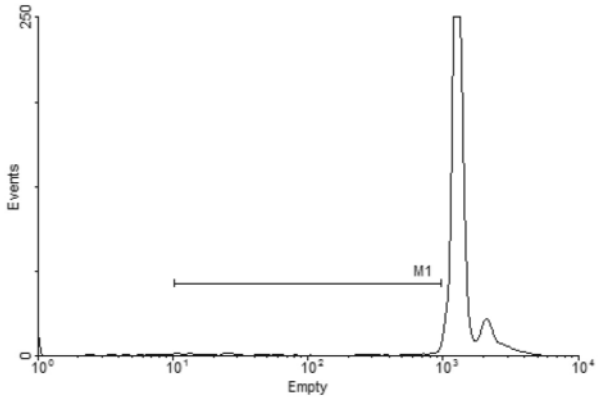

Fig. 8. RS-1 Stem Witness

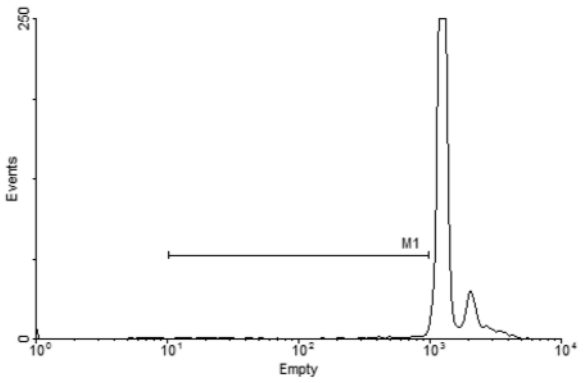

Fig. 9. RS-1 Stem Irradiated sample

Table 2 - Percentage of apoptotic cells pursuant to irradiations

Type of investigated cells	apoptosis
RS-1_ _FCS2%_ M	16.75%
RS-1_ _FCS2%_ P	14.39%
RS-1_ FCS2%_STEM_M	36.09%
RS-1_ _FCS2%_STEM_ P	36.01%
RS-1_ FCS10%_ M	32.13%
RS-1_ _FCS10%_ P	28.02%

Conclusions

To isolate tumor stem cells and to demonstrate in vivo that isolated cells represent the true tumor stem cells represent a real challenge from a technical point of view.

Identification of markers that make it possible for us to isolate tumor stem cells from the rest of the tumor cells population enable us to understand some of the most important biological properties of these cells as regards: the cell of origin of a certain tumor, the signal that triggers off self-replication and/or differentiation of these cells, the existence of certain characteristic molecules expressed by stem cells regardless of their functional status, which may serve as therapeutic targets and the mechanisms by which these cells stay unaffected by the action of conventional therapies.

By getting to know these properties we can set a foundation of future innovative therapies which will affect tumor stem cells, thus preventing their growth, local invasion and metastasization.

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ORIGINAL PAPER

C-SECTION - CURRENT TRENDS AND ITS BENEFITS

F. Popa[1], V. D. Constantin[1], C. A. Ionescu[2], H. A. Haradja[2], M. Bănacu[2], Elena Poenaru[3], M. C. T. Dimitriu[2]

[1]University of Medicine and Farmacy „Carol Davila" Bucharest, Department of General Surgery „Sfântul Pantelimon", Clinical Emergency Hospital „Sfântul Pantelimon" Bucharest
[2]University of Medicine and Farmacy „Carol Davila" Bucharest, Department of Obstetrics and Gynecology „Sfântul Pantelimon", Clinical Emergency Hospital „Sfântul Pantelimon" Bucharest
[3] University of Medicine and Farmacy „Carol Davila" Bucharest, Department of Medical Informatics and Biostatistics

Summary

Background: after becoming almost extinct during the Communism period (in an effort to raise the birth rate at any price, forbidding elective tubal ligation), the C-section is regaining – as a matter of course – its place in modern Obstetrics. Thereby the c-section represents a way to prevent obstetrical complications (with very high perinatal morbidity and mortality) and not just a way to resolve these complications (when it's often too late). This transition to normality is happening for almost 25 years, but in Romania of the 3rd millennium there are still a lot of issues to solve.
Methods: Our study is based on the profound implications of the fact that restricted indications to perform a c-section were applied (sometimes forbidden) as a way to safely finalize a birth. We analyze National Statistical Data (2009-2013), Official International Data, and retrospective birth registers from The Department of Obstetrics and Gynecology from the Clinical Hospital „Sf. Pantelimon" in Bucharest (2005, 2006 and 2014).
Results: The statistical data collected and analyzed point to a rising of the c-section index in Europe, but also in Romania (more pregnant in the capital and in the Academic Centers from our country), with an evident improvement of the medical act of giving birth and also with a clear social benefit on the long term.
Conclusions: The rising dynamics of the median annual Apgar score that we reviewed (median annual Apgar score for all births, for c-sections, and for natural births) is proportional with the rising number of c-sections; although the total number of registered births is lower (a general trend seen throughout the country). Maybe the foremost conclusion of this study is that prophylaxis is the cheapest, most logical and safe method of treatment, since birth.

Résumé

L'opération césarienne - tendances actuelles et bénéfices

Introduction: Devenu carrément interdite pendant le communisme (dans une tentative de régime totalitaire d'augmenter le nombre de la population en évitant à tout prix, proprement criminelle, la stérilisation sur demande), la césarienne retrouve, comme il était naturel, aussi en Roumanie, sa place dans l'obstétrique moderne. Et c'est une place où elle devrait être la façon de prévenir les événements de dystocie (morbidité et la mortalité périnatale et néo-natale) et non seulement le moyen de résoudre (souvent en retard), ces problèmes. La transition vers la normalité a déjà 25 ans, mais la Roumanie du Millennium III a encore beaucoup à solutionner à cet égard.
Méthodes: La présente étude commence par les causes profondes du phénomène de "pointant avec difficulté" (interdit) de la césarienne comme methode de dénouement heureux de la naissance, et analyse les statistiques nationales officielles pour cinq années consécutives (2009-2013), ainsi que les données internationales officielles (2010-2013) et les données statistiques recueillies rétrospectivement à partir de naissances de l'Hôpital d'urgence "St. Pantelimon "de Bucarest (2005, 2006 et 2014).
Résultats: Les données statistiques ainsi recueillies et analysées fournissent des résultats qui convergent vers un indice de la césarienne dynamique en hausse en Europe, mais notamment en Roumanie (évidente dans la capitale et les centres médicaux universitaires dans le pays), avec une nette amélioration de la prestation des soins médicaux et les avantages sociaux réels à long terme.
Conclusions: La dynamique de l'augmentation moyenne annuelle nette de l'indice d'Apgar à tous les niveaux mis en étude et en discussion(le score d'Apgar total annuel moyen, l'indice d'Apgar total annuel moyen de césarienne, total moyen annuel de l'indice d'Apgar pour les naissances

Correspondence address: *Mihai Dimitriu, MD*
Medic primar Obstetrica Ginecologie, Asistent universitar UMF „Carol Davila"
Department of Obstetrics and Gynecology - Clinical Emergency Hospital „Sfântul Pantelimon",
Pantelimon Ave., no. 340-342, 3rd floor, Bucharest, Romania e-mail: drmihaidimitriu@yahoo.com

Key words: c-section, c-section on demand, vaginal birth, median annual Apgar score, c-section index, vaginal birth index, quality of obstetric medical care, obstetrics based on evidence, modern obstetrics

à voie vaginale), parallèle et directement proportionnelle à l'augmentation de l'indice de la césarienne, même si le nombre total de naissances enregistrées est en baisse (tendance à la baisse de naissances est valable pour l'ensemble du pays). Peut-être la conclusion la plus importante de ces études et de la statistique du travail est que la prévention est la méthode la moins chère, la plus logique et la plus sûre de traitement ... en partant de la naissance ...
Mots-clés: césariennes, la césarienne sur demande maternelle, naissance vaginale, l'indice d'Apgar, indice annuel moyen, l'indice de césarienne, indice de la naissance à voie vaginale, de la qualité de l'obstétrique, l'obstétrique moderne fondée sur des preuves

Introduction

Blamed for a long period during the communist regime (in an effort to raise the birth rate and thus the population of the Socialist Republic of Romania - at any price, forbidding elective tubal ligation), after December 1989, the c-section progressively became a modern and efficient obstetrical tool to deliver healthy newborns as well as lowering neonatal and maternal mortality and morbidity.

In Romania at the turn of the millennium, the c-section index registered the most important rise from its entire history of modern obstetrics.

Material and Methods

The national c-section index has risen from the mutilating 4% in the communist regime to the actual 34, 2853251 % (2013). This represents a 8.25 times increase in just 23 years (if we take into account the year 2013 – for which the National Institute of Statistics reported 67.959 c-sections from 198.216 births) [1].

Also, the European Health for All Database (April 2014) reported a c-section index of 363, 07/1000 live births (in 2011) compared to a 267, 48/1000 live births in the European Union and 252, 60/1000 in Europe during the same year. Thus regarding the c-section index, we rank second after Italy (381, 10 c-sections per 1000 live births), among European countries. At the opposite end of the ranking sits The Netherlands with only 155, 86 c-sections per 1000 live births in 2010 [2].

In 2011, the National Institute of Statistics reported 58.087 c-sections from a total of 196.242 live births, which represents 29, 5996779% [1]. We notice a rise of 4, 69% rise in the number of c-sections in just 2 years (2013 compared to 2011).

In the European Health for All Database (published in April 2014), Romania was listed with 91,64% live births with a birth weight of more than 2500g for the year 2012 (the third worst in Europe, just ahead of Portugal 91,50 % and Hungary 91,40%), compared to a median European average of 93,78% and 92,95% in The European Union [2].

Another ranking published in The European Health for All Database (2014) is the percentage of births assisted by medical personnel. Romania was listed with 98,70% (in 2008), whereas other European countries were listed with 100% years before – Austria (1991), The Netherlands (1998), Lithuania (2006), Letonia (2006). The average of live natural births assisted by medical staff throughout Europe in 1998 was 99,34% [2].

Results

The natural evolution of the total number of births and the c-section index from 2009-2013, as reported by The National Statistical Institute is shown in table 1 [1].

The city with the highest number of births and thus the highest number of c-sections in Romania is occupied by Bucharest. We present the evolution of births in Bucharest in table 2 [1].

We notice the accelerated rise of c-sections in Bucharest, from 58, 33% (2009) to 74, 52 % (2013). The capital city of Romania and one of the most important Academic centers in the country has witnessed a form of "liberalization" for performing the c-section, although the total number of births has seen a constant downfall. This phenomena are interesting and are influenced somewhat by the patients' demand (c-section on demand), not only by the obstetricians and the heads of departments.

The first ranked districts regarding the total number of births (except Bucharest) are Iași, Constanța, Suceava, and Bacău (with over 7000 births per year). The last

Table 1 - Births and C-sections in Romania from 2009 – 2013:

Year of reference /Indicator	2009	2010	2011	2012	2013
Total births	222.388	212.199	196.242	201.104	198.216
Total number of c-sections	63.680	64.476	58.087	63.333	67.959
C-section index	28.63%	30.38%	29.60%	31.49%	34.28%
Natural birth index	71.37%	69.62%	70.40%	68.51%	65.72%

Table 2 - Births and c-sections – Bucharest 2009 – 2013:

Year of reference /Indicator	2009	2010	2011	2012	2013
Total births	21.447	21.147	19.103	19.221	19.161
Total number of c-sections	12.512	12.846	11.594	12.736	14.279
C-section index	58.33%	60.74%	60.69%	66.26%	74.52%
Natural birth index	41.67%	39.26%	39.31%	33.74%	25,48%

places in this ranking are occupied by the following districts – Tulcea, Covasna, Giurgiu, Caraș-Severin and Mehedinți, with less than 3000 births per year during the selected period. The evolution in these districts is seen in table 3 [1].

Another important observation is the ranking among other Academic centers in the country except Bucharest (ranks first among all categories – as expected) – table 4 [1].

It is also worth mentioning that there isn't an uniform conduct in dealing with obstetric cases that need c-section delivery among Academic Centers around the country. Thereby Mures and Constanta are districts that record a lower c-section index than Timis, Iasi or Arad (where we noticed a rising trend of the c-section). The middle ranked districts are Sibiu (except 2009, when it recorded one of the lowest c-section indexes of only 9, 19%). On the other end

Table 3 - Births and c-sections from the top and the bottom of the national ranking (based on the total number of live births from 2009 - 2013)

District	Ranking	Indicator	2009	2010	2011	2012	2013
Iasi	I	Births/year	9.917	9.499	8.604	9.256	9.628
		C-sections/year	3.886	3.729	3.254	3.718	3.830
		C-section index	39.18%	39.25%	37.81%	40.16%	39.77%
		Vaginal birth index	60.81%	60.74%	62.18%	59.83%	60.22%
Constanta	II	Births/year	8.398	8.161	7.262	7.535	7.258
		C-sections/year	2.887	2.474	1.747	1.652	1.756
		C-section index	34.37%	30.31%	24.05%	21.92%	24.19%
		Vaginal birth index	65.62%	69.68%	75.94%	78.07%	75.80%
Suceava	III	Births/year	8.261	8.001	7.876	8.189	8.303
		C-sections/year	2.451	2.322	2.273	2.231	2.335
		C-section index	29.66%	29.02%	28.85%	27.24%	28.12%
		Vaginal birth index	70.33%	70.97%	71.14%	72.75%	71.87%
Bacau	IV	Births/year	7.542	7.305	6.858	6.981	6.672
		C-sections/year	1.934	2.074	1.907	2.036	2.048
		C-section index	25.64%	28.39%	27.80%	29.16%	30.69%
		Vaginal birth index	74.35%	71.60%	72.19%	70.83%	69.30%
Mehedinti	XXXVII	Births/year	2.938	2.586	2.481	2.591	2.310
		C-sections/year	722	613	256	697	724
		C-section index	24.57%	23.70%	10.31%	26.90%	31.34%
		Vaginal birth index	75.42%	76.29%	89.68%	73.09%	68.65%
Caras-Severin	XXXVIII	Births/year	2.880	2.699	2.444	2.503	2.343
		C-sections/year	372	386	363	358	303
		C-section index	12.91%	14.30%	14.85%	14.30%	12.93%
		Vaginal birth index	87.08%	85.69%	85.14%	85.69%	87.06%
Giurgiu	XXXIX	Births/year	2.829	2.673	2.617	2.603	2.476
		C-sections/year	364	359	345	333	338
		C-section index	12.86%	13.43%	13.18%	12.79%	13.65%
		Vaginal birth index	87.13%	86.56%	86.81%	87.20%	86.34%
Covasna	XL	Births/year	2.478	2.468	2.272	2.406	2.387
		C-sections/year	514	526	493	515	595
		C-section index	20.74%	21.31%	21.69%	21.40%	24.92%
		Vaginal birth index	79.25%	78.68%	78.30%	78.59%	75.07%
Tulcea	XLI	Births/year	2.274	2.171	2.022	2.032	1.948
		C-sections/year	460	477	395	460	445
		C-section index	20.22%	21.97%	19.53%	22.63%	22.84%
		Vaginal birth index	79.77%	78.02%	80.46%	77.36%	77.15%

Table 4 - Births and c-sections in other Academic centers other than Bucharest (the ranking is made after the number of births in the corresponding district from 2009-2013)

Academic center (District)	Ranking	Indicator	2009	2010	2011	2012	2013
Iasi (Iasi)	I	Births/year	9.917	9.499	8.604	9.256	9.628
		C-sections/year	3.886	3.729	3.254	3.718	3.830
		C-section index	39.18%	39.25%	37.81%	40.16%	39.77%
		Vaginal birth index	60.81%	60.74%	62.18%	59.83%	60.22%
Constanta (Constanta)	II	Births/year	8.398	8.161	7.262	7.535	7.258
		C-sections/year	2.887	2.474	1.747	1.652	1.756
		C-section index	34.37%	30.31%	24.05%	21.92%	24.19%
		Vaginal birth index	65.62%	69.68%	75.94%	78.07%	75.80%
Timis (Timisoara)	III	Births/year	7.046	6.837	6.497	6.573	6.731
		C-sections/year	3.023	2.844	1.636	2.747	3.072
		C-section index	42.90%	41.59%	25.18%	41.79%	45.63%
		Vaginal birth index	57.09%	58.40%	74.81%	58.20%	54.36%
Mures (Targu-Mures)	IV	Births/year	6.451	6.113	5.854	5.781	5.727
		C-sections/year	1.125	1.126	1.134	1.203	1.206
		C-section index	17.43%	18.41%	19.37%	20.80%	21.05%
		Vaginal birth index	82.56%	81.58%	80.62%	79.19%	78.94%
Sibiu (Sibiu)	V	Births/year	4.885	4.616	4.275	4.445	4.393
		C-sections/year	449	862	963	1.074	1.412
		C-section index	9.19%	18.67%	22.52%	23.55%	32.14%
		Vaginal birth index	90.80%	81.32%	77.47%	76.44%	67.85%
Arad (Arad)	VI	Births/year	4.482	4.255	3.989	4.139	3.962
		C-sections/year	1.603	1.435	852	1.530	1.601
		C-section index	35.76%	33.72%	21.35%	36.96%	40.40%
		Vaginal birth index	64.23%	66.27%	78.64%	63.03%	59.59%
Olt (Craiova)	VII	Births/year	3.971	3.615	3.356	3.447	3.237
		C-sections/year	883	947	939	1.049	1.088
		C-section index	22.23%	26.19%	27.97%	30.43%	33.61%
		Vaginal birth index	77.76%	73.80%	72.02%	69.56%	66.38%

of the ranking lies Timis with the highest c-section index of 45, 63% recorded in 2013.

Discussions

Although the c-section should be considered by all obstetricians as a way to prevent dystocia (most frequently) and other complications that imply maternal and neonatal morbidity and mortality, it is regarded in some maternities (and some Academic Centers) just a way to solve the dystocia (often too late, when the situation is out of control).

This attitude, not to consider prophylaxis and push the limits until out of control, is the reality that Romanian obstetricians are facing. This leads to a significantly high number of peripartum complications –important neonatal and maternal morbidity and mortality.

Also it leads to preventable loss of human lives and iatrogenic complications (with particularly traumatic marks) in situations when, actually, we should look after the pregnant woman and deliver a healthy baby [4,5].

This problem has many causes, but the collective fault is ours - whether we like it or not- the obstetricians. One of the most important causes is maybe that the Romanian school of obstetrics is tributary to the communist system that prohibited the c-section (out of absurd reasons). Our society is so indoctrinated by the old system's rules that after more than 25 years, there are still some obstetricians and neonatologists who consider that a baby delivered through c-section can't get an Apgar score of 10 at birth.

Also in our country, there are obstetricians who ask their superiors with mindless obstinacy for permission to perform a c-section; the c-section being considered a favor that the doctor offers to the patient.

Worse still, by conditioning the c-section, the professional independence of the doctor is infringed – he is the only one responsible for the therapeutic decision and by law he shouldn't be influenced by any bureaucratic procedures. By this conditioning, the patient's rights are violated not being able to get the recommended treatment indicated by his doctor – and having to depend on the decision of his superiors [3].

In addition, this harmful, illegal practice is disseminated to the next generations (of doctors and patients). During the past years these 'customs' have gotten to the conscience of the populations (our patients) who sometimes strongly

Table 5 - Birth statistics from the Department of Obstetrics and Gynecology of The Clinical Emergency Hospital "Sf. Pantelimon" Bucharest (during the years 2005, 2006, 2014) and the average annual Apgar score registered

Reference year	2005	2006	2014
Toral number of births registered	1.812	1.724	1.139
Home births/Ambulance (no Apgar score)	17	21	14
Total number of dead fetuses (Apgar 0) antepartum or intrapartum	22	15	7
Total number of c-sections performed for uterine scar	86	98	178
Total number of births (Apgar score 1-10)			
Vaginal + C-section	1.773	1.687	1.119
Tota number of natural births with Apgar (Apgar score 1-10)	1.263	1.134	407
Total number of c-sections with Apgar			
(Apgar score 1-10)	510	553	712
Average Apgar score for all births (natural and c-section)	8,741680767	8,714285714	9,130473637
Average Apgar score for natural births	8,746634996	8,741394528	8,98034398
Average Apgar score for c-sections	8,729411765	8,674502712	9,216292135
Vaginal birth index (Apgar) annually from total number of births (with Apgar)	71,2351946%	67,219917%	36,3717605%
C-section birth index (Apgar) annually from total number of births (with Apgar)	28,7648054%	32,780083%	63,6282395%
Annual percentage of c-sections performed for uterine scar from the total number of c-sections with Apgar score of	16,8627451%	17,721519%	25,00%
Annual percentage of c-sections performed for uterine scar from the total number of births with Apgar score of	4,85053582%	5,80912863%	15,9070599%

believe that the c-section is a dangerous surgical procedure, that should be avoided by any means.

At least for the next generations' sake, we should all admit to the evidence (of real studies that offer proof) and apply it in our daily practice.

For these reasons, to find out the truth, using modern statistical ways we studied the live births from the Department of Obstetrics and Gynecology of The Clinical Emergency Hospital "Sf. Pantelimon" Bucharest (during the years 2005, 2006, 2014). What we found out is intriguing – the Apgar score at birth is not lower by c-section timely performed – but surprisingly higher as can be seen in table 5 (also presented are the c-section index, natural birth index, the average Apgar score by c-section and natural birth, tha annual Apgar score).

Conclusions

After a thorough analysis of these statistical data (the gathering and processing of the data was not announced and thus is not influenced by any interests) we clearly observe the dynamic ascending trend of the average annual Apgar score relative to all the parameters studied (total annual average Apgar score, annual average Apgar score for c-sections and natural births) simultaneously and directly influenced by the rising number of c-section index (63, 62% in 2014 compared to just 28, 76% in 2005). Nevertheless, the total number of live births registered is decreasing (this trend is illustrated in Table 1, and is the same for the whole country)

Further, we notice that in 2014 the total number of c-sections exceeded that of natural births (63, 62% - the c-section being performed more freely, and in a prophylactic way opposed to a more rigid 28, 76% in 2005), the Annual average Apgar score for babies delivered through c-section surpasses by 0,23594815 the same index for vaginal births.

In other words, the more the c-section is performed in a prophylactic (not just curative) way, the better the medical and obstetrical practice becomes. This also refers to the classic obstetrics which promotes vaginal birth – because we noticed a net increase in the annual average Apgar score for all births including the vaginal births. Therefore, if performed by a responsible and trained medical professional team, the c-section raises the number of eutocic births.

It's also worth mentioning that the statistics gathered from around the country and other maternities from Bucharest are following the same pattern as our Department of Obstetrics and Gynecology from the Clinical Emergency Hospital "Sf. Pantelimon" Bucharest.

Of course that these kinds of studies are very useful for every maternity in the country and should be made on an annual basis and centralized by the Ministry of Health – thus providing the insight that will help us reach a correct and real conclusion. By this we will be able to practice more and more an evidence based medicine as we should (by this occasion I would like to challenge the responsible authorities of the Romanian Obstetrics to take note).

Maybe the most important conclusion of the studies and statistic labor that we conducted is that a prophylactic attitude is the cheapest, most logical and safest way of treatment, beginning with birth. Perhaps all of us that are part of the system (obstetricians, neonatologists, decisional forums, the academic staff and the patients) should get more involved with the birth, education and formation of the

future generations and also become more concerned and responsible with what we leave behind. The children born today are the future and the generations that we form and educate now are the ones that will be responsible with our care. For this, we should start caring more, thinking, and not take for granted the preconceptions.

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ORIGINAL PAPER

ELECTIVE CESAREAN SECTION - FOR OR AGAINST?

M. C. T. Dimitriu[1], V. D. Constantin[2], C. A. Ionescu[1], H. A. Haradja[1], M. Bănacu[1], Elena Poenaru[3], F. Popa[2]

[1]University of Medicine and Pharmacy "Carol Davila" Bucharest, Department of Obstetrics - Gynecology, "Saint Pantelimon" Emergency Clinic Hospital "Saint Pantelimon" Bucharest
[2]University of Medicine and Pharmacy "Carol Davila" Bucharest, Department of General Surgery "St. Panteleimon" Emergency Clinic Hospital "St. Panteleimon" Bucharest
[3]University of Medicine and Pharmacy "Carol Davila" Bucharest, Department of Medical Informatics and Biostatistics

Summary

Introduction: In Romania and, in fact, throughout the whole Europe, the patients are nowadays allowed to choose to abort an unwanted pregnancy, they are allowed to choose to do plastic surgery (e.g. breast prosthesis), are allowed to opt for surgical sterilization, are allowed to choose assisted human reproduction (from an anonymous sperm donor or from an anonymous oocytes donor and a surrogate mother aged up to 65 years or from the simple intrauterine insemination up to the intracytoplasmic sperm injection). These patients are allowed to refuse surgery, including Cesarean (!) by the refusal to sign the informed consent. So they are taking all these decisions (on their behalf and on the behalf of their children, too) ... but they are not allowed to choose how to give birth! Since elective Cesarean is not yet legalized ... it is allowed only with strict surgical indication.
Methods: To correctly analyze the real situation in Romania we have imagined three working methods: 1. A strictly anonymous interview (type A – an opinion questionnaire with 26 questions) addressed to the patients and the general public about their choices regarding the elective Cesarean and the usefulness of the legalization of such a procedure; 2. A strictly anonymous interview (type B – an opinion questionnaire with 15 questions) addressed to the obstetricians, about their choices and the need of legalization of the elective Cesarean; these answers were statistically analyzed; 3. We compared the number of Cesarean procedures (including their indications) during 2009-2014 in several major maternity hospitals in the country.
Results: We gathered a database with over 1,000 type A filled questionnaires (respondents of all ages, sexes, educational levels, religious confessions from three regions of the country), we have more than 100 type B filled questionnaires (respondent obstetricians of all ages, grades, gender, seniority) from five major maternity hospitals in the country) and we analyzed over 8,000

Résumé

L'opération césarienne de choix - pour ou contre?

Introduction: les patients de Roumanie et de l'Europe du troisième millénaire sont autorisés à choisir d'interrompre une grossesse non désirée sur demande, sont autorisés à choisir de faire de la chirurgie plastique (par exemple la prothèse mammaire), sont autorisés à opter pour la stérilisation chirurgicale, autorisés à choisir la procréation assistée (du donneur anonyme de sperme, donneurs anonymes des ovocytes et mère porteuse jusqu'à l'âge de 65 ans - à partir de la simple injection intracytoplasmique de spermatozoïdes jusqu'à l'insémination intra-utérine de sperme); ils peuvent aussi refuser la chirurgie (y compris par césarienne - le refus de signer le consentement informé) et de prendre toutes ces décisions (en leurs noms et leurs enfants) ... mais pas le droit de choisir la façon de donner naissance !!! Parce'que la césarienne n'est pas encore certifiée ... elle n' est autorisée qu'avec indication chirurgicale stricte ...
Méthodes: Pour analyser correctement la situation réelle en Roumanie on a imaginé trois méthodes de travail: 1. Interviewer les patients strictement anonymes (par le biais d'un avis de questionnaire) et le public sur leurs choix vis-à-vis de l'application de la légalisation césarienne et l'utilité de la application (type A questionnaire avec 26 questions); 2. L'interview strictement anonyme des obstétriciens (questionnaire avec 15 questions type B) vis-à-vis de leur choix et le besoin de la légalisation de la césarienne sur demande - ces réponses seront analysées statistiquement; 3. Comparaison dynamique statistique (2009 -2014) de l'index et le nombre des césariennes (et leurs indications) dans plusieurs grands hôpitaux- maternité dans le pays.
Résultats: Nous avons compilé une base de données qui compte déjà plus de 1000 questionnaires remplis type A (répondants de tous les âges, sexes, niveaux d'éducation, des confessions religieuses dans trois régions du pays), plus de 100 questionnaires

Correspondence address: *Dr. Mihai Dimitriu, MD, PhD*
Obstetrics and Gynecology, Assistant Professor at "Carol Davila" Medicine and Pharmacy University
Department of Obstetrics – Gynecology, Emergency Hospital "St. Pantelimon" in Bucharest
Bucharest, Sector 2, Pantelimon Road. 340-342, 3rd floor. *e-mail: drmihaidimitriu@yahoo.com*

child deliveries between 2009 - 2014 (from five major maternity hospitals in the country). Statistics are presently in full process of analysis.
Conclusions: The analysis of these broad statistical data will enable us to answer several key questions: patients have the right to choose how they want to give birth? If so, why don't we allow them to choose? If not, why don't they have this right? Who is opposing this legalization and why? Which steps should be followed? Which are the foreseeable consequences of these actions? The ultimate goal of this study is not only to elucidate reality and patients and obstetricians option vis-a-vis of the analyzed subject, but also a much larger project of initiation and more ambitious, in partnership with all stakeholders, issuing a possible project law that will allow pregnant women in Romania to give birth in decent, free elected and knowingly consented conditions.
Key words: elective Cesarean section, choosing birth's path, legalization of elective Cesarean section, dignity of birth, patient's dignity, patient's rights

complétés type B (pour les obstétriciens de tous les âges, grades, sexes, de 5 grands hôpitaux - maternité dans le pays), et plus de 8000 naissances dans les années 2009 et 2014 (pour les 5 importantes maternités du pays). Les statistiques sont dans le processus d'analyse.
Conclusions: L'analyse de ces grandes données statistiques nous permettra de répondre à plusieurs questions clés: les patients ont le droit de choisir comment ils veulent donner naissance? Si oui, pourquoi pas le garantir? Si non, pourquoi pas? Qui s' oppose à la légalisation? Quelles sont les étapes à suivre et quelles sont les conséquences prévisibles de ces actions? Le but ultime de cette étude n'est pas seulement d'élucider la réalité, et l'option de les patients et obstétriciens vis-à-vis de l'objet analysé, mais aussi un projet d'initiation beaucoup plus grand et ambitieux, en partenariat avec touts les facteurs responsables, proposition d'un projet de loi qui permetra aux femmes enceintes de donner naissance en Roumanie dans des conditions décentes, choisies librement et en connaissance réelle de cause.
Mots-clés: la césarienne sur demande, choisir la voie de naissance, la légalisation de la césarienne sur' demande, la dignité de naissance, la dignité du patient, les droits des patients

INTRODUCTION

Earth ... European Union ... Romania ... 2015 ... Third Millennium ...

Whether we want it or not, we are witnessing medical phenomena, social and bioethics issues that are, at least, paradoxical. In Romania's 2015 patients (and thus citizens) are allowed to refuse medical or surgical treatment proved curative and assume that (including the refusal to this treatment, which is tantamount to aggravation of illness and even suicide). Extrapolating this fundamental right of the patient to refuse surgical act (to not be operated without informed consent and freely expressed will), we concluded that a parturient woman may refuse even the Cesarean section (even if her refusal may be equivalent to infanticide and/or patient suicide!).

Further, in the same era and on the same European lands, patients are allowed to choose the number of children they want and the moment when they want to have these children (including mothers who give birth when they are 65 years old), are allowed to decide whether to keep an unwanted pregnancy or to have an abortion (attention, through a surgical act! abortion on request is legal in Romania since 1990, up to 12 weeks gestational age to take this decision on their behalf and on the behalf of the child), are allowed to opt for breast prosthesis or for any aesthetic surgical act (and to assume this), are allowed to use assisted human reproduction (from an anonymous sperm donor or from an anonymous oocytes donor and a surrogate mother aged up to 65 years for the simple intrauterine insemination up to the intracytoplasmic sperm injection ICSI) [1, 2].

So despite all the liberties, patients of this millennium, citizens of Europe (the cradle of world culture and progress) are not allowed to choose how to give birth, as an elective Cesarean section is not legal! In other words, without a very carefully documented and a definite medical indication, the patient is unable to give birth otherwise than on vaginal way, Cesarean section not being a legal option ... but may refuse it even when it is an absolute medical indication that can save her and her baby!

Gazing on the origins of this legal, medical and ethical paradox, we can discern, from the outset, some of the causes of this phenomenon at least bizarre.

First, vaginal natural birth is seen in society as a physiological act by which mother gives birth to her child, while Cesarean section is seen as a surgical act, "surgery" that may "sometimes" solve maternal-fetal problems occurred during labor and birth. The obstetricians regard vaginal birth as an normal event, but they recognize its dystocia potential. It seems that the Cesarean section is for them a good solution for this dystocia potential found in the vaginal birth and due to this, there is no way for them not to think recommending it to their patients.

Even in the recent literature, the child delivery is defined as "the natural, spontaneous elimination of fetus and its annexes from the uterus at the end of pregnancy" or "all the active and passive events that lead to the expulsion of the fetus and its annexes", while that the "Cesarean section is defined as a surgical incision involving the anterior wall of the uterus to extract the fetus" or "fetal birth after laparotomy and hysterectomy" [3,4,2,5].

Secondly, medicine and Romanian society is still tributary to the communist era, when, in order to avoid surgical sterilization on request (which now became, ironically, also legal), the maximum index (note well: The maximum!) of Cesarean sections accepted by the Communist Party was 4%.

That index gives nightmares even nowadays to obstetricians who started their practice before 1989; this index wrote countless black pages in the history of the Romanian society at least by the fact that the increased intra- and perinatal morbidity and mortality came at the highest levels ever,

levels that have never been achieved before in Modern Europe.

Certainly, during the Communist regime, that such an index ("scientifically" calculated by the Communist Party) had to have some "serious" medical reasons as, for example, the one saying that C section would seriously harm mother's and her offspring's health (e.g. the low Apgar score at birth - which was nothing more than the result of the postponement at maximum for the surgical intervention after straining a dystocia). For the same Communist Party the vaginal birth was only bringing unparalleled advantages, from a quick and „safe" installation of lactation up to the thriving individuals with „healthy origins" that could only do honor "the multilateral developed society").

Classic obstetrics "bloomed" in the last decades of communism, and the application of forceps "at any price" and with all its "beneficial" consequences (both maternal and fetal) that reached the highest levels during those times. In return, Cesarean section was practiced so rare that nowadays a resident in obstetrics and gynecology practices more Cesareans sections in the 5 years program of residency than obstetricians practiced in communist times throughout their whole careers.

Here are two phrases that may amuse us today, but in 1955 urged doctors (in one of the most important obstetrics treaties of those times) to practice Cesarean section with "discernment", because "considered as the safest method, able to save both mother and the child lives, without prejudicing them too much, the Cesarean section gave rise to abuses, being used improperly, even when the birth was possible not only by the simple obstetrical interventions but by natural forces, too"; "The use of Cesarean sections in all cases is an impermissible simplification, which descends the obstetrics to the level of a rude trade, threatening hundreds of women to challenge the most serious trauma and leaving traces for life" ... [6].

We do not know exactly how many traumatized children at birth are contemporary today with us, but everybody (gynecologists, surgeons and urologists - old and new) treated the urinary incontinence and the perineal tears of their mothers and grandmothers.

The social costs of these births of "the new type of man" were tremendous: care of the traumatized children at birth and their "heroine" mutilated mothers. Now we can talk about the exact costs of the today's society due to that communist medical era and that professional rule blaming the C section, all of that in that period of time when the quality of life was not the priority ... And so, the first dialogue on this subject should be about the cost of the surgical cure of the urinary incontinence, which is one of the most common surgeries practiced today in the departments of gynecology, surgery and urology. We shouldn't be exceptional mathematicians to realize that the price of the vaginal birth plus the care for the mother's morbidities (morbidities that result only in the absence of practicing the Cesarean section) plus the cure of the urinary incontinence, dyspareunia and genital prolapse (saying nothing about the vaginal fistulas) far outweigh the price of Cesarean section. So, not even the accounting arguments do not justify such a "healthy" health policy.

Unfortunately, the fact that the Romanian school of obstetrics and gynecology is still rooted in that "4%" continues and will continue to cost us, yet few generations.

Another cause that might be incriminated in the pathogenesis of this paradox is today's education (tributary to the same old times school) who still considers Cesarean as a "gift" that a „generous" obstetrician may offer to the patient if the patient makes it "worth" or as a 'last resort' to serious medical problems that may arise during parturition.

Birth is still seen as a natural phenomenon, while the Cesarean section is, as its name implies, "surgery". Medical popular culture and the popular medical "ballads" still postulate folklore "axioms", propagated as authentic, demonstrating by statistical data which have never being validated (not to say that can ever be invalidated) that the "recovery after Cesarean is much harder and longer"; during Cesarean "the infant comes suddenly out from the environment which he used and this may cause serious health problems"; "Vaginal birth results in healthier and smarter children than by Cesarean" and the list goes on ...

In such a medical and social climate, Cesarean became a "currency exchange" between doctor and patient. Let's honestly admit, elective Cesarean is practiced under the cover of some medical "manufactured" indications. The voices of those who claim that Cesarean is in nimble and trained hands often much safer and less risky than the vaginal birth, gradually begin to cover those of obstetricians who applied and apply, yet with ease and skill, the centuries-old Tarnier forceps.

Of course, the conflict between generations is one who always born progress!

Yes or not has the pregnant women the right to choose how they want to give birth in the third millennium?

If they have it, why not give it to them? Who's opposing to give them this right?

If they haven't this right which are the logical, ethical, economic and scientific (especially medical) arguments that limit them to have this right?

If we give them this right, in fact ... something that rightfully belonged to them!) which are the predictable consequences of this regulation? From economic to social and demographic data up to the medical ones...

If you do not give them this right, we will ever have the right to complain when we see "at TV" disastrous consequences of this "prohibition"? And who gives us the right to decide whether or not is this a patient's right?

Material and Methods

These are just some of the questions that we all, specialists in the field, will have to respond quickly, which is why I imagine some polling tools and obstetricians opinion about this problem that risks becoming (if it's not solved responsible and within a schedule) a real "public health problem" in Romania and other civilized countries.

The first tool is an survey addressed to the general

population opinion on the Elective Cesarean Procedure (table 1). It is addressed to all socio-economic, cultural, religious, occupational, ethnic, age or sex (from ordinary patients or their caregivers, to nurses and highly qualified, with or without direct obstetric concerns).

The Questionnaire A (addressed to general population) contains 26 questions that should be answered by an unique answer. The first two questions concern the general demographic situation (sex and age of respondent) and the following three questions refer to the respondent's level of education (primary school, high school / college, post-secondary school, college and / or over this level) and the quality of being or not (binary answer: yes or no) doctors, nurses / midwives and having or not medical training or

Table 1 - Questionnaire type A

Elective Cesarean - Opinion Survey

This is an anonymous questionnaire regarding your honest opinion about the necessity or, conversely, the futility of the legalization and introduction into clinical practice of ELECTIVE CESAREAN (i.e. at the patient's request, as an alternative to vaginally birth). Please mark with an "X" the answer you choose. Thank you for HONESTLY answer the following questions which will form a database for statistical survey on your opinion on this health problem. Based on this study, will be carried papers that will contribute to improving healthcare in terms of birth and your data and your opinions will remain anonymous

1	You are a person of sex:	Female	11	You or someone very dear to you gave birth until now?	Yes
		Male			No
2	Your age is:	under 18	12	Did you or someone very close to you give birth by vaginally delivery?	Yes
		18-25 years			No
		26-35 years	13	Did you or someone very close to you give birth by Cesarean delivery?	Yes
		36-45 years			No
		46-55 years	14	Did you remain with some unpleasant memory after birth?	Yes
		56-65 years			No
		66 years & over	15	If you were to choose how you or your daughter will deliver, which one would you choose:	Natural birth
3	Your level of education (completed) is:	1-8 primary school			Cesarean delivery
		9-12 lyceum	16	Do you find it normal that the patient can choose how to give birth?	Yes
		Secondary School			No
		University & more	17	By which kind of delivery do you think that it would be easier for a woman to give birth?	Natural birth
4	Are you a doctor?	Yes			Cesarean delivery
		No	18	Do you consider that the natural birth can be dangerous for the mother / fetus?	Yes
5	Are you nurse / midwife?	Yes			No
		No	19	Do you consider that the Cesarean delivery can be dangerous for the mother / fetus?	Yes
6	Do you have medical training?	Yes			No
		No	20	Which one do you consider riskier for the mother / fetus?	Natural birth
7	Do you live in a:	City			Cesarean delivery
		Village	21	Do you think that the pain of natural childbirth can be a real reason of fear for the mother?	Yes
8	At what age did you started your sex life:	Under 18 years			No
		18-20 years	22	Do you think that the fear of surgery / pain during the Cesarean birth may be a good reason of fear for the mother?	Yes
		20-25 years			No
		over 25 years	23	Would you agree with the legalization of birth by Cesarean section at the request of the patient?	Yes
		Not started yet			No
9	The number of your sex partner(s) from the beginning of sexual life is:	One	24	If the elective Cesarean would be legal, it should be free?	Yes
		Between 2 and 5			No
		Over 5	25	Currently is there a person in your family who is pregnant or recently gave birth to a baby?	Yes
		None			No
10	In your couple were there abortions on demand?	Yes	26	Are the issues raised by this opinion survey important to you?	Yes
		No			No

professional (medical students, nursing schools and students educated people medical, but not practicing such items, will be found in this population's niche).

The following 4 questions are also demographic and social (urban or rural living environment, age of sexual debut and number of sexual partners so far - all these data will help in understanding sexual behavior and the behavior related to the couple's life of the respondent). The question no. 10 questions the existence or not of an abortion on demand in the respondent's couple - this question will elucidate the behavior of the respondent vis-a-vis the problem of already acquired Romanian law, to waive the request to an unwanted pregnancy).

Questions 11 to 14 are addressed to the interviewee's personal history regarding birth / births (it differentiates the situation in which births occurred versus the situation with no births in the history of the respondent and also how these births differentiate between them: vaginal, Cesarean or both). The 14th question questions the presence or absence of "unpleasant" memories related to these births.

The following 8 questions (15 -22) explicitly question the choices that the interviewee would make for people very dear to him (e.g. own daughter for male respondents), regarding the route of birth (in case they were allowed to choose), respondent's opinion about normality of deciding on the birth path itself, respondent's opinion about the way birth seems easier for the patient (vaginal versus Cesarean) and its opinion on the materno-fetal risks for the two ways of birth. Questions 21st and 22nd want to elucidate whether the respondent feels fear and therefore if the fear of pain might be a reason that may influence the decision to give birth in one way or another.

Questions 23rd and 24th respectively, directly question the interviewee for his/her agreement for the legalization of Cesarean section on demand (using a binary answer yes / no) and if it will be legal, should it be free or not? (all binary answers: yes / no).

The penultimate question, the 25th, quantifies the degree of immediate interest for the interviewee to request a Cesarean ("e.g.: now there is no person in your family who is pregnant or recently born?") (Also answered with yes / no).

Last question, the 26th, concerns the degree of interest of respondent vis-a-vis the issue of Cesarean on demand.

We carefully timed completion of this type of questionnaire by a person with average skills in reading and responding with "X" on the 26 questions, and the mean result was about 90 seconds.

The 2nd opinion anonymous questionnaire (Questionnaire B) (table 2) is addressed strictly to currently practicing obstetricians and contains only 15 questions with unique answer. The average time of completion of this type of questionnaire was only 30 seconds (people more involved and fewer questions).

After completing the demographic data type sex and age (questions 1 and 2), the interviewee is asked to specify the length of obstetrics and thus professional degree (0-5 years old resident physician, specialist - 6-10 years old or primary 11 years and over, age categories are graded and grouped in obstetrics: 11-20 years, 21-30 years, 31 years and older, within this last category we will find doctors who practice obstetrics even before 1989, under the communist regime. (see question 3).

Question 4 invites the respondent to define the place where they are performing most of their obstetrical activity: at a state hospital or within a private hospital, being known that many obstetricians currently work in both categories of hospitals and their practice vis-a-vis of the chosen route of delivery can be significantly influenced by the custom of the place in which they mainly operate and were they mainly perform their medical activity.

Question 5 calls for absolute sincerity of respondent (the questionnaire is anonymous) and tries to elucidate if ever the interviewed obstetrician carried out a Cesarean section on demand under the guise of "manufactured" medical indications (binary response by yes / no).

Next, in a natural order, a single answer question (question 6) invites the respondent to quantify the percentage of "covered" Cesarean on demand they practiced (out of Cesareans practiced lately) in one of the following groups: 0%, 1-20%, 21-30%, 31-40%, 41-50% and over 50% group.

Question 7 invites the respondent (through a similar model) to quantify the rate of Cesarean practiced in the last 12 months (of total births attended by him/her) (all being percentage groups).

Question 8 is a binary response type yes or no and asks the doctor if its personal index of Cesarean (Cesarean vs. of all births attended by him) increased in the last 5 years or not.

Questions 9 and 10 are binary also and elucidate whether or not the respondent would agree with legalizing Cesarean on request and asks its opinion about gratuity or, conversely, the need to (legal) "charge" for Cesarean on request. The question is justified if we consider that this medical service should be performed by the clinician on request. However, the fee cannot be very large because it would disadvantage those on low incomes and cannot be ethical not to enjoy a right because you cannot afford it (definite inequity).

Question 11 - interviewee is asked to answer which birth method would will prefer for his/her daughter (the answer is binary) (The idea had in mind for this question is that obstetrician will normaly choose the safest method for his/her family).

The following two questions (12 and 13) are binary too and ask the doctor if it is normal for the patient to choose the route of delivery (vaginal / Cesarean section) and if it has the habit to ask patients how they want to give birth (yes / does not).

The last two questions of the questionnaire type B (14 and 15) are binary too and ask the question if the obstetrician is interested about the subject of Elective Cesarean and about his sincere interest for or against the legalization of Cesarean on request: "Do you think that you will have professional benefits if elective Cesarean would be legalized?" (Possible answer: yes / no).

Table 2 - Questionnaire B

Elective Cesarean - Opinion Survey

This is an anonymous questionnaire regarding your honest opinion about the necessity or, conversely, the futility of the legalization and introduction into clinical practice of ELECTIVE CESAREAN (ie. at the patient's request, as an alternative to vaginally birth). Please mark with an "X" the answer you choose. Thank you for HONESTLY answer the following questions which will form a database for statistical survey on your opinion on this health problem. Based on this study, will be carried papers that will contribute to improving healthcare in terms of birth and your data and your opinions will remain anonymous.

1	**Your Gender:**	Male
		Female
2	**Your age is (completed years):**	23-30 years
		31-40 years
		41-50 years
		51-60 years
		61-65 years
		66 years & over
3	**Practice of Obstetrics and Gynaecology:**	0-5 years (resident)
		6-10 years (specialist)
		11-20 years (primary)
		21-30 years
		31 years & over
4	**In which kind of hospital do you deploy the majority of your activity?**	State owned
		Private
5	_____	Yes
	___	No
6	**The proportion of Cesareans on demand (out of all practiced Cesarean)**	0%
		1-20%
		21-30%
		31-40%
		41-50%
		Over 50%
7	**From all births that you have managed in the last 12 months, Cesareans are represented by a percentage of:**	1-20%
		21-30%
		31-40%
		41-50%
		Over 50%
8	**Does the number of Cesareans practiced by you has increased in the last 5 years? (their percentage in the total births attended)**	Yes
		No
9	**Would you agree with the legalization of Cesarean on patient's request?**	Yes
		No
10	**If you would legalize elective Cesarean, it should be free?**	Yes
		No
11	**If you were to assist birth of your daughter, what would you choose for her?**	Natural birth
		Cesarean delivery
12	**Do you find normal that the patient can choose the way how to give birth (in the case that a medical Cesarean is not required?**	Yes
		No
13	**Do ask your patients how they want to give birth?**	Yes
		No
14	**Do you feel that the topic discussed by this questionnaire is important??**	Yes
		No
15	**Do you think that you will have professional benefits if elective Cesarean would be legalized?**	Yes
		No

Results

Besides these two types of anonymous questionnaires, we will be helped to elucidate the actual dimension of this issue using the registries of birth found in several hospitals and by several statistic studies related to the real rate of Cesareans performed in hospitals, the Apgar scores at birth (Vaginal versus Cesarean).

These studies will be multi-center and comparative between them and on different years (periods).

The two opinion surveys were distributed in several different population groups (hospitals, obstetrics - gynecology and surgery departments, private medical clinics, places with many employees and through the knowledge and the ways of disseminating of their contacts and these multi-center loads will be compared with each other. We will thus obtain more valuable statistical results. We will also analyze statistical data resulting from the merger of these lots.

The results thus obtained will be the subject of communications and subsequent publications.

Discussion

For the best possible statistical validity of the data thus collected and recorded, we proposed a minimum target of 1,000 surveyed by questionnaire type A (general) (we already completed and entered into the database 900 questionnaires type A) and a minimum of 100 surveyed by questionnaire type B (especially for obstetricians) (we already completed and entered into the database 80 questionnaires type B).

We will also seek to statistically compare each 8000 births with a minimum difference of 5 years (4000 births from 2014 with 4000 births from 2009) (multi-centric analysis), which is why we collect and centralize data from

four important maternities in the country). We seek to discern whether Cesarean rate rose in reality and what are the real causes of the dynamics of this rate.

Another question we want to answer in this statistical analysis is the real proportion of Cesarean done at the request of patients under the cover of manufactured medical indications.

Another thing of importance that we want to quantify is the dynamic proportion of uterus' scars after Cesarean sections.

Conclusions

We hope that following this strategy with our working methods, we can draw from such statistical data and analyzed results many useful conclusions to elucidate the problem posed by cesarean section on demand today (here and in the world).

The ultimate goal of this study is not only to elucidate reality and the option of patients and obstetricians relative to the analyzed subject, but also a much larger and ambitious project of initiation of a partnership with all stakeholders (Ministry of Health, College of Physicians, Ombudsman, National Society of Obstetrics - Gynecology in Romania, the National Bioethics, interested NGOs etc) of a possible bill allowing pregnant women to give birth in decent conditions, on a free and voluntary choice knowledge based. This legal provision could substantially improve the obstetrics in Romania, nowadays and is the future and so we would be ranked among the pioneers of medical progress and bioethics in the world.

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ORIGINAL PAPER

THROMBOPHILIA AS A RISK FACTOR FOR LOW BIRTH WEIGHT

Luiza Dincaref[1], Valerica Horhoianu[1], Simona Albu[1], G. Niculescu[2]

[1]*University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania*
[2]*University of Medicine and Pharmacy, Craiova, Romania*

Summary

Introduction: Thrombophilia having the role of increased thrombus formation and associated with the hypercoagulable state of pregnancy leads to impaired placental development quality. (1, 2) involved in apparition of obstetric complications. The presence of thrombophilis and especially the presence of obstetric complications in particular, were pointed out in the result expressed by fetal weight at birth.
Material and Methods: In this study were included pregnant women hospitalized in the Department of Obstetrics and Gynecology Bucharest University Emergency Hospital between 1st of January 2008 and 31st of December 2012 with the approval of the institutional research in accordance with international ethics at the baseline. We had the informed consent of patients who were approached at birth or in the immediate postnatal period. To try to answer the determined objectives we compared two groups of pregnant women, monitoring fetal weigh and triggers that made fetuses be born with low weight also, the response to anticoagulation therapy. - Group I of study, which involved 2235 pregnant women with thrombophilia and with or without personal or family history of complications. - Group II, with 1845 pregnant woman , with similar characteristics as the previous group with hereditary thrombophilia negative review but had 2 or 3 pregnancies in history.
Conclusions: The thrombophilic pregnant women had higher frequency of lightweight fetuses. Compared with the control group, protein C deficiency, and G20210A mutation are the types of thrombophilia most often associated with low weight fetuses among pregnant women (47.06 % of pregnant women with protein C deficiency, and 45.41 % of the G20210A mutation gave birth to fetuses with low bodyweight).
Key words: thrombophilia, weight fetal complications

Résumé

La thrombophilie en tant que facteur de risque du poids réduit à la naissance

Introduction: La thrombophilie ayant le rôle de la formation accrue de thrombi et associée à une condition d'hypercoagulabilité dans la gravidité conduit à diminuer la qualité de développement placentaire altérée, (1, 2) impliquée dans l'apparition de complications obstétricales. La présence de la thrombophilie et surtout la présence des complications obstétricales a été soulignée par le résultat exprimé dans le poids fœtal à la naissance.
Matériel et méthodes: On a introduit dans cette étude des femmes hospitalisées dans le Département d'obstétrique - Gynécologie de l'Hôpital Universitaire d'Urgence de Bucarest entre le 1er Janvier 2008 et le 31 Décembre 2012, avec l'approbation de la recherche institutionale conformément aux lois de l'éthique internationale. Nous avions le consentement signé des patientes abordées à la naissance ou immédiatement dans la période post-natale. Afin d'obtenir la réponse aux objectifs proposés, nous avons comparé deux groupes de femmes enceintes, en monitorisant le poids fœtal et les causes qui ont rendu que les fœtus soient nés avec un poids réduit, ainsi que la réponse à la thérapie anticoagulante. Le Ier groupe d'étude qui a inclu 2235 de femmes enceintes avec de la thrombophilie et la présence ou l'absence de complications d'antécédents familiaux. Le IIe groupe avec 1845 de femmes enceintes, aux caractéristiques similaires au groupe antérieur avec une revue négative de thrombophilie héréditaire, mais qui ont eu 2 ou 3 grossesses dans les antécédents.
Conclusions: Les femmes enceintes thrombophiliques ont une fréquence accrue d'avoir des fœtus à poids réduit. Par rapport au groupe de contrôle, le défaut de la protéine C et la mutation du gène G20210A sont les types de thrombophilie associés le plus souvent au poids réduit des fœtus des femmes enceintes (47,06% des femmes enceintes avec un défaut de la protéine C, et 45,41% avec de la mutation du gène G20210A donnent naissance aux fœtus à faible poids).
Mots clés: thrombophilie, complications fœtales de poids

Correspondence address: *Luiza Dincaref , MD*
MedLife Bucharest *e-mail: luizadincaref@yahoo.com*

INTRODUCTION

Normal pregnancy induces complex haemostasis changes meant to protect the pregnant body of the bleeding effects during implantation, birth and placental expulsion. They accentuate near the term and subside quickly after birth. (3)

Accordingly, pregnant women are at increased risk of thrombosis. Thrombophilia not only increases the risk of native thrombosis, but also enhances the risk of obstetrical complications. (4)

The favorite place of action of the thrombophilis modifications, of clinically importance in the occurrence of these complications is at the placental level and affects the placental development quality (1,2) involved in presence of obstetric complications.

Thrombophilia and the presence of complications, especially obstetric ones were best highlighted in following the birth result expressed by fetal weight.

Our aim is to investigate the relationship between the presence of these complications and thrombophilia (because studies are contradictory in terms of its role in pregnancy) and also the need for screening and especially the need to establish the treatment.

MATERIAL AND METHOD

In this study there were included pregnant women hospitalized in the Department of Obstetrics and Gynecology Bucharest University Emergency Hospital between the 1st of January 2008-31st of December 2012 with the approval of the institutional research in accordance with international ethics at baseline. I had the informed consent of patients who were approached at birth or in the immediate postnatal period.

During the study period in the clinic have been hospitalized a number of 22665 pregnant women who were included in the first batch 2235 patients diagnosed with thrombophilia in the time of pre-conception or during pregnancy and in the control group II of 1,845 pregnant women who have similar characteristics as descriptive study group, with negative tests of hereditary thrombophilia but who had a history of 2 or 3 pregnancies in the past.

Thrombophilia incidence was 9.86% of all pregnant women hospitalized in the period 2008-2012.

We followed detection of following types of thrombophilia:

- protein S deficit -4.43%
- protein C deficit 1.52%
- The presence of the factor V Leiden -0.18 %
- The presence of the G20210A mutation in the Prothrombin -50.72 %
- antithrombin deficiency -28.22 %
- MTHFR mutations = 14.85 %

We watched fetal weights, spread over two lots observing that in group I of the 2235, 862 (38.57 %) gave birth to fetuses weighing < 2500 g, compared to 223 (12.09 %) of 1845 in group II with the following distribution. (fig. 1)

In group I, the fetal weight was 3010.2 g, with a standard deviation of 745.7 g.

In group II, the average fetal weight was 3515 g, with a standard deviation of 747.7 g.

We tried to examine the influence of the types of the thrombophilis in the group of fetuses with low body weight, especially if there are significant differences between the two groups regarding the complications that led to the births of small fetuses. (fig. 2)

RESULTS

At first glance, there is a higher incidence of fetal weight < 2500 g in group I versus group II, but to check for an association between low weight of the fetus and the group to which it belongs pregnant, we'll apply the chi-square test. The significance level of $p < 0.05$ determined rejection of the null hypothesis, which means that the pregnant partly influences whether or not the fetus will weigh less at birth. Coefficients Phi and Cramer (0298) indicates a direct relationship, but weak link between the two variables. The low weight fetuses tend to be more numerous in the group of women with thrombophilia.

Complications encountered in women with low weight fetuses are presented in the fig. 3.

Following every complication that led to the birth of low weight fetuses by statistical analysis we can observe in the fig. 4.

To decide whether at low weight fetuses the growth restriction is affected by maternal Thrombophilia, we use Chi-square test. The null hypothesis affirms that the variables: premature birth and the group where pregnant woman is part of are independent.

P = 0.48 indicates acceptance of null hypothesis, so between the two groups there are no significant differences in terms of growth restriction of the lightweight fetuses. (fig. 5)

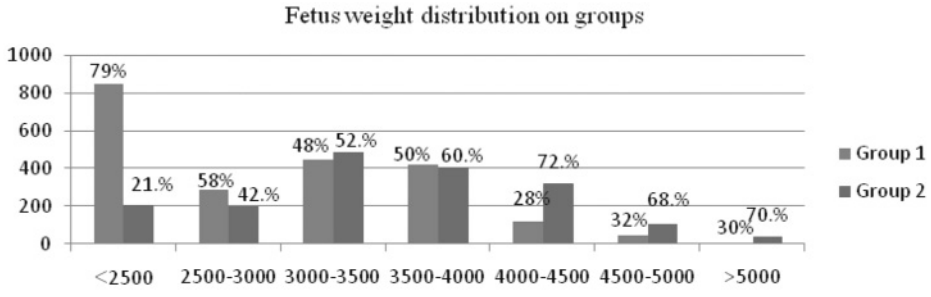


Figure 1

Figure 2

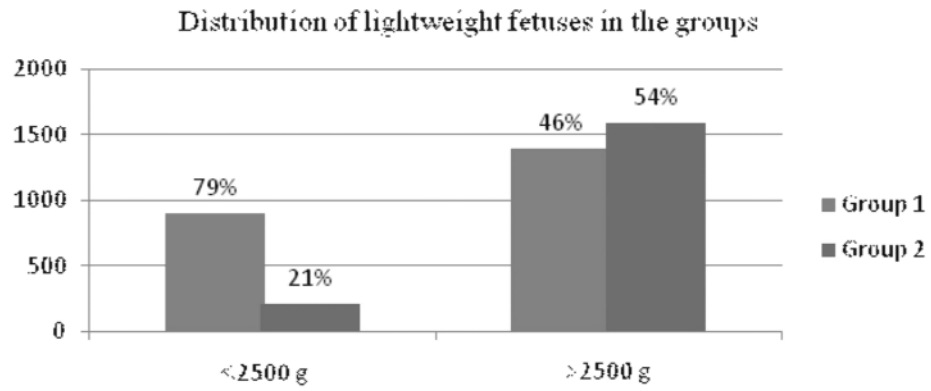


Figure 3

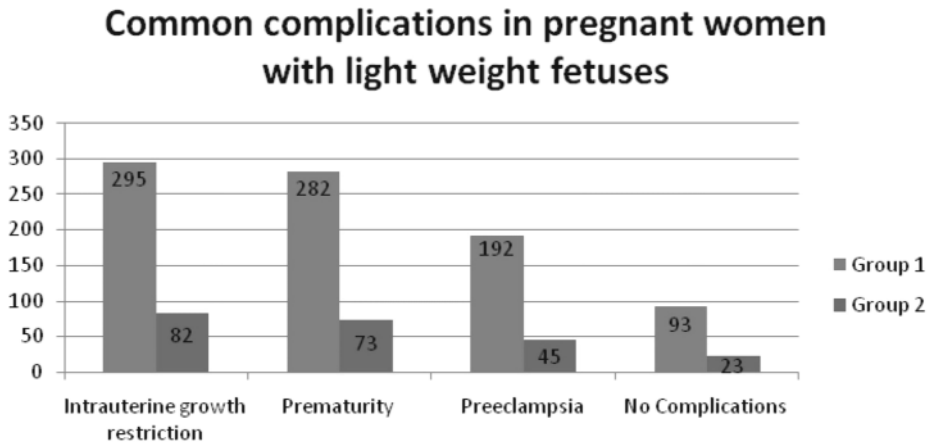


Figure 4

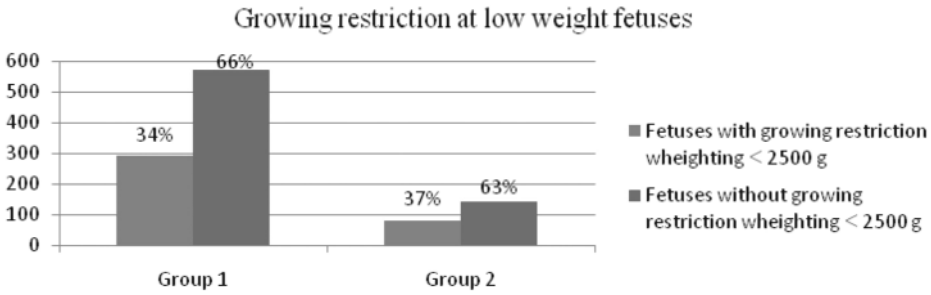
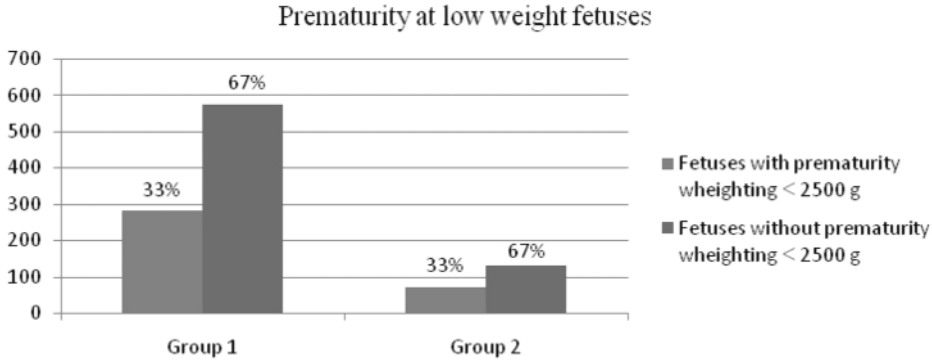


Figure 5



Checking if the maternal thrombophilia influences premature birth of the low weight fetuses will be done using Chi-square test. Null hypothesis states that premature birth and the group that the pregnant woman is part of are independent. With p = 0.995 null hypothesis is accepted, thus on low weight fetuses we cannot say that there is any connection between maternal thrombophilia and fetal premature birth (fig. 6).

To determine whether maternal thrombophilia influences the presence of preeclampsia during pregnancy in women with low weight fetuses, we use Chi-square test, the null hypothesis of which concerns the independence between the two variables studied (thrombophilia and preeclampsia) (fig. 7).

The null hypothesis is accepted because materiality p. = 0.5, so we can say that statistically there is a significant relationship between maternal thrombophilia and preeclampsia in pregnant women with lightweight fetuses.

Note that 38.57 % of pregnant women with thrombophilia gave birth to fetuses with birth weight < 2500 g, compared to 12.1% of healthy pregnant women who have low weight fetuses. Protein C deficiency and mutation G20210A are the types of thrombophilia most often associated with low fetal weight among pregnant women (47.06 % of pregnant women with protein C deficiency, and 45.41 % of pregnant women who have G20210A mutation gave birth to fetuses with low weight). (fig. 8).

To test if the treatment followed by pregnant women having thrombophilia has influenced the fetal weights at birth we'll Chi-square test. The null hypothesis test is rejected because p = 0.0, thus we can say that there is an association relationship between the type of treatment and weight of the fetus at birth. The weight of the fetuses of pregnant women with thrombophilia is influenced by the treatment followed by them, unfractionated heparin being a more efficient treatment than Aspenter.

(On the other hand, we tested for significant differences in fetal weight in pregnant women under treatment -

Figure 6

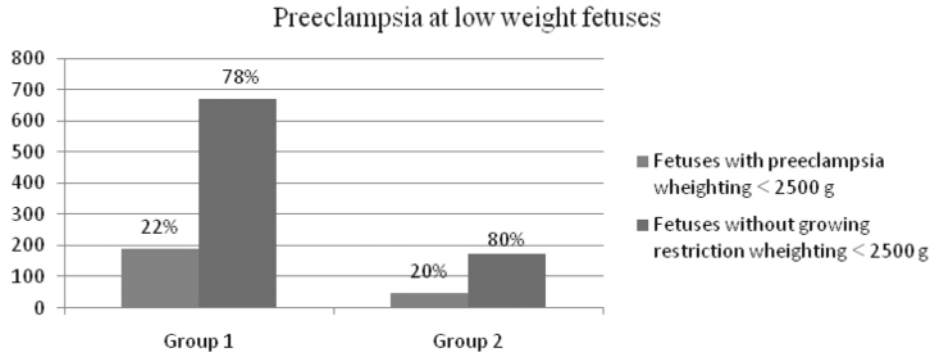


Figure 7

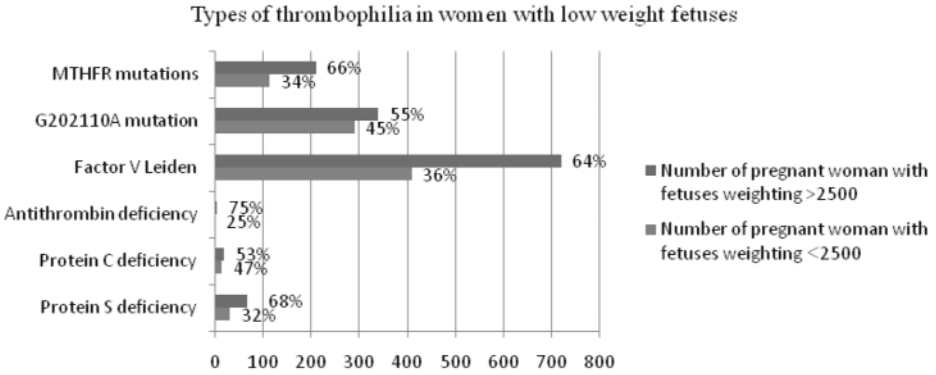


Figure 8

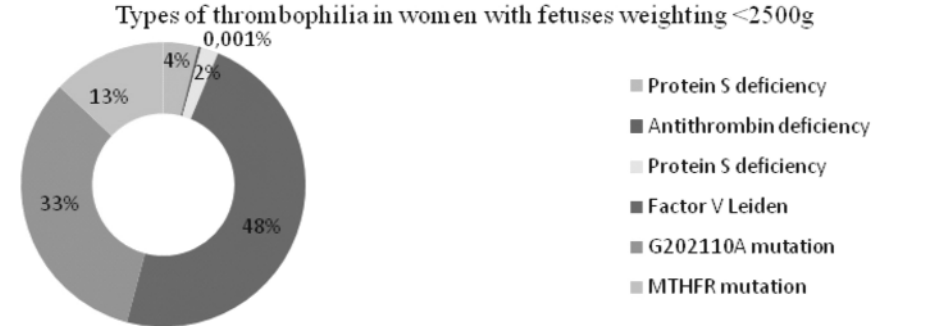


Table 1 - Treatment for pregnant women with low weight fetuses 748-1903

The type of thrombophilia	Unfractionated Heparin	Aspenter	No treatment
Protein S deficit -99	1	3	28
Protein C deficit -34	5	5	6
Antithrombin -4 deficiency	1	0	1
V Leiden factor -1134	92	131	189
Mution G20210A-632	129	62	96
Total	231	198	319

heparin or Aspenter- and healthy. The conclusion was that although under treatment, women with thrombophilia tend to give birth to more fetuses weighting under 2500g compared to healthy pregnant women).

Discussion

In consequence there is a statistical difference between the average weight between the two groups but more important is the high percentage of fetuses under 2500g in the group with thrombophilia shortfall of protein C and G20210A mutation types of thrombophilia, the most often associated with low weight among fetuses of pregnant women who have them (47.06 % of pregnant women with protein C deficiency, and 45.41 % of the pregnant women with the mutation G202110A gave birth to low weight fetuses).

Although there are a greater number of fetuses with low weight in the group with thrombophilia, following determinants that led to the pregnant women with low fetus weight at birth (prematurity, preeclampsia, intrauterine growth restriction with the emergence or not of the fetal acute suffering) between the two groups it was observed that there was no statistically significant difference between thrombophilia and causes leading to low weight fetuses.

In terms of response to treatment as we have presented earlier, the connection between the administered treatment and the fetal weights at birth, is that there is a trend related to a lower incidence of fetuses with low weight in the heparin group compared to the group with aspenter and especially with the group without treatment, but also between aspenter group and the group without the treatment. However despite being under treatment, women with thrombophilia tend to give birth to more fetuses born weighting less than 2500g compared to healthy pregnant women.

According to studies infants of women with a history of VTE have a significantly lower birth weight than babies of general population (5).

Women with cesarean who gave birth at a earlier gestational age and had lightweight fetuses due to increased incidence of the following complications: premature birth, preeclampsia, intrauterine growth retardation / ante partum death / detachment of normally inserted placenta and fetal distress compared to those with vaginal birth.

The birth of a premature newborn may require significant additional actions from the financial community. Family, physical, intellectual, emotional and long-term sequelae of occurrence of fetal growth restriction, such as - diabetes, hypertension, obesity

Conclusions

1. Althought that there is an association between thrombophilia and low weight birth of fetuses with protein C deficiency and the types of thrombophilia G20210A mutation, most commonly associated with low fetal weight, there is no statistical relationship between thrombophilia and causes (prematurity, detachment of the normally inserted placenta, intrauterine growth restriction, preeclampsia) that led to fetuses born under 2500g
2. The weight of the fetuses born by pregnant women with thrombophilia is influenced by the treatment followed by them unfractionated heparin being more effective treatment than Aspenter or without treatment but even though they are under treatment, women with thrombophilia tend to give birth to more fetuses weighing less than 2500g compared to the healthy pregnant women.

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ORIGINAL PAPER

THE INCIDENCE OF HEREDITARY THROMBOPHILIA DURING PREGNANCY IN THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY OF THE BUCHAREST UNIVERSITY EMERGENCY HOSPITAL BETWEEN 1ST OF JANUARY 2012 AND 31ST DECEMBER 2012

Luiza Dincaref[1], Valerica Horhoianu[1], Simona Albu[1], G. Niculescu[2]

[1]University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
[2]University of Medicine and Pharmacy, Craiova, Romania

Summary

Introduction: The existence of different pregnancies developments, without highlighting clinical or laboratory differences led to the testing laboratory expansion, discovering and new diseases that can complicate a pregnancy, such as thrombophilia. Thrombophilia is described as a hypercoagulable state that predisposes to the formation of intravascular thrombosis (1)
Objective: Highlighting the frequency of different types of thrombophilia in pregnancy.
Material and Methods: In this study were included pregnant women hospitalized in the Department of Obstetrics and Gynecology University Emergency Hospital Bucharest between 1st of January 2008 and 31st December 2012 with the approval of the institutional research in accordance with international ethics at the baseline . We had the informed consent of patients who were approached at birth or in the immediate postnatal period. During the supervised period in the clinic have been hospitalized a number of 22665 pregnant woman detailed by year and there were interned an average of 4355 pregnant woman per year with a downward trend in the number of hospitalized pregnant annually.
Conclusions: In the study group hereditary Thrombophilia frequency was 14.85% representing 9.86% of total births most frequent presence of factor V Leiden 50.7% (5% of the total) and G20210A mutation 28, 28% (2.79% of total), followed by this mutation MTHFR -14.85% (1.46% of total) and with the lowest frequencies the protein S deficiency -4.43% (0.44% in total) and protein C deficiency (1.52% and 0.15% of total) and the rare presence of antithrombin deficiency 0.18% (0.018% of the total).
Key words: hereditary thrombophilia, pregnancy, hypercoagulable state

Résumé

L'incidence de la thrombophilie héréditaire pendant la grassesse dans le Département d'Obstétrique - Gynécologie de l'Hôpital Universitaire d'Urgence de Bucarest, entre le 1er Janvier - 31 décembre 2012

Introduction: L'existence des différents développements grossesses, sans mettre en évidence les différences cliniques ou de laboratoires, a conduit à l'expension des analyses de laboratoire, la découverte de nouvelles maladies qui peuvent compliquer une gravidité comme la thrombophilie. La thrombophilie est décrite comme un état d'hypercoagulabilité qui prédispose à la formation de la thrombose intravasculaire.
But: Mettre en evidence la fréquence de divers types de thrombophilie dans la grossesse.
Matériel et méthodes: On a indus à cette étude des femmes enceintes hospitalisées dans la section d'Obstétrique-Gynécologie l'Hôpital Universitaire d'Urgence de Bucarest, entre le 1er Janvier 2008 et le 31 Décembre 2012, avec l'approbation de la recherche institutionnalisée conformément à l'éthique internationale. Nous avions l'accord signé des patients abordées à la naissance ou immédiatement dans la période post-natale. Pendant la période surveillée a été hospitalisé dans la clinique un nombre de 22665 enceintes détaillé par choque année et une moyenne de 4355 femmes enceintes choque année à une tendence descendante du nombre d'enceintes au niveau annuel.
Conclusions: Dans le groupe d'étude la fréquence de la thrombophilie congénitale a été de 14,85%, représentant 9,86% du total des naissances, la présence la plus fréquente du facteur V Leiden 50,7% (5% du total) et la mutation du gène G20210A 28,28% (2,79% du total), suivie de cette mutation MTHFR -14,85% (1,46 % du total); la fréquence la plus réduite a eu la protéine S - 4,43% (0,44% du total) et la protéine C (1,52% et 0,15% du total) et une présence rare a eu le défant d'antithrombine 0,18% (0,018% du total).
Mots clés: thrombophilie héréditaire, grossesse, état d'hypercoagulabilité

Correspondence address: *Luiza Dincaref , MD*
MedLife Bucharest *e-mail: luizadincaref @ yahoo.com*

Introduction

The main cause of maternal death in developing countries is bleeding, but in Western Europe and the United States, in which bleeding complications are dealt with efficiently, thromboembolic diseases are a major cause of maternal mortality (2) and fetal pathology. (3) Thrombophilia is described as a hypercoagulable state that predisposes to formation of intravascular thrombosis.

This, associated with increased predisposition to thrombosis in pregnancy as a measure to protect women from bleeding caused by abortion or childbirth, lead to increased incidence of thromboembolic maternal and fetal complications: habitual miscarriages, abortions in the second trimester, prematurity, intrauterine death, fetal hypotrophy, severe hypertension, preeclampsia (3).

Materials and Methods

In this study were included pregnant women hospitalized in the Department of Obstetrics and Gynecology University Emergency Hospital Bucharest between 1st of January 2008 and 31st December 2012 with the approval of the institutional research in accordance with international ethics at the baseline. We had the informed consent of patients who were approached at birth or in the immediate postnatal period.

During the supervised period in the clinic have been hospitalized a number 22665 pregnant women detailed by year, as shown in the fig. 1.

During the studied period, 4,355 pregnant women were hospitalized averagely per year. There is a decreasing trend in the number of pregnant women annually hospitalized.

If for the majority of the pregnant women from the study, the reason for thrombophilia screening was the one of the obstetric complications: recurrent abortions in the first trimester (> 3 miscarriages), pregnancy lost in trimesters II or III, preeclampsia / eclampsia, intrauterine growth restriction, normal inserted placental detachment, maternal (thrombotic: DVT, MET, arterial thrombosis) and family history of thrombophilia or venous or arterial thrombosis at young age <50 years; The study also included pregnant women found with thrombophilia by chance, without any history of thrombophilia or associated pathologies. The average age in the study group was 30.19 years (approximately 30 years 2 months 2 weeks) with a standard deviation of 5.94 years (approx. 5 years 11 months).

Table 1

2008	2009	2010	2011	2012	Total
377	382	392	509	575	2235
7,54%	7,67%	8,14%	13,10%	14,75%	9,86%

A number of pregnant women of 2235 who were diagnosed paraclinically with thrombophilia, in the gestational and perinatal periods were introduced in the study by the year distribution in the table 1.

There is a trend of sustained growth in the Thrombophilia incidence among pregnant women, their share has almost doubled within 5 years.

The lot including women with thrombophilia represents 9.86% of all pregnant women hospitalized in the period 2008-2012.

We watched detection of thrombophilia following types:

- Protein S Deficiency;
- Protein C Deficiency;
- The presence of the V Leiden factor;
- Prothrombin mutation G20210A - present;
- Antithrombin deficiency;
- MTHFR mutation.

Results

The results were interpreted according to the period in which they were harvested, according to the state of the pregnancy (in case of protein S deficiency with adjusted values by 30% in the second quarter and by 24% in the third quarter), as shown in fig. 2 and table 2.

Expressed in percentages:

In the study group Thrombophilia hereditary frequency was 14.85% representing 9.86% of all births with the highest frequency the factor V Leiden 50.7% (5% of the total) and the G202110A mutation -28.28% (2.79% of the total), followed by this mutation MTHFR -14.85% (1.46% of the total) and lowest frequencies presence of protein S deficiency -4.43% (0.44% of the total) and protein C deficiency (1.52% and 0.15% of the total) and frequency of rare presence antithrombin deficiency 0.18% (0.018% of the total).

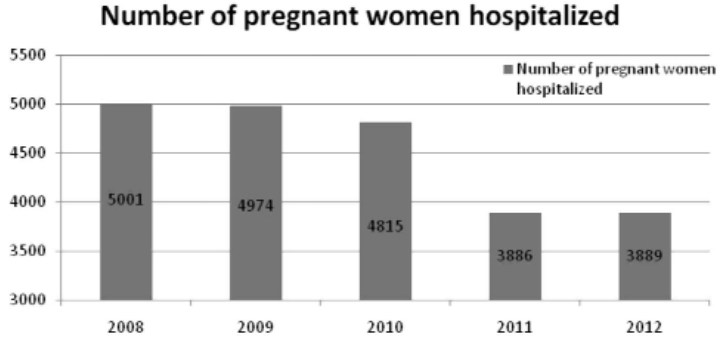

Figure 1

Figure 2

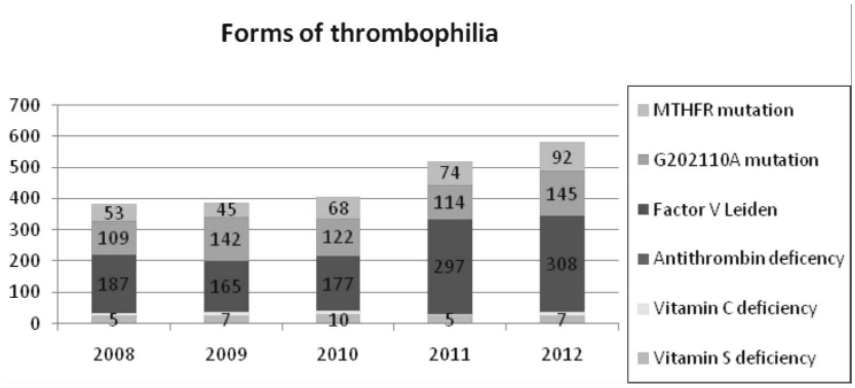

Table 2

	2008	2009	2010	2011	2012	TOTAL
Protein S Deficiency	6,10%	5,77%	3,82%	3,34%	3,83%	4,43%
Protein C Deficiency	1,34%	1,83%	2,55%	0,98%	1,21%	1,52%
Antithrombin deficiency	-	0,26%	-	0,39%	0,17%	0,18%
Factor V Leiden	49,60%	43,19%	45,15%	58,35%	53,57%	50,72%
Mutation G20210A	28,91%	37,17%	31,13%	22,40%	25,22%	28,28%
MTHFR mutations	14.05%	11,78%	17,35%	14,54%	16,00%	14,85%
TOTAL	377	382	392	509	575	2235

DISCUSSION

The study was conducted in the period 1st of January 2008 -31st December 2012 and by following the births during this period it reveals a trend of decreasing number of births from 5001 in 2008 to 3989 in 2012 probably because of the increasing number of private maternity hospitals opened in this period, but with increasing number of thrombophilia from 7.54% in 2008 to 14.41% in 2012 to an average of 9.86%. It should be noted that the relatively high frequency of thrombophilia compared to the number of births is due to the fact that the obstetrics ward in the hospital is multidisciplinary which means that here are directed all the pregnant woman with associated pathologies. Another reason for the differences in Thrombophilia frequency encountered in the studies is the inclusion mode, because women were referred to a multidisciplinary hospital concerning pregnant women with a pathology. Depending on the calendar period the samples were taken, we can notice annual differences of the incidents of various types of thrombophilia, because in recent years there is an increased trend in recommending thrombophilia analyses from both the doctors and especially from women, with increased accessibility to the information. Another important role in the annual differences of incidence of various types of thrombophilia is the emergence of several laboratories performing these tests, but it is important to note the development of new laboratory tests widely available. The study is limited in terms of Thrombophilia frequency to the selected population because of the significant costs of these tests and their lack of compensation, but also of the large number of uninvestigated or improperly investigated pregnant.

The low incidence seen in population does not require routine harvesting of these analyzes, the costs are quite high and it would be recommended to do a rigorous medical history selection of those that require to complete the usual analysis with those to determine Thrombophilia. Thus it would be advisable to follow more closely in the following clinical situations:

- Thrombotic events occurred in young patients (< 50 years), (4),
- Recurrent thrombosis,
- Family history of thromboembolic disorders ,
- Multiple pregnancy complications,
- Venous thrombosis in "unusual" anatomic territories: the portal vein, hepatic veins, mesenteric, brain, etc.

If the order of frequency of different types of thrombophilia is consistent with that found in other studies, the frequency found in our study is lower than in other complementary studies, due to as explained, the reduced accessibility to these analyzes among pregnant women and the presence of large numbers of pregnant women monitored incorrectly.

Compared to the prevalence of the presence of factor V

Table 3

	total-22665
Protein S Deficiency	0,44%
Protein C Deficiency	0,15%
Antithrombin deficiency	0,018%
Factor V Leiden	5,00%
Mutation G20210A	2,79%
MTHFR mutations	1,46%
Total trombofilii	9,86%

Table 4

REFERENCE	Factor V Leiden (95% CI)	G20210A gene mutation (95% CI)	MTHFR C677T mutation (95% CI)
Grandone et al(12)	16.3 (4.8–54.9)	10.2 (4.0–25.9)	2.1 (1.0–4.5).
Gerhardt et al (5)	9.3 (5.1–16.9)	15.2 (4.2–52.6)	—
McColl et al (13)	4.5 (2.1–14.5)	4.4 (1.2–16)	0.45 (0.13–1.58)
Dilley et al (14)	18.3 (2.7–432)	—	1.3 (0.3–3.1)
Martinelli et al (9)	10.6 (5.6–20.4)	2.9 (1.0–8.6)	—

Leiden, met in our study of 50.72% (representing 5% of the total number of pregnancies), in the study by Gerhardt et al (5), the prevalence of defects in hereditary coagulation was small, with an incidence of 43.7% for factor V Leiden, on the other hand, Grandone et al, who investigated the Italian population, he found the prevalence of factor V Leiden 16%, 27 (12) while in study Sarig et al it was 18%, (6) and even up to 32% in the study by Brenner et al (7), in a similar study population of Serbia (8) and Martinelli (9)

As compared to a rate of 28.28% found in our study of the incidence of G20210A mutation, in other studies it has been observed a significant difference up to 16.9% in the study by Gerhardt et al. (5).

Other incidents found in other studies are summarized in table 4.

Data on the prevalence of thrombophilia in thrombophilia complications is therefore dependent on study inclusion criteria and ethnicity of the study population (10,11) as shown.

Conclusions

Existing data regarding the prevalence of thrombophilia in women with complications of pregnancy are conflicting.

1. Thrombophilia low frequency of -9.86% of the population therefore does not require routine harvesting of these analyses, the costs are quite high and it would be recommended to do a rigorous medical history selection of those that require completing the usual analysis with those to determine Thrombophilia.
2. The presence of factor V Leiden, gene mutation G20210A of the prothrombin and MTHFR gene mutation are the most common types of hereditary thrombophilia encountered in our study, followed by protein C deficiency, protein S deficiency and antithrombin III deficit being the most rare type of thrombophilia met.
3. The association of uteroplacental thrombosis with thrombophilia, although controversial, it determines the increase of obstetrical complications such as recurrent abortion, fetal loss in the second quarter and third, perinatal fetal death, preeclampsia, normally inserted placental detachment and intrauterine growth restriction.
4. The prevalence of complications recommends thrombophilia screening only in carefully selected cases: thrombotic -Events occurring in young patients (<50 years)
   - recurrent thrombosis;

   Family previous history of thromboembolic disorders,
   - multiple complications of pregnancy
   - venous thrombosis in "unusual" anatomic territories: the portal vein, hepatic veins, mesenteric, brain, etc.

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ORIGINAL PAPER

EFFECTS OF LEVOTHYROXINE TREATMENT ON THE QUALITY OF LIFE OF WOMEN DIAGNOSED WITH SUBCLINICAL HYPOTHYROIDISM

Elena Roxana Novac, Nicoleta Roșu, A. Cotârleț

Emergency Hospital Moinești, Romania

Summary

Context: subclinical hypothyroidism means the presence of a high TSH with normal thyroid circulating hormones. Until now, studies that looked into the effects of substitutive treatment on the quality of life couldn't quite demonstrate the opportunity/ inopportunity of administering LT4.
Objective: to establish the effect of subclinical hypothyroidism on quality of life and the way that the treatment influences these parameters. Design: case-control study, open-labeled on administering levothyroxine. Setting: the study took 6 months in the Emergency Hospital of Moinesti, Romania Patients: 42 women with ages between 16-71 years with a medium TSH of 5,9uUI/ml, whom hadn't been priorily diagnosed with hypothyroidism. They were given 25-50 ug of LT4 for 6 months. The patients were asked to fill in an adapted SF-36 questionnaire at the beginning and in the end of our study.
Results: we followed these parameters: decreased moderate activity (seen in 61% patients), inability to walk more than 1 km (83%), inability to end daily activity or work-related activity (61%), myalgia (90,47%), affected quality of life (71%). After 6 months of treatment with thyroid hormones, different dosage depending on the initial value of TSH and patient's weight (25ug on TSH < 6uUI/ml, and 50ug on TSH > 6uUI/ml), we noticed an improvement on studied parameters : decreased moderate activity in 42% ($p < 0.001$); inability to walk more than 1 km was improved in 30.62%, myalgia was present only in 12 patients after 6 months of treatment (28.57%), so was the need to reduce time spent at work, and above all we noticed an improvement on the QoL of 26%. We didn't find any differences regarding improvement of emotional estates (depression, lack of motivation, decreased self-trust).
Conclusion: the treatment of subclinical hypothyroidism with thyroid hormones has a good effect improving fatigue, increasing capacity of effort, increasing in this way the quality of life in relation to the decreased TSH.
Key words: subclinical hypothyroidism, levothyroxine, myalgia, life quality

Résumé

Les effets du traitement avec de la lévothyroxine sur la qualité de la vie des femmes diagnostiquées avec l'hypothyroïdie sous-clinique

Le contexte: l'hypothyroïdie sous clinique signifie la présence élevée du TSH avec des hormones thyroïdiennes circulatoires normales. Jusqu'à présent, les études qui ont analysé les effets du traitement substitutif sur la qualité de la vie des femmes n'a pas pu démontrer si bien l'opportunité/ inopportunité d'administrer LT4
L'objectif: établir l'effet de l'hypothyroïdie sous-clinique sur la qualité de la vie des femmes et le mode comme le traitement influence ces paramètres. Le design: étude cas-contrôle, ouvert à l'administration de la lévothyroxine. Location: l'étude a été faite pour 6 mois dans l'Hôpital d'Urgence de Moinești, Roumanie. Les patients: 42 femmes âgées entre 16-71 ans avec la valeur moyenne de la TSH de 5,9 uUI/ml, qui n'ont pas été diagnostiquée avec hypothyroïdie. On leur a administré 25-50 ug de LT4 pour 6 mois. Les patients ont été priés à compléter un questionnaire au début de l'étude. Les résultats: on avait suivi ces paramètres: activité diminuée modérément (observée aux 61% des patients), inhabilité d'aller plus de 1 km (83%), inhabilité de finir des activités quotidiennes or celles de travail (61%), la myalgie (90,47%), la qualité de la vie affectée (71%). Après 6 mois de traitement par des hormones thyroïdiennes, avec des doses différentes qui ont été administrées en tenant compte da la valeur initiale de la TSH et du poids des patients (25 ug pour TSH < 6 uUI/ml, et 50 ug pour TSH > 6 uUI/ml), on a observé une amélioration des paramètres étudiées: activitée diminué modérément de 42% ($p < 0.001$); inhabilité d'aller plus de 1 km a été améliorée de 30.62%, la myalgie a été présente seulement pour 12 patientes après 6 mois de traitement (28.57%), aussi comme dans la nécessité de la réduction de la période de travail.
Conclusion: le traitement de l'hypothyroïdie sous-clinique par des hormones thyroïdiennes a un effet bon, en améliorant la fatigue, en grandissant la capacité d'effort, en croissant dans ce mode la qualité de la vie en relation avec la diminution de la TSH.
Mots clefs: hypothyroidisme sous-clinique, levothyroxine, myalgie, qualite de la vie

Correspondence address: *Elena Roxana Novac, MD*
Emergency hospital Moinești, Department of Endocrinology
Zorilor Street, no.1, Moinești, Bacau, România *e-mail: dr.roxananovac@gmail.com*

Introduction

Thyroid hormones play an important role in maintaining many organic functions and lack of these hormones causes a variety of diseases and symptoms. Hypothyroidism is one of the well-known causes of different neuro-muscular diseases like simple myalgia or fibromyalgia.

Thyroid hormones are due to the stimulation of the TSH from the pituitary gland. The free thyroid hormones that are active play a negative feed-back on the TSH secretion. So when the thyroid can't produce enough hormones, the pituitary gland reacts by releasing more TSH. The fall of T4 in severe hypothyroidism causes the symptoms and signs of myxœdema.

Subclinical hypothyroidism is a disease that affects 6-17% of the general population. By definition it is characterized by a normal level of T4 with high TSH adapted age.

The symptoms of subclinical hypothyroidism are less aggressive than that of clear hypothyroidism, that's why this disease usually passes unobserved or its symptoms are assumed to aging or physical exhaustion.

There are a few data that show that the subclinical hypothyroidism could be responsible to lots of the typical symptoms of hypothyroidism. Some of these recent studies show that subclinical hypothyroidism affects neuromuscular activity, cognitive functions but there are few studies that can prove its effect on the quality of life.

Another controversy with SH is represented by its presence on old people (the prevalence on women and men over 60 years old is about 16,2%, respectively 9,5%) which is thought by some authors to be a variant of normal, considering that the decreased thyroid function is physiologic with age.

There are also lots of controversies regarding the treatment with thyroid hormones in SH. The fact that the symptoms decrease in young people can't be generalized on old people on whom we speak about problems regarding the association of another medicine in a patient that already is multidrug dependent, we also speak about the use of some financial resources for testing and treating especially when there are studies that demonstrate that on old patients treatment with levothyroxine (LT4) can aggravate the ischemic cardiac symptoms or can induce thyroid-dependent osteoporosis.

Protocols have been made that indicate the treatment with LT4 on young patients with TSH above 7uUI/ml and above 10uUI/ml on old patients or above 7uUI/ml if the patient is symptomatic.

The purpose of this study is to evaluate some physical and psychological aspects of subclinical hypothyroidism and the impact of LT4 treatment on them.

Patients and Method

Patients

Patients, 42 women with ages between 16-71 years, were recruited among patients that addressed to the Endocrinology Service of the Emergency Hospital of Moinesti city. Each patient had to have the hormonal test in order to be eligible for the study that attested subclinical hypothyroidism (TSH > 4,2 uUI/ml and normal free T4). Subjects with chronical disease or who used drugs that could have influenced the thyroid function were excluded, so were the pre-diagnosed patients with psychiatric disease. In order to evaluate the muscular accuses we excluded the patients who presented with a neuromuscular dysfunction or took medication that could influence the symptomatology. All study participants signed an informed consent.

Clinical and psychological evaluation

All subjects were evaluated with a clinical questionnaire and underwent a psychological evaluation. This was made by the same psychologist at the beginning of the study and also during the 6 months.

Clinical score

The signs and symptoms that are specific to hypothyroidism were analyzed with the Billewicz scale that studies the decrease of perspiration, dryness of the skin, cold intolerance, gain of weight, constipation, voice timbre change, paresthesia, low hearing acuity, low movement, rough cold skin, periorbital edema, bradycardia, low achilean reflex. Usually a score above 20 is specific to hypothyroidism and a score below -30 is characteristic to euthyroid state. Most of our patients were in the "insecure zone" (-29- +19).

Evaluation of quality of life

We used an adapted SF-36 questionnaire. The 36 short form questionnaire (SF-36) is a generic tool that measures general health that was tested and developed in New England Medical Center during Medical Outcomes Study, that uses eight scales: physical function, social function, role limiting (by emotional or physical causes), mental health, energy, somatic pain, general health state.

Study protocols

After clinical and hormonal diagnosis of subclinical hypothyroidism patients had to complete an adapted SF-36 questionnaire that followed: moderate activity limitation (seen in 61%), ability to walk more than 1 km, inability to end daily activity or work- related activity, myalgia, affected quality of life. After that they were administered LT4 daily according to the initial measurement of TSH and their weight. So the patients with a TSH bigger than 4,2uUI/ml but under 6uUI/ml and weight under 70 kilos were given 25ug of LT4/day, and the other ones whom had a TSH > 6uUI/ml and more than 70 kilos took 50ug/day.

Patients were recalled 6 weeks later for dose adjustment

6 months later they were asked to complete the same questionnaire that had one extra question regarding their opinion on the levothyroxine treatment on themselves.

RESULTS

We included 42 patients, newly diagnosed with thyroid dysfunction, in order to study the effect of levothyroxine treatment on their accuses and quality of life.

We didn't include patients who were once diagnosed with hypothyroidism and who underwent a levothyroxine treatment.

We followed:

- moderate activity limitation (seen in 615 of our subjects);
- inability to walk more than 1 km (83%);
- inability to end daily activity or work-related activity (61%);
- myalgia (90,47%);
- affected quality of life (71%).

The diagnosis of subclinical hypothyroidism was made after measuring the TSH and FT4. TSH was between 4,7uUI/ml and 11,2uUI/ml (our laboratory considers high normal value 4,2uUI/ml) (fig. 1). FT4 was in the normal range, and this established the subclinical hypothyroidism. Subjects had a thyroid ultrasonography and anti-thyroglobuline dosing. In most of the cases we found chronic autoimmune thyroiditis.

Substitution with 25-50ug of levothyroxine was made (aprox. 0,35ug/kg/day). 6 weeks later patients had to come to our clinic for dose adjustment. In four cases we had to increase the dosage because TSH remained above the upper limit. None of the patient needed decreasing the dose. Patients that needed increasing the dose were recalled 6 weeks later to establish the euthyroidism.

After 6 months of substitution of thyroid hormones, we noticed an improvement regarding: moderate activity limitation that represented an accuse only in 42% of patients ($p < 0.001$; 19% improvement); inability to walk more than 1 km was improved in 30,62%, myalgia was present only in 12 patients after 6 months of treatment (28,57%), the same happened with the need to reduce time spent at work and overall we have seen an improvement of life quality in 26% of the interviewed subjects (fig. 2). we couldn't find any differences regarding improvement of emotional states (depression, lack of motivation, low self-esteem).

DISCUSSIONS

It was thought for a long time that subclinical hypothyroidism means a state in which patients don't have clear signs of myxœdema, because they have a normal level of thyroid hormones, the only abnormality being the high TSH. Our study tries to demonstrate that subclinical hypothyroidism associates signs and symptoms that can reduce the quality of life and that right substitution can eliminate them, the patient regaining physical and emotional equilibrium.

Over time many studies have been made that addressed some of the parameters of our study

Research by Bono and al. and Kong and al. regarding psychiatric symptoms in patients with high TSH showed a decrease in depression and anxiety after proper treatment. Both studies were made on TSH higher than 6 uUI/ml. Jorde and al. studied patients with small modification in TSH and couldn't demonstrate the benefits of LT4 treatment on initial symptomatology. The subject studied by Jorde had more than 60 years of age.

Psychiatric symptoms is controversial in literature

That's why the study of Texeira and al. shows the presence of psychiatric symptomatology related to the TSH value and not to the etiology of subclinical hypothyroidism. The study mentions the need of other studies on the effect of levothyroxine treatment on improving the symptomatology. Another study by Almeida and al. demonstrated mood disorders on patients with high TSH and normal FT4. Their research recorded a 2,3 higher prevalence of depression on the SH group vs euthyroid group. Our study didn't target

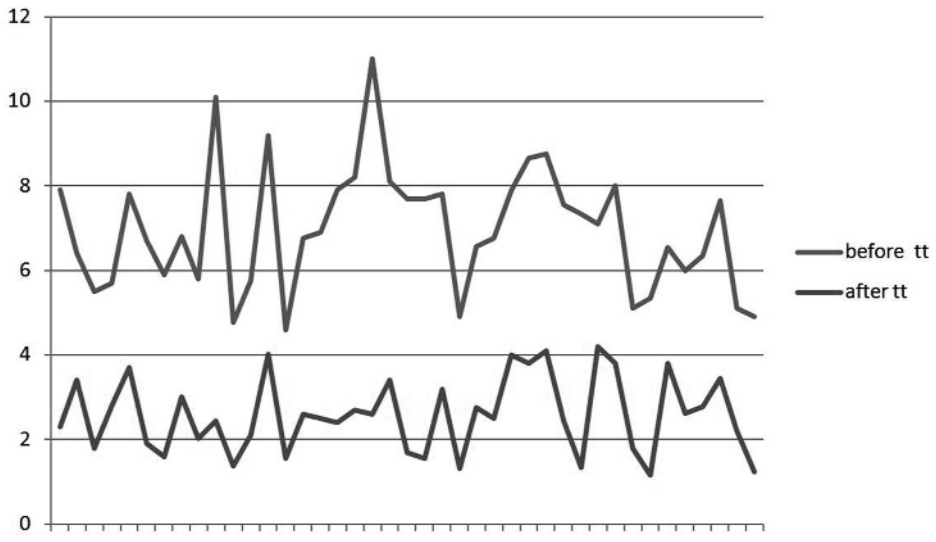

Figure 1 - TSH before and after treatment with LT4

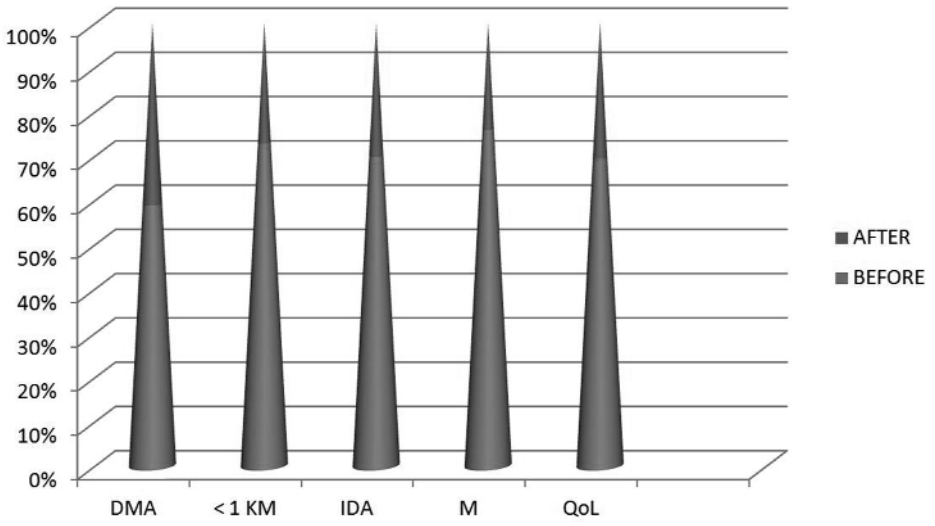

Figure 2 - Effect of treatment on different parameters; DMA= decreased moderate activity; <1 km= ability to walk more than 1 km; IDA= inability to get to an end daily activity; M= myalgia; QoL= quality of life

psychiatric accuses, it focused more on psychological aspects and treatment impact on them.

Conclusions

Our study tries to make an analysis over the effects of levothyroxine treatment on the quality of life of the patients that we included, by taking into account primarily their ability to get to an end current activity.

By analyzing the parameters that we already described it looks like the levothyroxine treatment is good, being able to improve the quality of life.

Many studies are needed, on greater number of patients in order to be able to fully support the substitutive treatment in subclinical hypothyroidism.

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ORIGINAL PAPER

ATRIAL FIBRILLATION AND COMORBIDITIES IN VERY ELDERLY PATIENTS

Camelia C. Diaconu[1,2], Alice Balaceanu[1,3]

[1]*University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania*
[2]*Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Romania*
[3]*Internal Medicine Clinic, Clinical Emergency Hospital "Sf. Ioan", Bucharest, Romania*

Summary

Background: Atrial fibrillation is the most common arrhythmia encountered in clinical practice. It is associated with increased morbidity and mortality, due to the risk of thromboembolic events and associated risk factors.
Methods: The purpose of the study was to analyze the clinical characteristics of very elderly patients (> 80 yo) with permanent atrial fibrillation admitted to the Internal Medicine Clinic of the Clinical Emergency Hospital of Bucharest over a period of one year.
Results: The distribution by sex in the study group: 81 men (41.53%) and 114 women (58.46%). The mean age was 84.5 yo. 42.56% of the patients were institutionalized in nursing homes. The main comorbidities were: arterial hypertension 78.46%, coronary artery disease 61.02%, heart failure 47.17%, chronic obstructive pulmonary disease 44.61%, peripheral artery disease 42.05%, cerebrovascular disease 40.51%, valvular heart disease 39.48%, diabetes 31.79%, dementia 14.35%, chronic kidney disease (eGFR < 60 ml/min/1.73 m^2) (MDRD) 9.74%. As compared to non-institutionalized patients, those residing in nursing homes were older and had higher comorbidity score. 173 patients (88.71%) received anticoagulants: 129 patients (74.56%) received cumarinic oral anticoagulants and 44 patients (25.43%) new anticoagulants (dabigatran). The mean CHA2DS2-VASc score was 5.2. In-hospital mortality rate in very elderly patients with atrial fibrillation was 10.76%. Rates of mortality, heart failure, coronary artery disease and stroke increased with older age and higher CHA2DS2-VASc scores.
Conclusions: Atrial fibrillation is a frequent arrhythmia in very elderly patients. Very elderly patients with atrial fibrillation have many comorbidities, arterial hypertension, coronary artery disease, heart failure and chronic obstructive pulmonary disease being the most frequent. In-hospital mortality rate of very elderly patients with atrial fibrillation is high. Adequate control of arterial hypertension and management of heart failure in patients with atrial fibrillation, alongside with stroke prevention are key priorities for

Résumé

Introduction: La fibrillation auriculaire est l'arythmie la plus fréquemment rencontrée dans la pratique clinique. Elle est associée à une morbidité et une mortalité accrues, en raison du risque d'événements thrombo-emboliques et les facteurs de risque associés.
Méthodes: Le but de l'étude était d'analyser les caractéristiques cliniques des patients très âgés (> 80 ans) atteints de fibrillation auriculaire permanente admis à la Clinique de médecine interne de l' Hôpital d'Urgence de Bucarest sur une période d'un an.
Résultats: La répartition par sexe dans le groupe d'étude: 81 hommes (41,53%) et 114 femmes (58,46%). L'âge moyen était de 84,5 ans. 42.56% des patients ont été institutionnalisés dans les maisons de santé. Les principales comorbidités étaient: hypertension artérielle 78,46%, maladie coronarienne 61.02%, insuffisance cardiaque 47,17%, la maladie pulmonaire obstructive chronique 44,61%, la maladie artérielle périphérique 42.05%, une maladie cérébro-vasculaire 40,51%, cardiopathie valvulaire 39,48%, diabète 31,79%, démence 14,35%, maladie rénale chronique (RFGe <60 ml/min/1,73 m2) (MDRD) 9,74%. Par rapport aux patients non institutionnalisés, ceux qui résident dans les maisons de soins de santé étaient plus âgés et avaient une score de comorbidité plus grande. 173 patients (88,71%) ont reçu des anticoagulants: 129 patients (74,56%) ont reçu des anticoagulants oraux de type coumarine et 44 patients (25,43%) de nouveaux anticoagulants (dabigatran). Le score moyen CHA2DS2-VASc était de 5,2. Dans l'hôpital, le taux de mortalité chez les patients très âgés atteints de fibrillation auriculaire était 10,76%. Les taux de mortalité, de l'insuffisance cardiaque, de maladie coronarienne et d'accident vasculaire cérébral ont augmenté avec l'âge et des scores plus élevés CHA2DS2-VASC.
Conclusions: La fibrillation auriculaire est une arythmie fréquente chez les patients très âgés. Les patients très âgés atteints

Correspondence address: *Camelia Diaconu, MD, PhD, FESC, FACP, FEFIM*
Internal Medicine Clinic, Clinical Emergency Hospital, 8 Calea Floreasca, 014461 Bucharest, Romania
e-mail: camiluciemi@yahoo.com

the management of very elderly patients with atrial fibrillation and improving quality of their life.
Key words: atrial fibrillation, elderly patients.

de fibrillation auriculaire ont de nombreuses comorbidités, l'hypertension artérielle, la maladie coronarienne, l'insuffisance cardiaque et la maladie pulmonaire obstructive chronique étant les plus fréquentes. Dans l'hôpital, le taux de mortalité de patients très âgés atteints de fibrillation auriculaire de mortalité est élevé. Un contrôle adéquat de l'hypertension et la gestion de l'insuffisance cardiaque chez les patients atteints de fibrillation auriculaire, aux côtés de la prévention des accidents vasculaires cérébraux, sont des priorités clés pour la gestion des patients très âgés atteints de fibrillation auriculaire, pour améliorer leur qualité de vie.
Mots-clés: fibrillation auriculaire, patients âgés

BACKGROUND

Atrial fibrillation is the most common arrhythmia encountered in clinical practice. It is associated with increased morbidity and mortality, mainly due to the risk of thromboembolic events. Atrial fibrillation may be caused by any condition associated with heart disease; in elderly patients, ischemic heart disease and valvular diseases are probably the most common conditions that trigger the developing of atrial fibrillation. Atrial fibrillation has a higher prevalence in male patients and also in elderly population (1). The risk of developing atrial fibrillation increases with age and with the presence of structural heart disease (2,3,4). The prevalence of atrial fibrillation has been shown to be between 9 and 18% in subjects over 80 years old compared to about 0.5% in subjects of 50-59 years old (4). The relationship between atrial fibrillation and advanced age was demonstrated in the ATRIA study, which was a cross-sectional study in the United States, on almost 1.9 million patients (1). This study demonstrated that the overall prevalence of atrial fibrillation in the population studied was 1% (1). 70% of the patients with atrial fibrillation were over 65 years old and 45% were over 75 years old. The prevalence of atrial fibrillation was higher in men than in women (1.1% versus 0.8%) (1). Also, the incidence of atrial fibrillation is increasing with advancing age and with the presence of cardiovascular diseases (4,5,6,7). Due to the growing proportion of elderly population, atrial fibrillation is likely to become a significant medical and socioeconomic problem. Elderly patients are more likely to have an increased number of comorbidities, such as arterial hypertension, chronic heart failure, chronic kidney disease etc, that confer these patients an increased risk of developing thromboembolic complications, together with complications of the anticoagulant therapy.

METHODS

The purpose of our study was to analyze the clinical characteristics and comorbidities of very elderly patients (> 80 yo) with permanent atrial fibrillation admitted to the Internal Medicine Clinic of the Clinical Emergency Hospital of Bucharest over a period of one year. The nature of the study was retrospective. We analyzed data from the hospital record database. In all patients electrocardiogram, transthoracic echocardiography, chest X-Ray, routine laboratory investigations were performed. The demographic data (age, gender) was obtained from the hospital medical archive.

RESULTS

The number of patients over 80 year-old with permanent atrial fibrillation that were admitted over a period of one year was 195. The distribution by sex in the study group was: 81 men (41.53%) and 114 women (58.46%) (fig. 1). The mean age of the patients was 84.5 yo. Almost half of the patients (42.56%) were institutionalized in nursing homes, majority in private establishments. The main comorbidities in the group of study were: arterial hypertension 78.46%, coronary artery disease 61.02%, chronic heart failure 47.17%, chronic obstructive pulmonary disease 44.61%, peripheral artery disease 42.05%, cerebrovascular disease 40.51%, valvular heart disease 39.48%, diabetes 31.79%, dementia 14.35%, chronic kidney disease (eGFR < 60 ml/min/1.73m^2) (MDRD) 9.74% (fig. 2). As compared to non-institutionalized patients, those residing in nursing homes were older and had higher comorbidity scores. 173 patients (88.71%) received anticoagulants at discharge (fig. 3): 129 patients (74.56%) received cumarinic oral anticoagulants and 44 patients (25.43%) new oral anticoagulants (mainly dabigatran). The mean CHA2DS2-VASc score in the group of study was 5.2. In-hospital mortality rate in very elderly patients with atrial fibrillation was 10.76% (fig. 4). Rates of mortality, heart failure, coronary artery disease and stroke increased with older age and higher CHA2DS2-VASc scores.

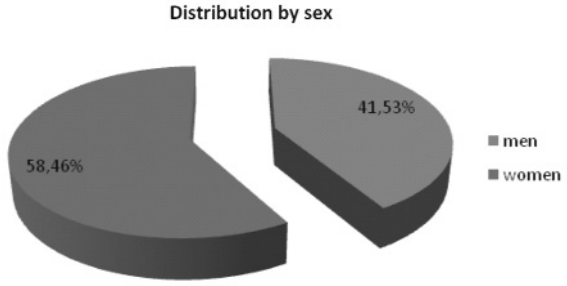

Figure 1 - Distribution by sex in the group of study

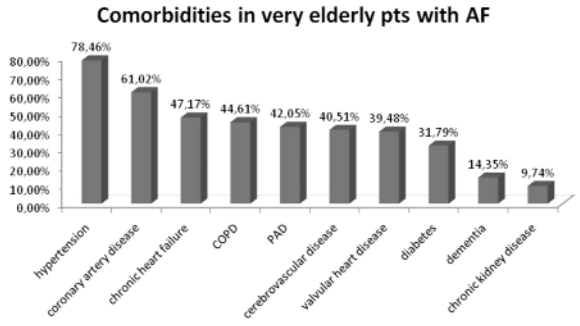

Figure 2 - The main comorbidities in the group of study

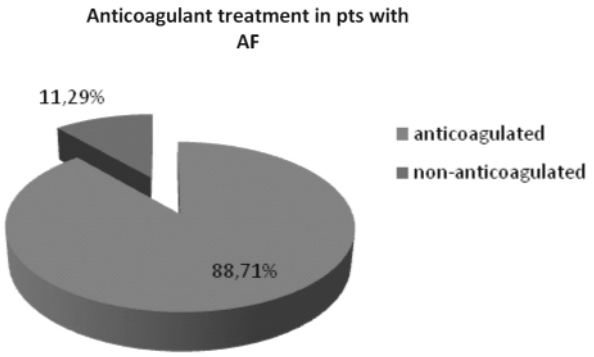

Figure 3 - Percentage of patients who received anticoagulant treatment at discharge

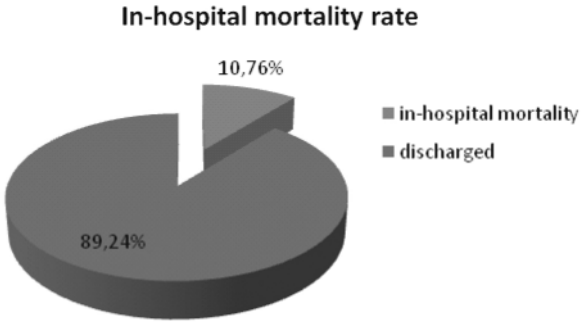

Figure 4 - In-hospital mortality rate of very elderly patients with AF

DISCUSSION

In our study, more women than men had permanent atrial fibrillation. The risk of stroke is increased in the presence of atrial fibrillation by three to seven fold, comparing with patients without atrial fibrillation (8). The presence of comorbidities increases the risk of stroke (9). Only 88.71% of the patients received long term anticoagulation treatment in our study. Long term treatment with vitamin K antagonists effectively reduces the risk of stroke in patients with atrial fibrillation, but these agents are underused, particularly in the elderly, who have the highest risk of stroke. A meta-analysis of studies with atrial fibrillation in elderly patients have found that patients with a high risk of falling are more likely to experience a cardio-embolic stroke and therefore should benefit more from anticoagulant treatment than those without a high fall risk (10). The current European Society of Cardiology, American Heart Association, American College of Cardiology guidelines for the management of atrial fibrillation recommend anticoagulant treatment based on the risk of ischemic stroke (11,12). This risk is calculated using known risk factors identified by the CHA2DS2-VASc scoring system (12). These guidelines recommend that the selection of the antithrombotic agent should be based upon the absolute risk of stroke and bleeding and the relative risk and benefit for a given patient (class IA recommendation) (12). In practice, elderly patients had an increased risk of falls and secondary injury, making the decision to anticoagulate more difficult. Physicians are caught between a rock and a hard place: if not anticoagulated, the elderly patients have an increased risk of embolic stroke, if anticoagulated they have an increased risk of bleeding secondary to their fragility and falls. Another reason is the difficulty of monitoring the anticoagulant treatment in elderly patients, due to their decreased mobility; the compliance to treatment is another shortcoming, because very elderly patients have cognitive impairment (14.35% had dementia in our study). The majority of our patients (74.56%) received cumarinic oral anticoagulants; only 25.43% received new anticoagulants when discharged. The possible explanation is the increased cost of the new anticoagulants and the presence of chronic kidney disease in 9.74% of the patients from our group of study, which limited the use of new anticoagulants.

Our patients with atrial fibrillation exhibited a high risk profile for thromboembolic events, due to the high frequency of arterial hypertension, diabetes, coronary heart disease, cerebrovascular disease and heart failure.

In our study we have found that the main comorbidities of very elderly patients with permanent atrial fibrillation were arterial hypertension, coronary heart disease and chronic heart failure. The presence of these comorbidities is a main limiting factor in prescribing the drug treatment according to guidelines. In individual patients, interactions between anticoagulant treatment and treatment of other diseases may occur and contraindications may conflict with indications. Therefore, the complex nature of interactions between risks associated with atrial fibrillation, anticoagulant treatment in atrial fibrillation and treatment of comorbidities should be carefully addressed, especially in very elderly patients.

Type 2 diabetes is frequently associated with AF and the combination of diabetes and AF confers a greater mortality risk than AF alone (13). In our study, almost one third (31.79%) of very elderly patients with atrial fibrillation had diabetes.

CONCLUSIONS

Atrial fibrillation is a frequent arrhythmia in very elderly patients. Very elderly patients with atrial fibrilla-

tion have many comorbidities, arterial hypertension, coronary artery disease, heart failure and chronic obstructive pulmonary disease being the most frequent. These comorbidities should be carefully considered when deciding the appropriate treatment for patients with permanent atrial fibrillation. In-hospital mortality rate of very elderly patients with atrial fibrillation is high. Adequate control of arterial hypertension and management of heart failure in patients with atrial fibrillation, alongside with stroke prevention are key priorities for the management of very elderly patients with atrial fibrillation and improving quality of their life.

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ORIGINAL PAPER

THE ENDONASAL APPROACH IN SINONASAL TUMORS - PRACTICAL CONSIDERATIONS

R. GRIGORE[1,2], A. POLATOS[3], C. DANCIU, A. FILIP, A. NICOLAESCU, B. POPESCU[1,2], O. PĂUN[1], C.R. POPESCU[1,2], L. NIȚU, Ș.V.G. BERTEȘTEANU[1,2]

[1]"Colțea" Clinical Hospital Bucharest - E.N.T. Head and Neck Surgery Clinic
[2]"Carol Davila" University of Medicine and Pharmacy Bucharest - E.N.T. Department
[3]"Elias" Emergency Hospital Bucharest - E.N.T. Clinic

SUMMARY

Endoscopic endonasal approach in treating nasosinusal tumors is a technique with hotspots, precise indications and has raised a lot of controversies. First of all, it is important to have a correct diagnosis and accurate staging based on CT/ MRI scan. Selection of the surgical technique and extension of the resection depends on the site and size of the lesion, its closeness to vital structures (internal carotid artery, optic nerve, orbital cavity, cavernous sinus, middle and anterior cranial fossa), age of patient, severity of signs and symptoms, malignancy or possibility of malignant degeneration. Endoscopic sinus surgery or classic surgery, both have their own pros and cons, limited by the optimum assessment on MRI/CT scan.
Key words: sinonasal tumors, endoscopic sinus surgery

RÉSUMÉ

L'approche endoscopique des tumeurs rhino-sinusales - remarques pratiques (observations)

L'approche endoscopique des tumeurs rhinosinusales est une technique aux points d'inflammation, limitée et avec contre-indications. Il est important d'avoir un diagnostic correct sur la base de CT/ IRM. La sélection de la technique chirurgicale et l'extension de la résection dépendent du site et de la taille de la lésion, sa proximité avec les structures vitales (artère carotide interne, nerf optique, la cavité orbitaire, sinus caverneux, moyenne et antérieure la fosse crânienne), l'âge du patient, la sévérité des signes et des symptômes, la malignité ou la possibilité de dégénérescence maligne. La chirurgie endoscopique des sinus ou la chirurgie agressive, les deux ont leurs propres avantages et inconvénients, limitées par l'évaluation optimale sur IRM / CT.
Mots-cle: tumeurs rhino-sinusales, chirurgie sinusale endoscopique

BACKGROUND

Ten years ago, endoscopic sinus surgery was used just for inflammatory pathology, malformative disease or treatment of epistaxis. For the sinonasal tumors endoscopic endonasal approach has been limited only to diagnostic purposes (performing biopsies).

Basic principles of endonasal endoscopic approach are defined by the correct diagnosis based on endoscopy, MRI/CT scan and histopathology (1). Selection of the surgical technique and extension of the resection depend on the site and size of the lesion, its closeness to vital structures (internal carotid artery, optic nerve, orbital cavity, cavernous sinus, middle and anterior cranial fossa), age of patient, severity of signs and symptoms, malignancy or possibility of malignant degeneration. Very large lesions can require anterior craniofacial resection. Classic surgery is justified by the high percentage of recurrences. Micro-endoscopic approach is contraindicated when one of the following situation is present: extensive involvement of the frontal sinus, massive bone erosion (except for the medial wall of the maxillary sinus and anterior wall of sphenoid sinus), intradural invasion, intraorbital invasion, scar tissue due to previous surgery, association with malignancy.

Correspondence address: *Dr. Polatos Angelica*
"Elias" Emergency Hospital Boulevard Mărăști no 17 - Bucharest
e-mail: polatosangi@yahoo.com

But, all these situations had become accessible due to new development of technologies. A combination of endoscopy, MRI and CT (fig. 1) scan is now established as the optimum assessment of sinonasal malignancy. It is of particular value in assessing the skull base, orbit and pterygopalatine and infratemporal fossa. Although MRI offers better differentiation of the tumor from the surrounding tissue and fluid, coronal CT is still required for the demonstration of bone erosion particularly in the region of the cribriform plate (7).

Key informations to be provided by imaging are:

- location, extent, site of origin;
- potential impairment of drainage pathways;
- extension beyond paranasal sinuses;
- position in respect to the lamina papyraceea and inferior and posterior frontal sinus wall;
- presence of possible complication (intracranial and/or intraorbital);
- vascularization of the lesion.

Diagnostic tools and considerations

The diagnosis of rhinosinusal tumors is often delayed, initial symptoms are nonspecific, such as unilateral nasal obstruction. Patients are initially treated for benign conditions, delaying diagnosis. Imaging studies play a key role in selecting the appropriate treatment. Proper evaluation when suspecting tumoral pathology helps us distinguish tumors from inflammatory reactions, nature of the tumor and his extent.

Benign tumors of the sinonasal tract are rare. Osteomas are the most frequent but a lot are diagnosed by chance and often do not require surgery. Papillomas (inverted, oncocytic, fungiform) are the most common indication for surgery. While the possibility of characterizing the lession based on CT imaging is quite low, the endoscopic appearance may be highly suggestive. MRI can differentiate inflammatory changes from the lesion and identify the so-called "cerebriform" or "columnar" pattern, which reflects the histological architecture of the lesion. The key issues in imaging patients with a malignant tumor of the sinonasal tract are mapping of anterior skull base and orbit involvement, and assessment of perineural spread.

The development of image guided systems has enabled sinus/skull base surgeons to monitor the position of surgical instruments, based on a preoperative CT scan, and to navigate the skull base and sino nasal cavities with more precision.

Positive diagnosis is based on clinical examination, nasal endoscopy and images, as well as histopathological findings. The sinonasal region is a region with the greatest histological diversity in the body.

The most common sinonasal tract tumors are osteomas, inverted papillomas, juvenile angiofibromas, adenocarcinomas, (malignant) melanomas.

Inverted papilloma is relatively uncommon benign epithelial tumor of the nasal cavity that generates considerable interest because they are locally aggressive, have a tendency to reccurrence, and are associated with malignancy (12% of cases). Patient with inverted papilloma should have thorough surgery to remove all mucosal disease. Reccurrent disease and metachronous carcinoma can develop up to a few years after surgery. The ethmoid region, the lateral wall of nasal fossa and maxillary sinus are the most frequent sites of origin of inverted papilloma, generally unilateral (6).

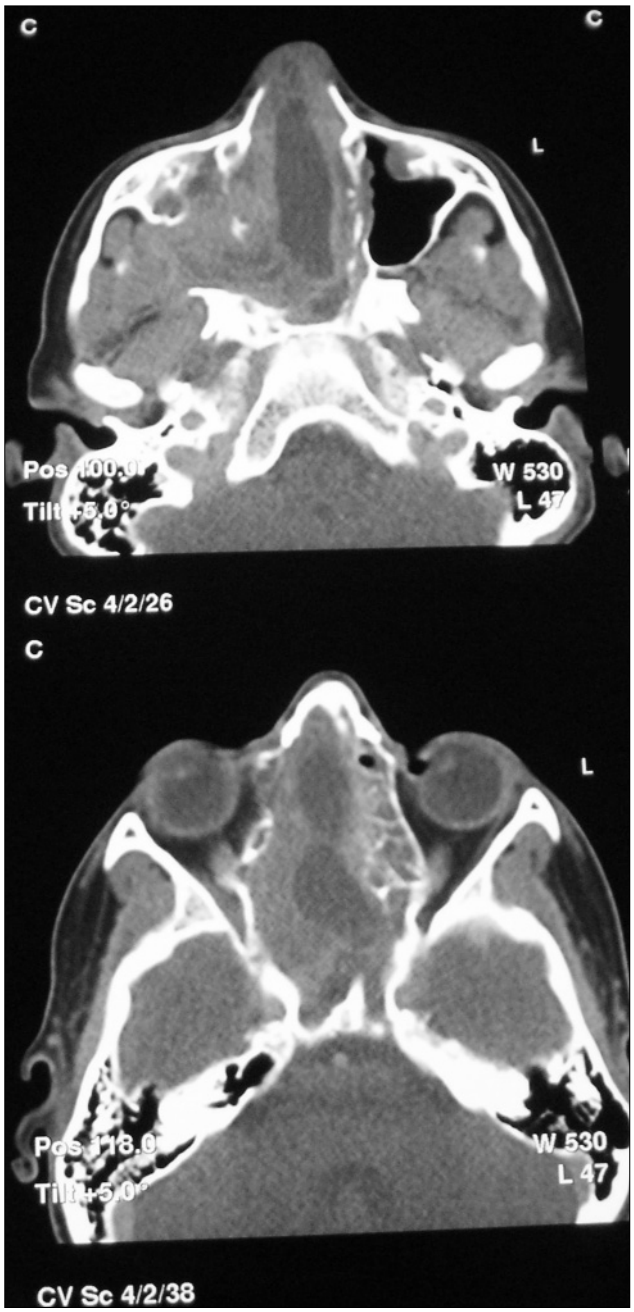

Figure 1 - Sagital plane CT slices revealing the extension of a right maxillary sinus tumor to the ethmoid cells, sphenoid, nasal fossae and skull base

CT is the choice for imaging prior to surgery. This can discern if there is any erosion of bone that would alert the surgeon to the possibility that there might be some malignancy. MRI can contribute clearly delineating whether opacification within the sinuses on CT is due to mucus or papilloma. This is very helpful when deciding the best

surgical approach for disease within the frontal sinus. Inverted papilloma within the frontal sinuses is uncommon but when it occurs it represents a surgical challenge. Often a median drainage procedure is required to allow angled endoscopes and instruments to be used from the controlateral side, to remove diseased mucosa lying laterally within the sinus.

External approach of inverted papilloma includes lateral rhinotomy, Caldwell-Luc procedure, mid facial degloving or various techniques that allow access to the frontal sinus. The introduction of the endoscope has meant that inverted papilloma can be removed with less surgical morbidity but the anterior wall and floor of the maxillary sinus are difficult for access. In these patients, a Caldwell-Luc procedure was done to remove diseased mucosa in these areas. Angled endoscopes now make possible to remove all diseased mucosa in the frontal sinus with the right curretes and forceps.

Juvenile angiofibroma is a benign tumor associated to young males. Some studies show genetic changes to be involved in the origin and other believe juvenile angiofibroma to be a vascular malformation. Tumor extension as well as the blood supply sources can be determined by CT, MRI and angiography and these investigations are helping us to select the least traumatic approach with secure haemostatic control and maximum preservation of the anatomy responsible for facial growth. Embolisation can be performed 24-48 hours before surgery; radiotherapy before the surgical treatment was also reported to offer best control of disease in advanced stages, but with post radiotherapy risks like skin carcinoma or nervous central system syndrome (dementia or encephalopathy). Chemotherapy with doxorubicine or dacarbazine was also used for reccurrences.

The endoscopic approach of juvenile angiofibroma is a minimally invasive procedure with low morbidity that has enabled the radical removal of disease for the small juvenile angiofibroma. Extended tumors are still a surgical challenge. Endoscopic resection of large or extended tumor is feasible in expert hands.

Adenocarcinoma is a glandular malignancy of the sinonasal tract. The central issue in the treatment of adenocarcinomas is to prevent loco regional reccurrences as most patients die as consequence of local reccurrence rather than because of metastasis either local or systemic. The treatment controversy is around tumors that extend to the skull base or orbit. The current gold standard for the treatment of these tumors remains a craniofacial resection. This has a significant morbidity and mortality. New endoscopic techniques for accessing previously difficult regions such as the frontal sinus, areas of the maxillary sinus and infratemporal fossa are now able to be overcomed. New endoscopic surgical techniques such as frontal drill or Draf III procedure allow full access to tumor extension into the frontal sinus or onto the posterior wall of the frontal sinus. Also endoscopic medial maxillectomy gives access to the entire maxillary sinus and the infratemporal fossa.

Malignant melanoma of the sinonasal mucosa is an uncommon disease and survival is poor. CT typically shows a uniform soft tissue mass with some retained secretions in an obstructed sinuses. The primary therapeutic modality is surgical resection with wide local margins. Postoperative radiation is often reccommended and chemotherapy is currently only used for disseminated disease and palliation. The endoscopic surgery is not limited but should always be done with the intention to cure the patient by removing the tumor with some margin as might be achieved by an open procedure. Malignant melanoma of the septum is associated with a better prognosis than elsewhere in the nose and paranasal sinuses.

SURGICAL TREATMENT

Endoscopic sinus surgery, which was initially conceived as a therapeutic method meant for chronic rhinosinusitis refractary to drug treatment, has become in time, thanks to technical advancements and increasing surgical experience in our country, an alternative to classic, radical surgery for treating nasosinusal tumor pathology. A mandatory condition for ensuring success is the skill of the surgeon and the experience in endoscopic sinus surgery. The aim of the endoscopic surgical intervention is represented by the complete resection of the tumor in order to avoid local recurrences and the decision of choosing between an open and an endoscopic surgical approach is made according to the size, localization and histopathological type of the tumor.(3)

Endoscopic approach is a successful way of treatment, with benefits in terms of lack of aesthetic deficiencies, shorter hospitalization period, as well as increasing the patients quality of life. If the tumor is large (fig. 2 and 3) and, due to its localization, a successful removal by endoscopy alone is not possible, the approach can be combined, open surgery and endoscopic sinus surgery (4).

Endonasal endoscopic approaches are ideal for lesions where the neurovascular structures are located near the tumor, (2) allowing access to the lesion with minimal manipulation of normal neurovascular structures.

Figure 2 - Large adenocarcinoma of the nasal cavity, frontal and ethmoid sinus, extended to facial skin

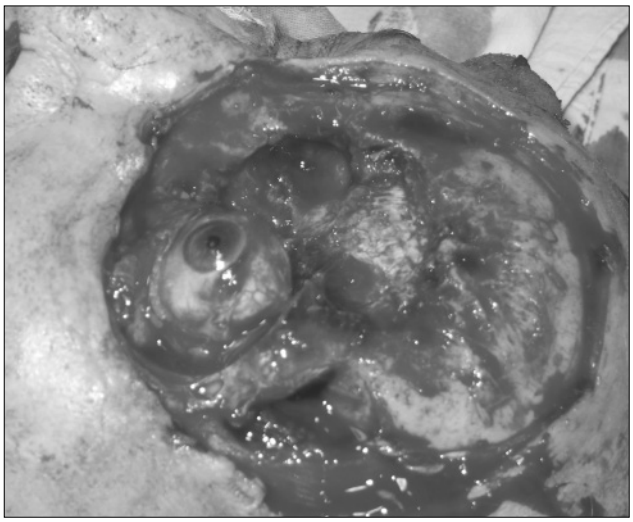

Figure 3 - Large adenocarcinoma of the nasal cavity, frontal and ethmoid sinus, extended to facial skin

Tumor type, size, shape, fibrosity, vascularity, extradural locoregional extension, vessel encasement, dural invasion and intradural extension are not anymore a contraindication to endoscopic endonasal approach.

The technical equipment, surgical abilities and experience of the surgeon are essential to ensure better results than those obtained by an external approach. The experience of the surgical team is important to maintain good visualisation, achieve hemostasis, deal with vascular complications and perform appropriate reconstruction is essential for optimal surgical results.

Conclusions

Since the usual principle of achieving a radical excision, which is the main goal of oncologic surgery, must be fulfilled as in any external procedure, the microendoscopic technique must be adapted to the different nature of the lesions. Therefore, dissection has to be carried out along the subperiosteal plane whenever the surgeon is dealing with benign lesions without any sign of bony resorption.

Resection of the underlying bone is routinely required instead for malignant lesions and also for benign lesions when crosssectional imaging suggests the presence of bony thinning or resorption.

En-bloc resection is feasible when the lesion is limited in size and involves the nasal fossa and/or the ethmoid, but it is difficult to achieve when the lesion entirely fills the nasal fossa or extends into the maxillary sinus. In such situations, one must resort to removing that portion of the lesion which is freely growing into the nasal cavity and does not invade the adjacent structures to create enough space for surgical maneuvers and to go for a piece meal resection.

In the case of malignant disease, involvement of the orbita, dura, retromaxillary fossa, intradural extension or brain infiltration all have a significant negative impact on survival. Size of the tumor, sphenoid sinus involvement, limited invasion of the dura and brain tissue, site of orbit invasion, age and sex have been a matter of debate. A higher rate of recurrences is observed for more advanced disease, regardless of the surgical technique. Some tumors have special prognostic features: malignant melanoma generally has a very poor overall survival; on the other hand, for inverted papillomas no prognostic factor of local control has been defined, whereas younger patients and smokers show a trend to recurence of these tumors. Staging should be correlated to prognosis and help in selecting the best strategy such as neoadjuvant chemotherapy and surgical approach.

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ORIGINAL PAPER

THE HEEL QUANTITATIVE ULTRASOUND AND FRAX ESTIMATED RISK OF FRACTURE: A CROSS-SECTIONAL STUDY IN 292 MENOPAUSAL WOMEN

Cătălina Poiană[1,2], Mara Cârșote[1,2], Simona Elena Albu[3], V. Rădoi[1], Alexandra Mihai[2], Andreea Geleriu[2], Gabriela Voicu[2], M. Coculescu[1,2]

[1] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2] *"C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania*
[3] *Emergency University Hospital, Bucharest, Romania*

Summary

Accessible methods as FRAX algorithm and quantitative ultrasound (QUS) are important in fracture risk assessment since fractures represent cost issues, and they are often underdiagnosed in menopausal women. We correlated the 10-year fracture risk based on FRAX and heel QUS (Achilles) parameter represented by the stiffness index in a cross-sectional study of 292 women aged 57.27±7.58 years (range 42-79) who were not previously treated for osteoporosis. FRAX risk and stiffness index are positively correlated for hip and major osteoporotic fracture regardless controlling for years since menopause. We performed an independent partial correlation between body fat mass % (bio-impedance) and FRAX risk with statistical significant results for hip and major factures (r=-0.24, r=-0.21, p<0.001 for both) that became stronger (r=-0.32, r=-0.32, p<0.001) after controlling for years since menopause. When controlling for years since menopause, QUS and FRAX correlations are weaker, while fat mass % and FRAX risk correlations are stronger. The introduction of years since menopause in fracture risk evaluation is useful since aging determines a different menopausal status.
Key words: FRAX, quantitative ultrasound, fat mass, stiffness index, postmenopausal years

Résumé

L'échographie quantitative et l'algorithme FRAX ont évalué le risque de fracture: étude transversale de 292 femmes à la ménopause

Les methodes accessibles comme l'algorithme FRAX et l'échographie quantitative (QUS) sont importantes pour l'évaluation du risque de fracture parce que les fractures représentent des côuts importants et elles sont souvent sous-diagnostiquées chez les femmes à la ménopause. Nous avons corrélé le risque de fracture pour 10 ans conformément aux FRAX et le paramètre QUS (Achilles) représenté par l'indice de rigidité dans une étude entrecroisée de 292 femmes âgées entre 57,27±7,58 ans (42-79 ans), qui n'ont pas été traitées antérieurement pour ostéoporose. Le risque FRAX et l'indice de rigidité sont corrélés positivement pour les fractures de la hanche et la fracture ostéoporotique majeure, indépendamment des ans depuis la ménopause. Nous avons fait une corrélation indépendante partielle entre la masse grasse corporelle % (bio-impédance) et le risque FRAX aux résultats significatifs pour les fractures de la hanche et pour celles majeures (r=-0,24, r=-0,21, p<0,001) qui devient plus forte (r=-0,32, r=-0,32, p<0,001) avec l'ajustement pour les ans depuis la ménopause. L'ajustement pour les ans depuis la ménopause permet une faible corrélation entre QUS et le risque FRAX, mais la corrélation entre la masse grasse corporelle et le risque FRAX devient plus forte. L'introduction des années de ménopause dans l'évaluation du risque de fracture est utile vu que le vieillissement détermine un statut différent de ménopause.
Mots clefs: FRAX, échographie quantitative, masse grasse, indice de rigidité, années post-ménopause

Correspondence address: *Mara Cârșote, MD*
Aviatorilor Ave 34-36, sector 1, 011863 postal code, e-mail: carsote_m@hotmail.com

Introduction

The socio-economic problems related to the number of low trauma fractures will intensify since the population at risk will increase based on the life expectancy growth. Moreover, lately, a very deep concern regarding the quality of life has become evident. Thus, the implementation of cost-efficient methods to detect at risk persons together with an adequate interpretation of their results is a major issue. The FRAX® model represents a modern and interesting tool recommended by guidelines for fracture risk evaluation. (1,2,3) It also represents a dynamic instrument since the number of countries with specific data is increasing. (1) On the other hand, the heel quantitative ultrasound (QUS) is an accessible, non-radiating method, recommended for bone assessment. (4) A number of previous studies has shown that QUS predicts hip fractures and could predict other osteoporotic fractures in postmenopausal women (5,6,7). Based on these, the validated QUS devices "predict fracture risk similarly". (4,8) The QUS prediction of fracture is "independent" of the bone mineral density (BMD) values provided by central Dual Energy X-Ray Absorptiometry (DXA). (4)

The aim of this study was to analyze the correlations between the parameters provided by the FRAX® algorithm based on body mass index (BMI), not BMD, and QUS. Another independent analyze was performed between FRAX® estimation and whole body fat mass percent provided by bio-impedance, not DXA, thus accessible and easy-to-do methods in postmenopausal women. Both analyses have been controlled for years since menopause.

Material and Method

This is a cross-sectional study, conducted in postmenopausal Caucasian women admitted to the "C.I. Parhon" National Institute of Endocrinology, Bucharest, between October 2011 and February 2013. They were referred to the hospital for another diagnosis than bone or calcium metabolism abnormalities, including osteoporosis. The patients were evaluated based on an anamnesis focused on: the age of menopause (the absence of menses for 12 months regardless of physiological or surgical secondary amenorrhea; the years since menopause were calculated from the last menstrual period), previous self-declared fragility fracture, previous diagnosis of osteoporosis and specific therapy, parents with hip fracture, smoking, and alcohol intake, pre-therapy with glucocorticoids, previous diagnosis of rheumatoid arthritis, chronic hepatitis, differentiated thyroid cancer and consecutive suppression long-term therapy with levothyroxine. The inclusion criteria were: 1. at least one year since the last menstruation, 2. age between 40 years and 80 years. The exclusion criteria were: 1. previous therapy for osteoporosis or fracture prevention such as bisphosphonates, teriparatide, strontium ranelate, selective oestrogen receptor modulators, 2. previous hormone replacement therapy, 3. previous therapy for bone metastasis or para-neoplasic hypercalcemia, 3. type 1 diabetes mellitus, 4. osteogenesis imperfecta, 5. Cushing's syndrome, 6. QUS assessment disturbances (bilateral fractures or prosthesis of the calcaneus or edema).

The anthropometry parameters weight (kg) and height (cm) were measured in order to calculate the BMI. The QUS assessment was performed with a GE Lunar Achilles device. An ultrasound coupling gel system was used. QUS measurement was performed on the left heel (trabecular bone). Quality control measurements were applied every day based on recommended procedures by the manufacturers. The QUS parameter used was the Stiffness index (SI) provided by the device as a derivate parameter from ultrasound characteristics. The whole body fat mass percent was analyzed by a Tanita Body Composition Analyzer (measurements based on bio-impedance). The FRAX® model was applied using the Romanian data, an algorithm based on BMI, not BMD or T-score. (1,9)The study was approved by the hospital's ethics board and each patient signed an informed consent.

The statistical analysis was carried out using SPSS 21 (IBM C). Using this program we measured means, standard deviations, ranges, and univariate partial correlations expressed as r and two tailed p-values expressed as p. A p value of <0.05 was considered to be statistically significant.

Results

292 postmenopausal women were included in the study. 244 women were under the age of 65 years (group 1 or younger women group) and 48 were 65 years and older (group 2 or older women group). The anthropomorphic, QUS, and whole body fat mass percent variables for the whole group, as well as for the both groups, are shown in table 1. The years since menopause vary from 8.42 to 22.39 in the two groups. SI decreases with age from 80.15 ± 18.16 to 71.85 ± 13.57 for the 2 age categories and it is statistically significant different ($p<0.05$). The fat mass percent and the BMI were similar between the groups (39.04% of all were obese women). A higher percent of active smokers (30.73% vs. 12.5%) was found in the younger women group as well as a discretely lower % of previous fragility fractures (15.57% vs. 18.75%).

The entire study population showed a negative, weak, highly statistically significant correlation between SI and the 10-year probability of hip fracture based on FRAX® ($n=292$, $r=-0.27$, $p<0.001$). This correlation was also found when grouping the patients according to age (under 65 years of age; 65 years of age or older). The first group showed a modest correlation ($n=244$, $r=-0.3$, $p<0.001$), while the second grouped showed a weak correlation which was not significant ($n=48$, $r=-0.25$, $p=0.08$). After controlling for postmenopausal years, the partial correlation between SI and the 10-year probability of hip fracture based on FRAX® became weaker with statistical significance for the entire study population ($r=-0.18$, $p=0.002$) and the younger women group ($r=-0.27$, $p<0.001$). (table 2) The correlation coefficient between SI provided by QUS and the 10-year probability of major osteoporotic fracture based on FRAX® was also negative and statistically significant:

Table 1 - Characteristics of the studied postmenopausal women

	all	< 65 years	≥ 65 years
	mean ± SD (range)	mean ± SD (range)	mean ± SD (range)
age (years)	57.27 ± 7.58 (42-79)	54.76 ± 5.32 (42-64)	70.02 ± 3.35 (65-79)
menopause age (years)	46.55 ± 5.54 (20-65)	46.34 ± 5.47 (20-57)	47.62 ± 5.8 (37-65)
years since menopause	10.71 ± 8.05 (2-35)	8.42 ± 6.09 (2-35)	22.39 ± 6.53 (8-35)
BMI (kg/m^2)	28.83 ± 5.72 (16-53)	29.13 ± 5.95 (16-53)	27.32 ± 4.12 (20-37)
whole body fat mas (%)	37.45 ± 7.16 (11.8-54.6)	37.52 ± 7.24 (11.8-54.6)	37.08 ± 6.83 (18.3-49.3)
stiffness index (Achilles)	78.79 ± 17.74 (42-134)	80.15 ± 18.16 (42-134)	71.85 ± 13.57 (48-103)
	% of patients	% of patients	% of patients
smoking (% of patients)	27.73	30.73	12.5
surgical menopause (% of patients)	19.86	21.72	10.41
fractures (% of patients)	16.09	15.57	18.75
obese (% of patients)	39.04	40.98	29.16

*Table 2 - Correlation coefficients between the Stiffness Index (provided by QUS) and the 10-year probability of hip fracture (based on FRAX®), respectively the 10-year probability of major osteoporotic fracture (based on FRAX®) without and with the control for menopausal years**

	SI(QUS) - 10-year probability of hip fracture (FRAX®)				SI(QUS) - 10-year probability of major osteoporotic fracture (FRAX®)			
	r	p	r *	p *	r	p	r *	p *
all	-0.267	< 0.001	-0.184	0.002	-0.288	< 0.001	-0.203	0.001
< 65 yrs	-0.299	< 0.001	-0.272	< 0.001	-0.277	< 0.001	-0.248	< 0.001
≥ 65 yrs	-0.249	0.088	-0.188	0.206	-0.244	0.095	-0.177	0.234

*controlled for menopausal years

*Table 3 - Correlation coefficients between the whole body fat mass percent (based on the Body Mass Analyzer assessment) and the 10-year probability of hip fracture (based on FRAX®), respectively the 10-year probability of major osteoporotic fracture (based on FRAX®) without and with the control for menopausal years**

	Fat Mass% - 10-year probability of hip fracture fracture (FRAX®)				Fat Mass % - 10-year probability of major osteoporotic (FRAX®)			
	r	p	r *	p *	r	p	r *	p *
all	-0.247	< 0.001	-0.325	< 0.001	-0.219	< 0.001	-0.31	< 0.001
< 65 yrs	-0.311	< 0.001	-0.421	< 0.001	-0.239	< 0.001	-0.353	< 0.001
≥ 65 yrs	-0.354	0.014	-0.342	0.019	-0.293	0.043	-0.277	0.05

*corrected for menopausal years

r=-0.28, p<0.001 for the entire study population and r=-0.28, p>0.001, for younger women, respectively r=-0.24, p=0.09 for the older group. After controlling for years since menopause, the correlation became weaker and still statistically significant for all the patients (r=-0.20, p=0.001), as well as for the patients under 65 years (r=-0.25, p<0.001). (table 2)

Negative linear statistically significant associations were found between the whole body fat mass percent and the 10-year probability of hip fracture for all the women (r=-0.24, p<0.001), as well as the younger group (r=-0.31, p<0.001) and for patients 65 years of age or older (r=-0.35, p=0.01). (table 3) After controlling for years since menopause, the partial correlation between fat mass % and the 10-year probability of hip fracture became stronger, with the entire study population showing a modest correlation (r=-0.33, p<0.001), the same as the subgroups (n=244, r=-0.42, p>0.001; n=48. r=-0.34, p=0.02). (table 3) Similar results were obtained when performing a univariate correlation between whole body fat mass percent and the 10-year probability of major osteoporotic fracture: r=-0.25, p>0.001 for the entire study population and r=-0.24. p<0.001, respectively r=-0.29, p=0.04 for the age groups. After controlling for postmenopausal years, the partial correlation was stronger: r=-0.31, p<0.001 for the entire study population and r=-0.35, p<0.001, respectively r=-0.27, p=0.05 for the groups. (table 3)

The correlation between SI and years since menopause is negative and statistically significant for the entire studied population (r=-0.22, p<0.001). The correlation between

Table 4 - Correlation coefficient between the Stiffness Index (provided by QUS) and years in menopause, respectively fat mass percent (based on the Body Mass Analyzer assessment) and years in menopause

	SI - years in menopause		Fat Mass % - years in menopause	
	r	p	r	p
all	-0.22	< 0.001	0.062	0.293
< 65 yrs	-0.129	0.044	0.139	0.03
≥ 65 yrs	-0.246	0.091	-0.099	0.502

*corrected for menopausal years

whole body fat mass percent and years in menopause is positive and statistically significant for all the females and for the younger ones group. (table 4)

Discussions

In this study, negative statistically significant correlations between SI and the 10-year probability of hip or major osteoporotic fracture were found. (fig. 1a, b) The comparisons between the zero order correlations of these parameters and the partial correlations controlled for postmenopausal years, suggest that the years since menopause might alter the FRAX® results, showing a reduced 10-year fracture risk for women who have a lower SI, but have just recently reached menopause. This may be due to the correlation that exists between SI and postmenopausal years for the entire studied population and for group 1 that was also found when controlling for years since menopause, although with a lower value of the correlation coefficient. On the other hand, the age-SI relationship exists since SI was significantly higher in younger women ($p < 0.05$) meaning a lower fracture risk. Age and postmenopausal status have been previously reported as correlated with QUS parameters in a multivariable model. (10) It is known that hip fracture incidence exponentially

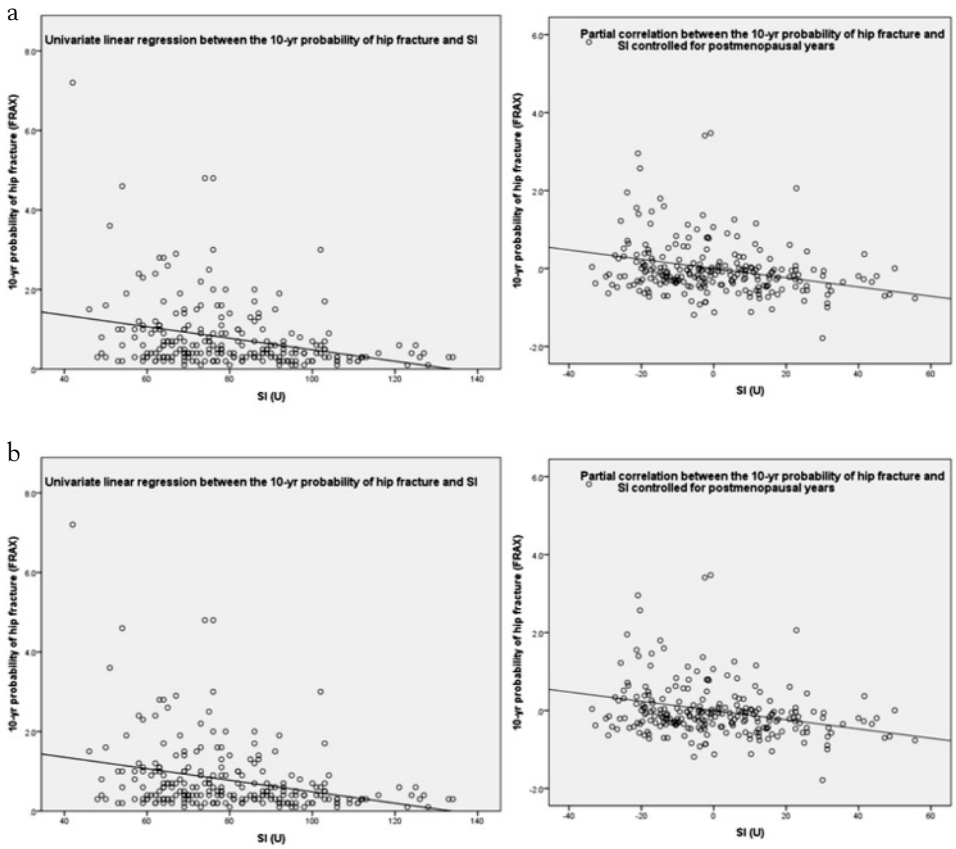

Figure 1 - (a) Correlation between the 10-year probability of hip fracture (based on FRAX®) and the Stiffness Index (provided by QUS) controlled for years since menopause in women < 65 years; (b) Correlation between the 10-year probability of major osteoporotic fracture (based on FRAX®) and the Stiffness Index (provided by QUS) controlled for years since menopause in women < 65 years

increases with age and that the stiffness index decreases with age, as seen here. (11,12) The correlation between fracture risk estimated by the FRAX® algorithm and the value of SI support the data found in the literature that QUS measurements are useful as a significant discriminator of hip fractures, for example, with odds ratio between 1.88 and 2.63 and areas under the ROC curve between 0.663 and 0.74 in a previous study. (13) Another team found a coefficient of correlation of 0.75 ($p < 0.00001$) between the stiffness index and the hip BMD in healthy postmenopausal women. (14) In this study, the surrogate of DXA-BMD is the BMI related FRAX® digital calculator, as a more accessible and easy to perform alternative of bone evaluation. We used a direct correlation between a QUS variable and the FRAX® results in order to have a better perspective in fracture risk evaluation, although a part of the clinical risk factors (not to mention age and BMI) included in the FRAX® algorithm have been found as correlated with QUS results but not all (previous fracture, maternal hip fracture, glucocorticoids use and current smoking). (4,15,16, 17,18) The FRAX® model does not include years since menopause, except for "secondary osteoporosis" where an input of menopause earlier than 45 years old might be introduced as an alternative for many other causes of bone loss such as chronic liver disease, malnutrition, etc. A previous study tried to include the broadband ultrasound attenuation values provided by QUS in a model regarding the 10-year absolute risk of fracture and one in six patients were reclassified in another risk category. (19) The combined QUS-FRAX® risk calculator is not routinely used, probably due to the lack of standardized QUS measures and the lack of longer than 5 years large prospective QUS studies. (20) Also, the EPISEM prospective cohort showed that including the clinical risk factors together with the QUS parameters increases the 10-year probability of fracture accuracy. (21) Further approaches will point out the real relevance of combined QUS and FRAX® results. (22) Our data found that the whole body fat mass percent is negatively correlated with both 10-year probability of hip and major osteoporotic fracture based on FRAX® in the cohort and in each age-group. Although we have found only modest correlations, these are statistically significant. The fat mass percent was correlated with years since menopause only in group 1 and it was not statistically significant different between the two age-group (a mean of 37.52% vs. 37.08%). (fig. 2a, b) One study we have found in the literature, which was done on 244 non-

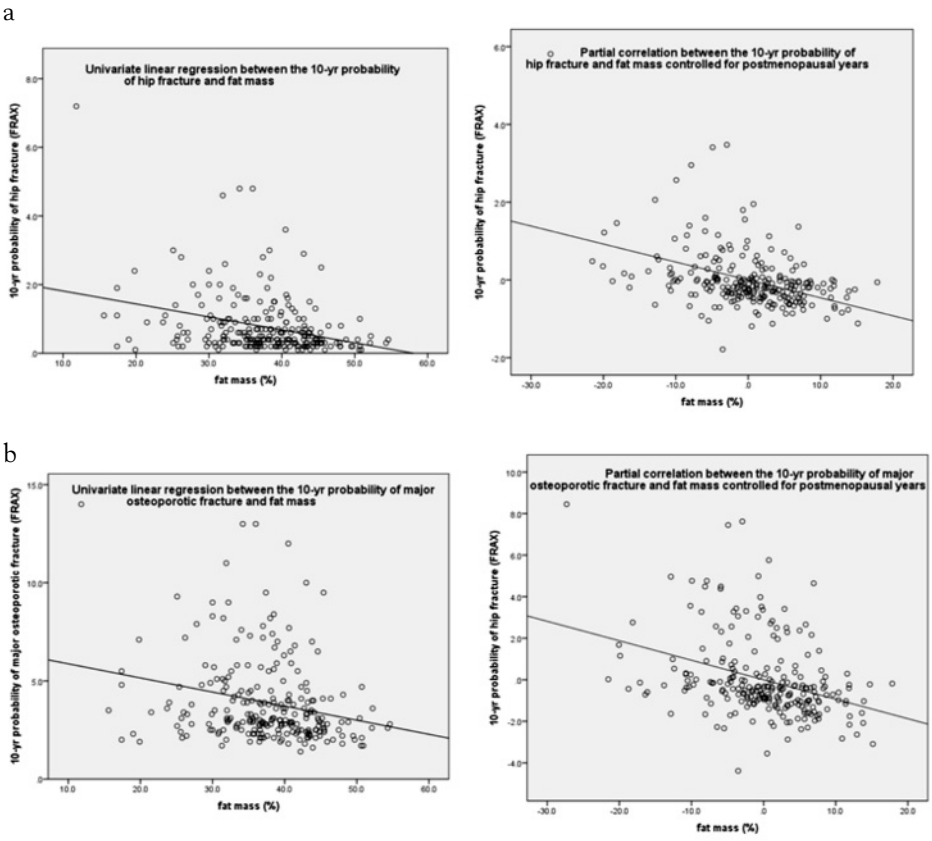

Figure 2 - (a) Correlation between the 10-year probability of hip fracture (based on FRAX®) and the whole body fat mass percent (based on the Body Mass Analyzer assessment) controlled for years since menopause in women < 65 years; (b) Correlation between the 10-year probability of major osteoporotic fracture (based on FRAX®) and the whole body fat mass percent (based on the Body Mass Analyzer assessment) controlled for years since menopause in women < 65 years

osteoporotic women with a mean age of 65.6 yrs showed a correlation coefficient of $r=-0.127$ ($p<0.05$) between the whole body fat mass (%) and years since menopause and it suggested that the fat mass is one of the most important determinants from the body composition in BMD at lumbar spine and hip.(23) An interesting result of our study lies in the comparisons between the zero order correlations of fat mass % and hip or major osteoporotic fracture risk and the partial correlations controlled for postmenopausal years. Due to the differences seen between these correlations, which show a stronger relationship when we control for postmenopausal years, we further suggest that postmenopausal status plays a role in determining the 10-year fracture risk. (fig. 2a, b) The whole body mass percent may add information to the simple BMI based analyze, a parameter that is already included in FRAX® as we used only the BMI - FRAX® version. (1) However, we mention that a recently published study done on 6049 women with a obesity frequency of 18.5% concluded (after a mean follow-up period of 9.03 years) that FRAX is more useful as a fracture predictor in obese when used with BMD. (24) The fat mass relationship with QUS or DXA as fracture risk tools evaluators has also been previously analyzed. The weight itself as a parameter was previously found as positively correlated with QUS variables, but not all the studies confirmed it, thus it is not a very reliable parameter. (10) An analyze in 198 postmenopausal women with a mean age of 67.5 years showed that whole body fat mass and weight are the strongest body composition determinants in lumbar and femoral neck BMD.(25) Recent observations suggest that the fat tissue assessment is an open door to skeletal evaluation. The data from the literature point out that while low BMI increases the fracture risk, obesity is associated with a higher risk of fracture in some sites and a lower risk in others. (26)The fat mass is closely related to the metabolic complications and, eventually, to bone loss, not only based on obesity studies, but also taking into account type 2 diabetes mellitus studies recently reported as an independent risk factor for low trauma fractures by cortical changes, and bone collagen matrix disturbances. (27) Previous information revealed that the whole body fat mass percent is correlated to both BMI and trunk fat mass and it increases after menopause and it is correlated with many other metabolic anomalies such as serum uric acid ($r=0.401$, $p<0.001$), etc. (28) We considered the two groups of women using a 65 years of age cut off. This was based on the osteoporosis screening indications included in the practice guidelines. (29) Assuming an age related gradient fracture risk of 1.5/SD with a 10% of on risk population, the positive predictive value increases from 11% at 50 years old to 24% at the age of 65 years. (30) Previous QUS studies described the same age-groups. For example, a relative risk of fracture (95%CI) of 1.68 (1.14-2.48, $p=0.008$) in women less than 65 years and 2.14 (1.51-3.06, $p<0.0001$) in women $\geq$ 65 years based on broadband ultrasound attenuation (BUA) was demonstrated in the EPIC-Norfolk study.(31) In our study, the correlation between fracture risk estimated based on QUS and FRAX® was not found in older women groups, not even after controlling for years since menopause, neither between SI and years since menopause. Another clinical practice aspect is that both QUS and FRAX® are best applied to untreated patients for osteoporosis, thus we introduced this aspect as an excluding criteria. We also excluded the women treated with hormone replacement therapy because, despite bone protection during the period they received medication, the menses are not always resumed and this might interfere with counting the years since last menstruation.

This study has its limits. The group of older women included only 48 patients. Probably this explains the lack of statistical significance in some correlations. We chose not to use in the statistical analyze the other two parameters of the QUS reports: speed of sound and broadband ultrasound attenuation and we reported the results only on the stiffness index which is a composite parameter of these two and it is generally accepted for current use, especially for QUS Achilles devices. (4) We included women with natural and surgical menopause in the same analyze (21.72 % in younger women group and 10.41% in older women group had surgical menopause, with a similar mean age of menopause in groups: 46.34 vs. 47.62 yrs) based on two aspects: we found no differences when re-doing the correlation coefficient between surgical and natural menopause sub-groups and also because FRAX does not take into account the type of menopause. One QUS study, though, found a SI of 67.3 ± 10.9 in a 93 women group with a mean age of 56.8 years with bilateral oophorectomy significantly ($p<0.01$) lower than a SI of 71.6 ± 14.1 in the 285 female group with natural menopause (mean age of 56.4 years). (32) Prospective studies would be necessary to reveal the absolute incidence of fractures and the way in which the present correlations from this cross-sectional study suggested it.

Fragility fractures are present in one-third of the population at menopause and, as such, important aspects related to morbidity, mortality and medical costs are involved. (33) Osteoporosis is frequently under-recognized and it is regarded as an inevitable effect of aging. (34) Aging might be similar with years since menopause but not necessarily. Life quality impairment related to osteoporotic fractures needs serious considerations. Thus the interpretation of very accessible methods such as QUS, FRAX® or Body Mass Analyze in skeleton assessment is essential in current clinical practice because they are rapid methods to adequately stratify the patients at risk and because cost issues should be taken into account while doing the evaluation especially in countries with sub-optimal economical profiles. We encourage the use of these methods regarding the skeleton health in all postmenopausal women especially in those patients who, as in our study, are referred to a specialist (endocrinologist, gynecologist etc.) for others diagnosis and not necessarily osteoporosis.

Conclusion

We have shown that, when controlling for postmenopausal years, the SI and FRAX® estimated risk of fracture correlations lose their strength, while the correla-

tions between the whole body fat mass and 10-year probability of fracture gain power. As such, the number of years since menopause could play a role in correlations between different tools of fracture risk assessment.

Conflict of interest

None

Acknowledgments

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ORIGINAL PAPER

FRAX PROFILE IN 287 MENOPAUSAL WOMEN WITH OSTEOPOROSIS AND OSTEOPENIA: A CROSS-SECTIONAL PILOT STUDY

Mara Cârșote[1], Elena Simona Albu[2], Ana Valea[3], V. Rădoi[4], Cătălina Poiană[1]

[1]Carol Davila University of Medicine and Pharmacy & C.I.Parhon National Institute of Endocrinology, Bucharest, Romania
[2]Carol Davila University of Medicine and Pharmacy & Universitary Emergency Hospital, Bucharest, Romania
[3]Iuliu Haţieganu University of Medicine and Pharmacy & Clinical Country Hospital, Cluj-Napoca, Romania
[4]Obregia Hospital, Bucharest, Romania

Summary

FRAX is a tool designed to assess the risk of fracture especially in populations at risk as menopausal women. This is a pilot cross-sectional study in 287 women with osteoporosis (N=108) and osteopenia (N=197). The two groups were statistically significant different as body mass index and bone mineral density but not as age (mean of 59 years). HF for osteoporosis group of 1.7% is higher than for osteopenia group of 1.31% (borderline significance p=0.07). MOF for osteoporotic subjects of 5.72% is higher than for osteopenic women of 5.00% (no statistical significance is seen between MOF of women with osteoporosis or osteopenia (p=0.09). The 10-year probability of fracture based on FRAX model independently appreciates the major osteoporotic fracture risk, as well as hip fracture from lumbar DXA bone mineral density in menopausal subjects with osteoporosis versus osteopenia.
Key words: menopause, osteoporosis, FRAX, fragility fracture, osteopenia

Résumé

Le modèle FRAX chez 287 femmes ménopausées avec de l'ostéopénie: étude transversale pilote

Le modèle FRAX est un instrument conçu pour évaluer le risque de fracture en spécial chez les populations à risque comme les femmes ménopausées. C'est une étude pilote transversale de 287 femmes atteintes d'ostéoporose (N = 108) et d'ostéoponie (N = 197). Les deux groupes étaient du point de vue statistique significativement différent en ce qui concerne l'indice de masse corporelle et la densité minérale osseuse, mais pas en ce qui concerne l'âge (âge moyen - 59 ans). La FH du groupe avec de l'ostéoporose de 1,7% est plus élevée que pour le groupe avec de l'ostéopénie de 1,31 % (limite de l'importance p = 0,07). Les FOM pour les sujets ostéoporotiques de 5,72% sont plus élevées que pour les femmes ostéopéniques de 5,00% (aucune importance statistique entre les FOM des femmes atteintes d'ostéoporose ou d'ostéopénie (p = 0,09). La probabilité pour une période de 10 ans d'une fracture basée sur le modèle FRAX apprécie indépendamment le risque majeur de fracture ostéoporotique, tout comme la fracture de la hanche de la densité minérale osseuse lombaire DXA chez les sujets ménopausés souffrant d'ostéoporose par rapport à ceux avec ostéopénie.
Mots clefs: ménopause, ostéoporose, FRAX, fracture par fragilité osseuse, ostéopénie

Introduction

The osteoporosis and the fragility fracture risk that is associated with osteoporosis represent a menopause worldwide problem thus the implementation of good economical profile instruments in order to assay the fracture risk is an exemplary solution. (1,2,3) One of these is the FRAX algorithm providing the 10-year absolute fracture risk for major osteoporotic fractures (MOF) and hip fracture (HF). The model is available

Correspondence address: *Mara Carsote, MD*
Aviatorilor Ave 34-36, sector 1, 011863 postal code, Bucharest, Romania
e-mail: carsote_m@hotmail.com

for specific countries including Romania since 2011. (4,5,6) Nevertheless osteopenia associates a lower fragility fracture risk than osteoporosis but a higher number of subjects are found in this group. (1,2,3)

Scope

We aim to analyse the FRAX profile in menopausal women with osteoporosis and osteopenia according to DXA central results.

MATERIAL AND METHOD

This is an observational transversal study in menopausal Caucasian Romanian women. The inclusion criteria were confirmed menopause (physiological or surgical) and the possibility to assess the 10-yr risk of fracture based on FRAX model meaning collecting all the necessary data. The exclusion criteria were previous bone conditions from osteoporosis to bone metastasis, and type 1 diabetes mellitus.

The patients were evaluated by the medical team based on anamnesis, anthropometry, medical history; prevalent fragility fractures. The risk of fracture was calculated by the online model. MOF and HP were provided using inputs as age, body mass index (BMI in kg/sqm), previous fractures, current smoking, previous corticoids use, previous diagnosis of rheumatoid arthritis, etc. (7) MOF and HP were based on FRAX model without neck bone mineral density. The central Dual Energy X-ray Absortiometry was assessed and provided the bone mineral density (BMD in g/sqm). The osteoporosis was diagnosed exclusively based on lumbar T-score $\leq$ -2.5. (8) The osteopenia was diagnosed based on WHO criteria using the lumbar T –score of $<$-1 and $>$-2.5. (8) The database was collected in Excel; statistical analysis considered significantly at $p < 0.05$. Mean and standard deviation (SD) were used to describe the cohort.

RESULTS

287 subjects were enrolled. 108 were diagnosed with osteoporosis (OP group) and 179 with osteopenia (op group). (fig. 1) The baseline characteristics were analysed. Lumbar BMD is lower in subjects with osteopenia and BMI is lower. (table 1) 19.51 % (N=56) from the entire cohort had surgical menopause and 18.81% (N=54) had at least one prevalent fragility fracture. HF for subjects with osteoporosis is 1.74 +/- 2.4 %, and for women with osteopenia is 1.31 +/- 1.59%. No statistical significance is seen between HF of women with osteoporosis or osteopenia (p=0.07). MOF for subjects with osteoporosis is 5.72 +/- 4.01 %, and for women with osteopenia are 5.00 +/- 3.08%. No statistical significance is seen between MOF of women with osteoporosis or osteopenia (p=0.09). (fig. 2)

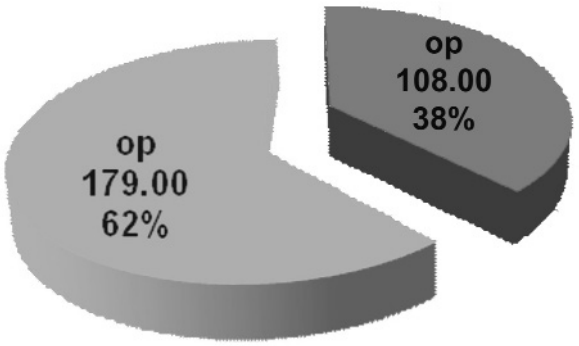

Figure 1 - The studies population (N=287): group with osteoporosis (OP) and osteopenia (op)

DISCUSSIONS

FRAX is a useful tool to assess the fracture risk having a great utility in a population as menopausal subjects who are supposed to associate a higher number of fractures. (9) The economical profile of the algorithm encourages its utility. Some studied describe different sites of fracture risk all models derived from the classical one which is available for Romania. (10) Yet the golden standard remains DXA all over the world. That is why we tried by this study to correlate a new tool to what is considered the best tool for fracture risk estimation. The data we found in two similar populations (as age) show that actually the HF and MOF were not statistically different between the population with osteoporosis and osteopenia although the mean BMI values were statistically significant different between the groups.

As limits of our study we mention the fact that we did not use the FRAX calculator based on BMD because we did not have enough data to use it for the final analysis.

Table 1 - The baseline characteristics of the studied population (N=287): OP (osteoporosis) group and op (osteopenia) group

Parameter	Descriptive parameter	OP group	Op group	Student t-test
age	mean	59.86	59.17	0.48 years
	SD	7.58	8.08	
BMI	mean	26.39	28.41	0.00 kg/sqm
	SD	5.16	16.83	
BMD	mean	0.79	0.96	0.00 g/sqcm
	SD	0.09	0.09	

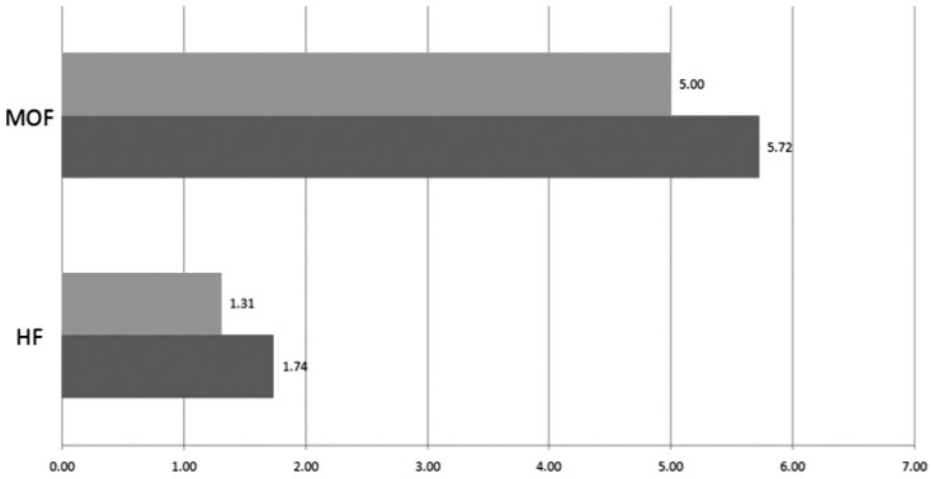

Figure 2 - FRAX estimated risk in studied population (N=287): group with osteoporosis (OP, red) and osteopenia (op, green); MOF=10-yr probability of fracture for major osteoporotic fractures; HF=10-yr probability of hip fracture

Conclusion

The 10-year probability of fracture based on FRAX model independently appreciates the major osteoporotic fracture risk, as well as hip fracture from lumbar DXA bone mineral density in menopausal subjects with osteoporosis versus osteopenia.

Conflict of interest

None

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ORIGINAL PAPER

DATA CONCERNING THE INCIDENCE OF RESPIRATORY PATHOLOGY IN DIFFERENT SEASONAL PERIODS

ANTONELLA CHEȘCĂ[1], A. GELLERT GYURKA[2]

[1]*Faculty of Medicine, Transilvania University of Brașov, Romania*
[2]*Tim Sandle, Head of Microbiolgy at BPL, UK*

SUMMARY

Introduction: The human body is vulnerable to different pathogens. From this point of view we can see a high incidence of diseases that are part of the respiratory pathology. At different periods of the year, the human's body's resistance decreases. For any of the forms of respiratory diseases, is useful for patients a preliminary investigation in order to diagnose and to treat the respiratory disease.
Methodology: The study included symptomatic patients from two different periods of the year, as first trimester of 2014 and last semester of 2014. This study includes statistical data, by age group and by gender. According to the statistic data, we can remark the incidence of respiratory diseases.
Results: The study results are expressed in sector graphics which show the respiratory pathology incidence for each of the population segments included in this study. Also, the data are presented for each month of two periods of study. Statistical data present the respiratory diseases incidence for seven different age groups. The incidence of the respiratory diseases are expressed in sector graphics also by genders, for each month from the study. In this context we can remark the increased incidence or the decreased incidence of respiratory diseases, in women and in men.
Conclusions: It is useful to consider implementing methods of public information and practical application of screening programs, for prevention, knowing a complexity of pathogens for a possible respiratory disease. Also is known the chidren as a vulnerable age group. Different forms belonging to the respiratory pathology are as consequence, or may occur in accordance with sinusal infections.
Key words: respiratory pathology, risk factors, incidence, statistical study, data analysis

RÉSUMÉ

Données sur l'incidence de la pathologie respiratoire dans des périodes différentes saisonnières

Introduction: Le corps humain est vulnérable aux différents agents pathogènes. De ce point de vue, nous pouvons voir une forte incidence des maladies qui font partie des pathologies respiratoires. À différentes périodes de l'année, la résistance du corps humain décroît. Pour chaque type de maladies respiratoires, il est utile pour les patients de faire un examen préliminaire afin de diagnostiquer et de traiter la maladie respiratoire.
Méthodologie: L'étude se fait sur des patients symptomatiques à deux périodes différentes de l'année, dans le premier trimestre de 2014 et dans le dernier semestre de 2014. Cette étude comprend des données statistiques, par groupe d'âge et de sexe. Selon les données statistiques, on peut remarquer l'incidence des maladies respiratoires.
Résultats: Les résultats de l'étude sont exprimés grâce à des graphiques secteur qui montrent l'incidence de la pathologie respiratoire pour chaque segment de la population représentée dans cette étude. En outre, les données sont présentées pour chaque mois des deux périodes étudiées. Les données statistiques présentent l'incidence des maladies respiratoires pour sept groupes d'âge différent. L'incidence des maladies respiratoires est aussi exprimée dans les graphiques en secteur par genre féminin ou masculin pour chaque mois de l'étude. Dans ce cas, nous pouvons remarquer la variation de l'incidence des maladies respiratoires sur les femmes et les hommes.
Conclusions: Il est utile de considérer la mise en œuvre de méthode d'information du public et l'application pratique du programme de dépistage, de prévention, en ayant connaissance de la complexité des agents pathogènes pour une possible maladie respiratoire. Il est également connu que les enfants représentent un groupe vulnérable. Différents types des pathologies respiratoires sont la conséquence, ou peuvent se produire avec des infections sinusales.
Mots-clés: pathologie respiratoire, facteurs de risque, incidence, étude statistique, analyse de données

Correspondence address: *Antonella Chește, MD*
Basic, Prevéntive and Clinical Sciences Department
N. Bălcescu Str., no. 56, Brașov, Romania e-mail: anto.chesca@gmail.com

Introduction

The incidence of diseases that are part of the broad spectrum of the respiratory pathology is extensive [1,7]. This is due to various determinant risk factors which lead to the expansion of the disease sphere which affects the upper respiratory tract and can spread to the lower respiratory tract [18, 19].

The affectation of the respiratory system by pathogens includes a complexity of bacteria, viruses, fungi [9, 21]. Among the more frequent are: Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, the syncytial respiratory virus in children; in addition, infection with Mycobacterium tuberculosis cannot be excluded and this bacterium can potentially affect the health of all citizens [14, 24].

Respiratory pathology can often be the consequence or may occur in accordance with sinus infection, specially maxillary or frontal. This has been observed in patients of different ages, where children are the most vulnerable [11,17] . Also, it has been observed that there is an expansion of viral or infectious types of pathology encountered at the sinus level and which continues with pathology on the segments of the respiratory system [5, 22]. From this point of view we can see the association of different forms of sinusitis with bronchitis or sinusitis with viral or bacterial pneumonia [4,20].

Also, the human body, because of some personal factors or factors related to the environment, becomes vulnerable to different pathogens [10, 13]. Thus, at different periods of the year, when the human's body's resistance pathology decreases, the person can become vulnerable to Mycobacterium tuberculosis infection [12, 16].

For any of the forms belonging to the respiratory pathology, it is useful, in order to alleviate the symptoms and for cure, that the patients go to professional physicians once they observe the first signs of the disease [15,25]. This is useful in order to determine the appropriate therapy scheme after a competent preliminary investigation of the patient [6, 8, 23].

The efficiency of the medical act, in order to improve and heal the patients diagnosed with respiratory disease, depends on medical professionalism and patient's adherence to treatment [2, 3].

Material and Metod

This study includes statistical data on the incidence of the respiratory pathology, bacterial type, viral and mycotic, in two different periods during the year 2014. The study included patients who were assessed as symptomatic via a specialized medical unit. Data evaluation was undertaken by age and gender, respiratory diseases affecting both women and men. For comparison, for this study we took the medical data from the first trimester of 2014 and those of the last trimester of 2014. We have chosen these two seasonal periods of the year because during these months, the human body makes the subject of temperature variation as well as those of immunity, leading to susceptibility in respiratory tract disease occurrence.

Results

From statistical data drawn from the study it can be observed how the respiratory disease incidence varies by age groups. Categorizing the data into different age groups allows the respiratory diseases incidences to be assessed. Further analysis shows the breakdown of children, young people, adults of different ages and elder people. A further analysis of respiratory diseases incidence is shown by gender.

The study results are expressed in sector graphics which show the respiratory pathology incidence for each of the population segments included in this study. Also, the data are presented for each month of the two periods of study.

So, figure 1 presents the respiratory diseases incidence for the different age groups. From this point of view, it can be observed that in January 2014, the most affected by diseases of the respiratory system were the groups of people aged 40 – 59 years, with 618 diagnosed cases. This was followed by patients aged between 60-79 years, where there were 320 diagnosed cases.

Given that the respiratory diseases incidence affects both women and men, in January 2014, the male gender was more greatly affected; this fact is represented in figure 2. In context, 727 male and 668 female patients were diagnosed with respiratory diseases.

The number of respiratory diseases in February was greater for the age group of 40-59 years, by 474 cases. This was followed by the group with ages between 60-79 years, with 367 cases diagnosed with respiratory diseases. The data are presented in figure 3.

The diseases of the respiratory system in February were diagnosed almost equally for both genders, this fact is represented in figure 4: 600 female and 591 male patients.

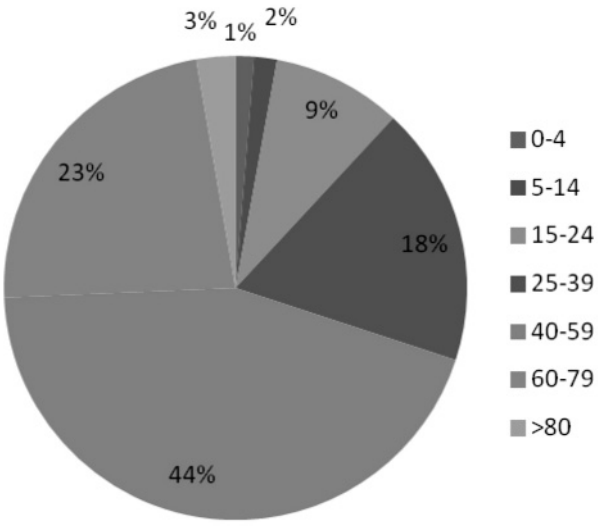

Figure 1 - Cases incidence by age group

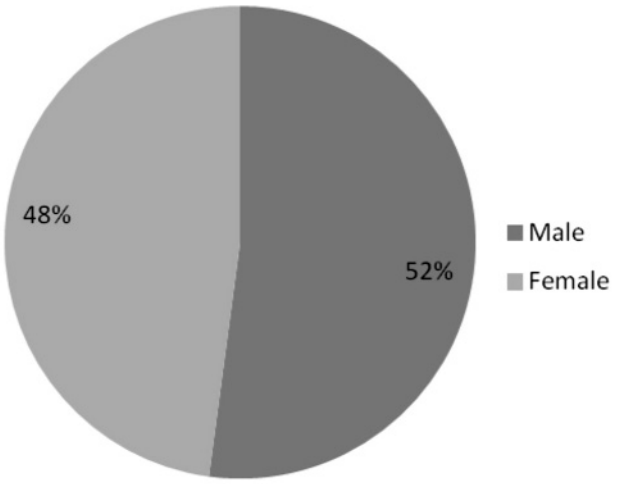

Figure 2 - Cases incidence by gender

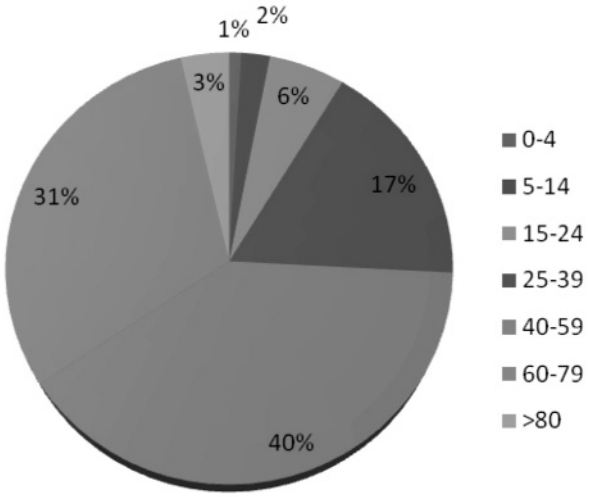

Figure 3 - Cases incidence by age group

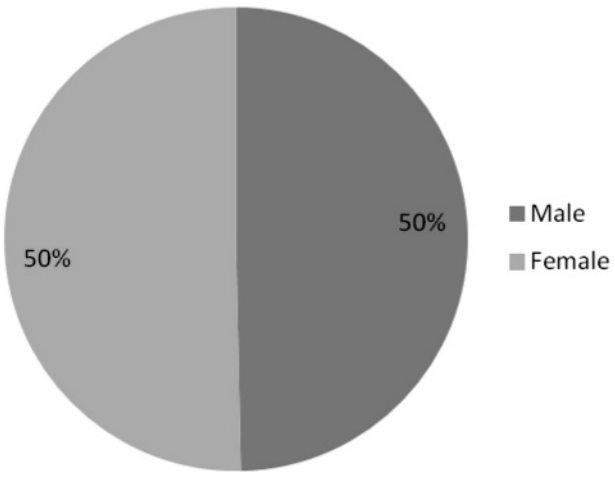

Figure 4 - Cases incidence by gender

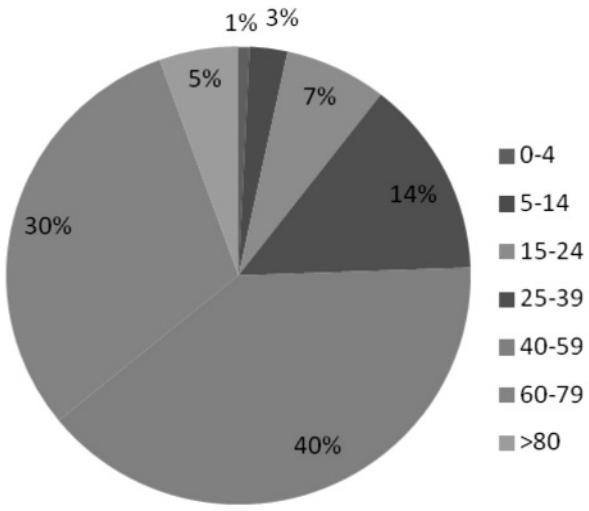

Figure 5 - Cases incidence by age group

The statistics showing the distribution of respiratory diseases for the last month of the first trimester of 2014, presented in figure 5. The same incidence as in previous months. Therefore, for the population segment aged between 40-59 years, there were 468 cases diagnosed and for the population segment aged between 60-79 years were 360 cases.

Respiratory pathology affected in March almost the same number of male and female patients, the incidence of these affections was a little higher in women. These data can be observed in figure 6 where there were 603 female patients and 579 male patients.

Data about the respiratory disease incidence during the months of the last trimester of 2014 are considered next.

According to the study idea, further data will be presented concerning the disease incidences which affects the respiratory system on the patients who have been

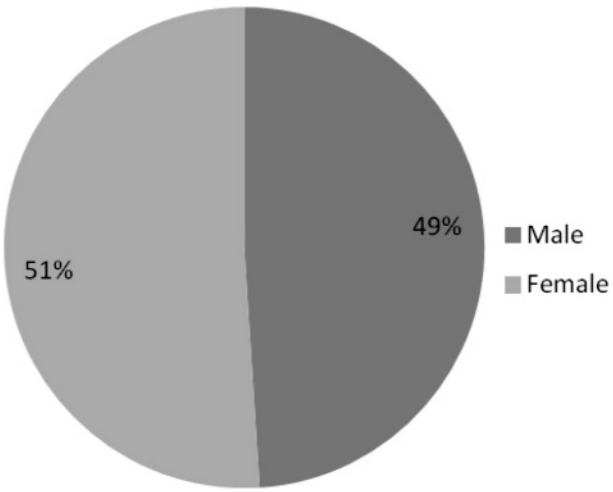

Figure 6 - Cases incidence by gender

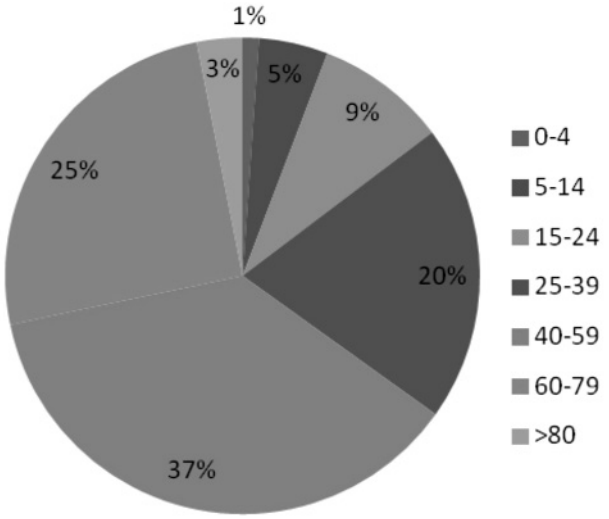

Figure 7 - Cases incidence by age group

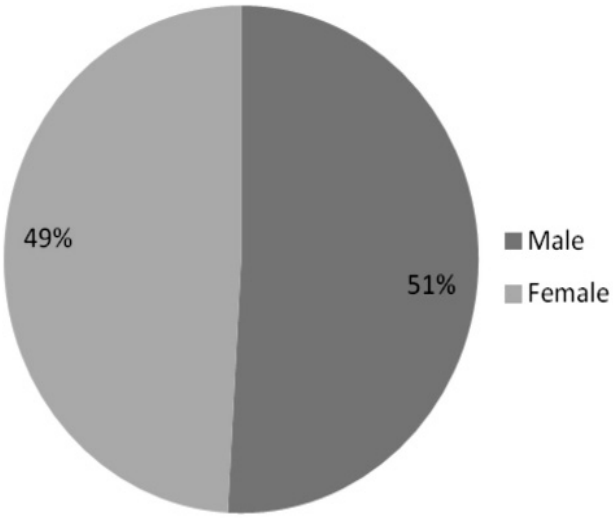

Figure 8 - Cases incidence by gender

presented to the specialty doctors during the last months of the last semester of 2014.

According to the statistic data, we can remark the high incidence on the same population segments as the previous ones. So, for October, the age group 40-59 years, allowed the diagnosis of 368 cases. This was followed by the age group 60-79 years, with 252 cases diagnosed with respiratory diseases. This is presented in figure 7.

Considering gender affection with respiratory diseases, in October 2014, both genders were equally exposed, with a slight difference, namely 509 cases in males and 491 cases in females. These data are presented in figure 8.

The incidence of the respiratory diseases in November changes the situation compared to the previous months analyzed in this study. So, if the most affected age group by respiratory diseases remains between 40-59 years with 489 diagnosed cases, this group is followed by the age group of 23-39 with 352 diagnosed cases. The presented data can be observed in figure 9.

The incidence of respiratory diseases by sex, in November 2014, it affects more the females, where there were 771 cases, compared to the male gender where there were 590 diagnosed cases. These data are presented in figure 10.

The incidence of respiratory diseases in December was of 381 cases diagnosed in the age group 40-59 years, almost equally, decreasingly followed by the age group 25-39 years with 157 diagnosed cases and the age group 60-79 years with 156 diagnosed cases. The data are presented in figure 11.

The incidence of the respiratory diseases by sexes, in December 2014, was higher in female gender, with 615 diagnosed cases comparatively to male gender with 236 diagnosed cases. These data are presented in figure 12.

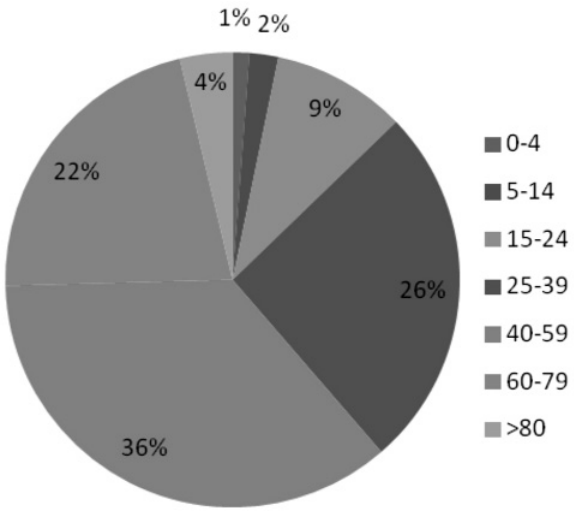

Figure 9 - Cases incidence by age group

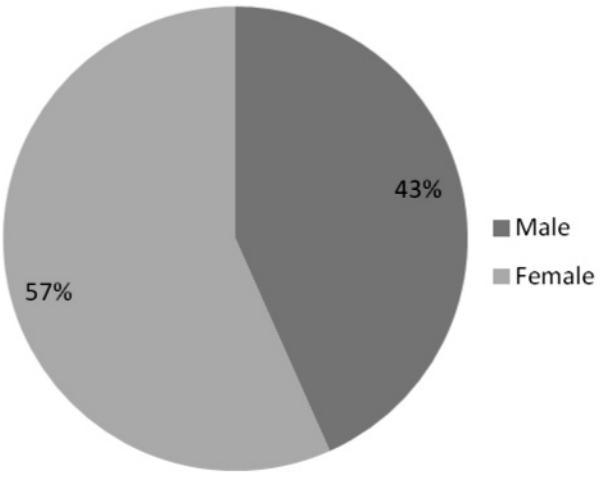

Figure 10 - Cases incidence by gender

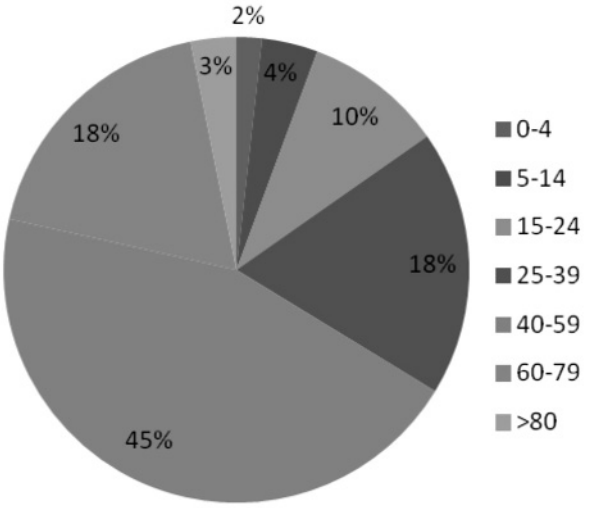

Figure 11 - Cases incidence by age group

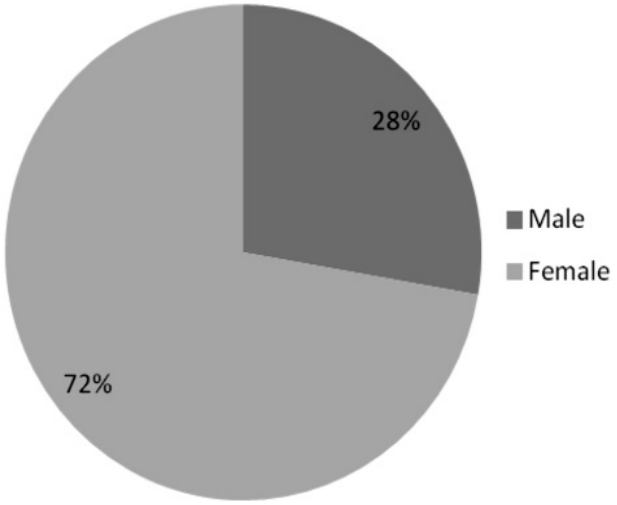

Figure 12 - Cases incidence by gender

CONCLUSIONS

The statistical analysis of the data in this study provides an overview of the incidence of respiratory disease across different seasonal periods. According to the data analysis conducted, it is important to establish and implement prevention and control measures. Therefore, it is prudent to consider implementing methods of public information and practical application of screening programs, concerning the health of each individual and the mass population. This is necessary, given that people of different ages spend most of the time in communities, which favors respiratory tract infections. Finally, we have to protect the family members who may be affected by lung diseases, given that the pathology of the respiratory system is readily transmissible.

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ORIGINAL PAPER

THE CORRELATION BETWEEN THROMBOCYTOPENIA AND SEVERITY OF ESOPHAGEAL VARICES

Liliana Dimitriu[1], Adina Stoica[2], V. C. Dimitriu[3]

[1]*UMF "Carol Davila", Clinical Hospital Colentina Gastroenterology, Bucharest*
[2]*Colentina Clinical Hospital Gastroenterology – Bucharest*
[3]*UMF "Carol Davila" - Clinical Hospital Coltea Surgery-Bucharest*

Summary

Background: The periodical evaluation of a cirrhotic patient depends on many aspects; one of them is the presence of severity signs on esophageal varices. This study investigated the association of thrombocytopenia (severe, moderate and mild) with severe esophageal varices, that will perhaps change the evaluation strategy.
Methods: Six hundred and fifty-seven patients with liver cirrhosis (no matter what the causes of it) hospitalized in Colentina Clinical Hospital, on Gastroenterology department, from 2012 until 2014, with esophageal varices diagnosed with endoscopy, were included.
Results: Four hundred forty-one patients from the total of six hundred and fifty-seven, had thrombocytopenia and the rest of them had normal blood platelet count. From those with normal thrombocytes count, fifty-four patients (21.68%) had severity signs of esophageal varices, and among those with cytopenia one hundred ninety-five (44.21%) had severity signs. The 441 cirrhosis patients with low platelet count were divided in three groups based on the cytopenia`s severity. In the first group (platelet count between 100000 and 150000) eighty-four patients had esophageal varices with severity signs (representing 43,75% of the total patients with severity signs). In the second group, (platelets between 50000 and 99000) there were sixty patients (32,25%) and among the third group (patients with severe thrombocytopenia, below 50000/mm^3) fifty one (80,95%) had severity signs of esophageal varices.
Conclusions: Low platelet count is associated more frequently with the presence of severe esophageal varices (that need treatment) than normal platelet count does. Among the low platelet count group of patients, only those with severe thrombocytopenia (below 50000/mm^3) had a statistical difference on the presence of severe esophageal varices. This study had shown that platelet count should be done periodically for cirrhosis patients and if the thrombocytes count is below 50000/mm^3 a new endoscopy should be perfomed even if the last procedure was recently done because the low value of

Résumé

La corrélation entre la thrombocytopénie et la sévérité des varices oesophagiennes

Contexte: L'évaluation périodique d'un patient cirrhotique dépend de nombreux aspects; l'un d'eux est la présence de signes de gravité sur les varices œsophagiennes. Cette étude a examiné l'association de la thrombocytopénie (sévère, modérée et légère) avec les varices oesophagiennes sévères, qui peut-être a changer la stratégie d'évaluation.
Méthodes: Six cent cinquante-sept patients atteints de cirrhose du foie (quelles que soient les causes de celle-ci) hospitalisés à l'Hôpital clinique Colentina, dans le département de gastro-entérologie, à partir de 2012 jusqu'en 2014, avec des varices oesophagiennes diagnostiqués par endoscopie, ont été inclus.
Résultats: Quatre cent quarante et un patients du total de 657, ont eu une thrombocytopénie et le reste d'entre eux avaient une numération plaquettaire normale du sang. De ceux qui comptent des thrombocytes normaux, cinquante-quatre patients (21,68%) avaient des signes de gravité de varices œsophagiennes, et parmi ceux avec thrombocytopénie 195 (44,21%) avaient des signes de gravité. Les 441 patients atteints de cirrhose avec une faible numération plaquettaire ont été divisés en trois groupes en fonction de la gravité de la thrombocytopénie. Dans le premier groupe (numération plaquettaire entre 100000 et 150000) quatre-vingt quatre patients avaient des varices œsophagiennes avec des signes de gravité (représentant 43,75% du total des patients avec des signes de gravité). Dans le second groupe, (plaquettes entre 50000 et 99000), il y avait soixante patients (32,25%) et chez le troisième groupe (patients présentant une thrombocytopénie sévère, ci-dessous 50 000 / mm^3) cinquante et un (80,95%) avaient des signes de gravité des varices oesophagiennes.
Conclusions: La faible numération plaquettaire est associée le plus souvent avec la présence de varices œsophagiennes sévères (nécessitant traitement) que la numération plaquettaire normale fait. Parmi le faible groupe de la numération plaquettaire des patients, seuls ceux présentant une thrombocytopénie sévère (ci-dessous

Correspondence address: *Dimitriu Liliana M.D.*
Str. Robanesti no 9, sect. 1, Bucharest *e-mail: lildimitriu@yahoo.com*

platelets is associated with increased incidence in severe esophageal varices that must be treated.
Key words: cirrhosis, thrombocytopenia, varices with severity signs

50 000 / mm³) avait une différence statistique sur la présence de varices œsophagiennes sévères. Cette étude a montré que la numération plaquettaire doit être faite périodiquement pour les patients atteints de cirrhose et si le nombre de thrombocytes est inférieur à 50 000 / mm³ une nouvelle endoscopie devra être réalisée même si la dernière procédure a récemment été faite parce que la faible valeur de plaquettes est associée à une incidence accrue dans les varices oesophagiennes sévères qui doivent être traitées.
Mots clés: cirrhose, thrombocytopénie, varices avec des signes de gravité

BACKGROUND

The periodical evaluation of a cirrhotic patient depends on many aspects; one of them is the presence of severity signs on esophageal varices. This study investigated the association of thrombocytopenia (severe, moderate and mild) with severe esophageal varices, that will perhaps change the evaluation strategy.

METHODS

Six hundred and fifty-seven patients with liver cirrhosis (no matter what the causes of it) hospitalized in Colentina Clinical Hospital, on gastroenterology department, from 2012 until 2014, with esophageal varices diagnosed with endoscopy, were included.

Severity signs are reprezented by:

- red signs(cherry-red spots) or wale mark, 2 mm large, produced by the extravasation of blood through the esophageal wall, between the varices and oesophageal mucosa;
- black signs that are older signs, with a lower risk of bleeding;
- whip sign that shows very tortuous venules, trademark for imminent bleeding.

RESULTS

Six hundred and fifty-seven patiens with liver cirrhosis and esophageal varices were included in our study. Four hundred forty-one patients had thrombocytopenia and the rest of them (two hundred sixteen) had normal blood platelet count (fig. 1):

Then the patients were divided into four groups based on the blood platelet count (fig. 2):

- First group – patients with normal blood platelet count ≥150000/mm³;
- Second group - mild thrombocytopenia: platelets between 100000-150000/mm³;
- Third group – moderate thrombocytopenia: 50000-100000/mm³ platelets;
- Fourth group – severe thrombocytopenia ≤ 50000/ mm³ platelets.

On every patient from our main group was perfomed upper gastrointestinal endoscopy, each patient had

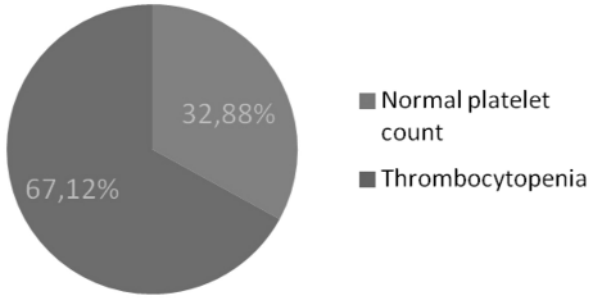

Figure 1 - Distribution of patients based on the existence or not of thrombocytopenia

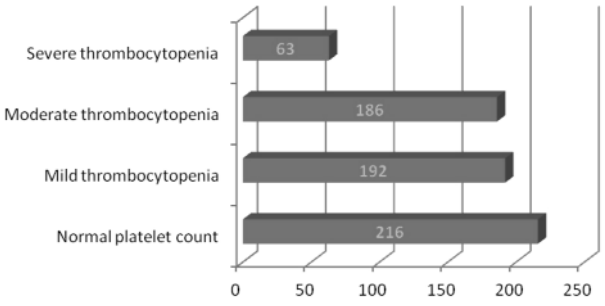

Figure 2 - Blood platelet count distribution in our main group

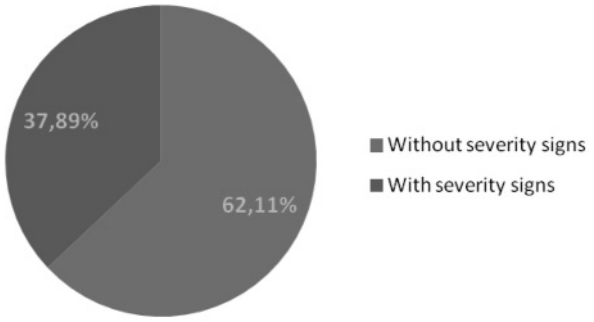

Figure 3 - The main group of patients divided on the severity signs

esophageal varices (this was a inclusion criteria). Only two hundred forty nine of them (37,89%) had severity signs. (fig. 3)

From the first group (patients with normal blood platelet

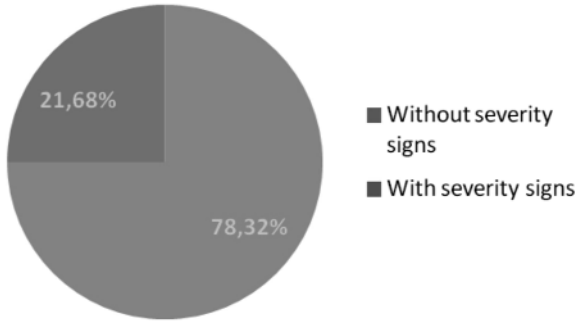

Figure 4 - Normal blood platelet count group divided based on the severity sign

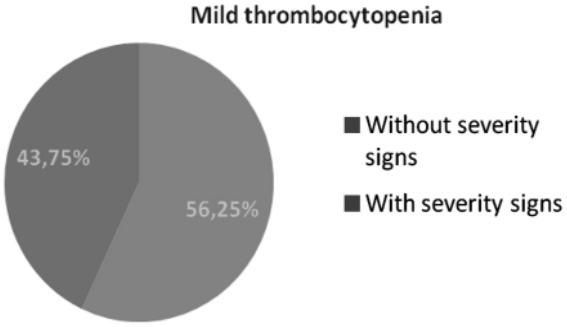

Figure 5

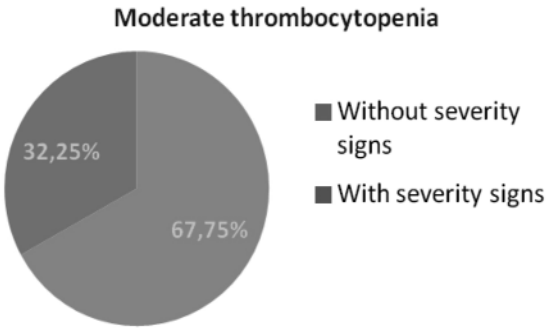

Figure 6

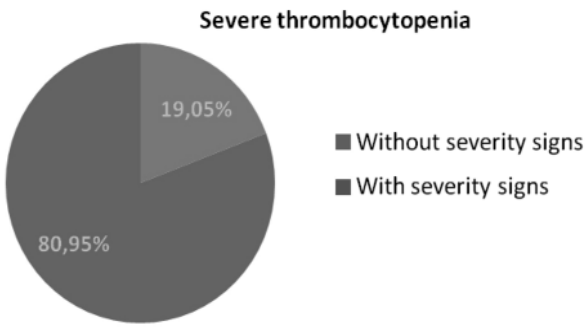

Figure 7

count) fifty four (21,68%) had severity signs and one hundred sixty-two (78,32%) didn't have severity signs. (fig. 4)

In the second group, only eighty-four patients (43,75%) had severity signs (fig. 5).

From the third group, with moderate thrombocytopenia (blood platelet count between 50.000-100.000), only sixty patients (32,25%) had severity signs. (fig. 6)

In the last group patients with severe thrombocytopenia, the majority of them had severity signs, from where we can conclude that the low number of platelet count may play a role on prediction of bleeding from the esophageal varices. (fig. 7, 8)

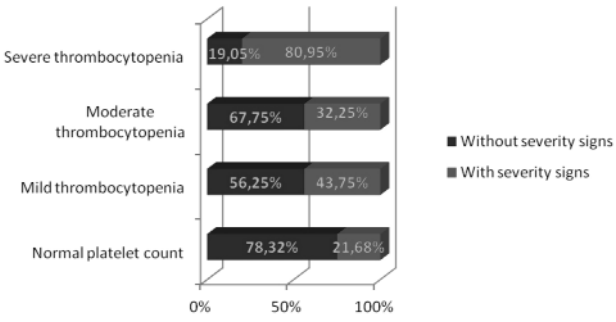

Figure 8

CONCLUSIONS

Low platelet count is associated more frequently with the presence of severe esophageal varices (that need treatment) than normal platelet count does. Among the low platelet count group of patients, only those with severe thrombocytopenia (below 50000/mm^3) had a statistical difference on the presence of severe esophageal varices. This study had shown that platelet count should be done periodically for cirrhosis patients and if the thrombocytes count is below 50000/mm^3 a new endoscopy should be perfomed even if the last procedure was recently done because the low value of platelets is associated with increased incidence in severe esophageal varices that must be treated.

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ORIGINAL PAPER

THE ROLE OF KINETIC THERAPY IN RHEUMATIC PATIENTS WITH SEVERE TEMPORO-MANDIBULAR JOINT DYSFUNCTION

Maria Daniela Crăciun

University "Ștefan cel Mare" Suceava

Summary

Introduction: Rheumatic diseases with temporo-mandibular joint location present raised morbidity indicators, potentially debilitating and severely deteriorating quality of life.
Material and methods: The study was carried out between January 2011 and March 2014 included 66 rheumatic patients with temporo-mandibular joint dysfunction: 32 patients with rheumatoid arthritis and 34 patients with osteoarthritis. The need of application for adapted kinetic treatment was required due to previous superficial treatments and targeted maintaining or restoring the functionality of temporo-mandibular joint.
Results: There was a significantly higher percentage of women in arthritis group (90.6%) (p = 0.001). On the studied cases, the average of the damage of the temporo-mandibular joint was 3.04 (± 2.20) in rheumatoid arthritis patients, and 2.93 (± 2.04) in patients with osteoarthritis. The average values are higher in VAS scores in patients with rheumatoid arthritis 6.53 (± 1.61) compared with patients with osteoarthritis 4.65 (± 1.18) (p = 0.001), and the development highlighted significant decrease in both groups (p = 0.001). The index ATM presented similar values at study onset: rheumatoid arthritis 15.41 (± 3.74), osteoarthritis 13.88 (± 3.40) (p > 0.01), the development highlighting significant decrease in both groups (P = 0.001).
Conclusions: Through a sustained and adapted kinetic treatment of clinical conditions one obtains diminishing symptoms, increasing local functionality and improvement quality of life of patients with severe rheumatic temporo-mandibular dysfunction.
Key words: temporo-mandibular joint, rheumatoid arthritis, osteoarthritis, kinetic treatment

Résumé

Le rôle du traitement kynésique aux patients rhumatoïdes avec une affection temporo-mandibulaire

Introduction: Les affections rhumatoïdes à localisation temporo-mandibulaire présentent des indicateurs élevés de morbidité, potentiellement déshabilitant et détériorent sévèrement la qualité de la vie.
Matériel et méthode: L'étude s'est déroulée pendant janvier 2011-mars 2014 sur 66 patients rhumatoïdes avec une affection temporo-mandibulaire: 32 patients avec arthrite rhumatoïde et 34 patients avec arthrose. La nécessité de l'application du traitement kinésique adapté s'est imposée comme une conséquence des traitements antérieurs superficiels et elle a visé le maintien ou le renouvellement de la fonctionnalité à niveau temporo-mandibulaire.
Résultats: Nous avons constaté un pourcentage plus élevé des femmes dans l'échantillon avec arthrite (90,6%), (p=0,001). Dans les cas étudiés, la durée moyenne d'affection de l'articulation temporo-mandibulaire a été de 3,04 (± 2,20) aux patients avec arthrite et de 2,93 (± 2,04) aux patients avec arthrose. Les valeurs moyennes du score VAS sont plus élevées aux patients avec arthrite 6.53 (±1.61) par rapport aux patients avec arthrose 4.65 (±1.18) (p=0,001) et l'évolution a mis en évidence des diminutions significatives pour les deux échantillons (p=0,001). L'index ATM a présenté des valeurs similaires au début de l'étude : l'arthrite 15.41 (±3.74), l'arthrose 13.88 (±3.40) (p>0,01), l'évolution mettant en relief des diminutions significatives dans les deux échantillons (p=0,001).
Conclusions: Par le biais d'un traitement kinésique soutenu et adapté à la situation clinique on obtient la diminution de la symptomatologie, l'augmentation de la fonctionnalité locale et de la qualité de la vie des patients rhumatoïdes avec une affection temporo-mandibulaire.
Mots-clés: articulation temporo-mandibulaire, arthrite rhumatoïde, arthrose, traitement kinésique

Correspondence address: *Daniela Crăciun, MD*
Universitatea Ștefan cel Mare Suceava, Romania *e-mail: daniela_mariacr@yahoo.com*

Introduction

Rheumatic diseases are pathological entities that affect the musculoskeletal apparatus, have raised indicators of morbidity, potentially debilitating and severely deteriorating quality of life. Temporo-mandibular joint (TMJ) develops in an increased proportion phenomena arthritic-destructive inflammatory arthritis that primarily generates pain, and significant functional repercussions. Inflammatory episodes of destructive processes are followed closely by destructive processes of cartilage and bone. (1)

TMJ osteoarthritis causes changes in the structure and shape of the disk peripheral thickening, thinning and central perforate it. At the edges of the joint bones surfaces productive reactions occur, deformation form of bone spurs and erosions causing pain and / or functional temporo-mandibular disorders (2).

The most common symptoms of the temporo-mandibular joint disorders (TMJD) are pain, limitation or asymmetrical jaw mobility, abnormal occlusion and joint noises. Pain is localized around the maxillary bones, temporo-mandibular joint and/or muscles of the face, head and neck that can associate headache, dizziness and tinnitus (3).

Material and Methods

In this context we conducted a comprehensive study outlining temporo-mandibular joint pain that occurs in conditions of rheumatic diseases.

The study was conducted from January 2011 to March 2014 and included 66 patients with severe rheumatic temporo-mandibular disorder: 32 patients with rheumatoid arthritis (RA) and 34 patients with osteoarthritis (OA).

The patients signed an informed consent form prior to study for clinical assessment, functional, laboratory and physical therapy treatment application.

Movement therapy, through its effects and noninvasive procedures applied may improve the existent symptoms in the temporo-mandibular joint and can change the patients' vision in relation to the disease.

This study aims to test certain kinetic methods that can lead to the decrease and combating temporo-mandibular symptoms.

Evaluation of patients was performed in collaboration with physician and included: assessment of pain intensity through VAS scale and evaluation of temporo-mandibular dysfunction through ATM index, which focused on testing the 14 parameters (pain intensity, pain duration, noise joint, morning stiffness, vicious habits, mobility of opening the mouth, laterality, protrusion, retraction, masseter, temporal, pterigoid internal, external pterigoid and sternocleidomastoidian muscles spasms)(4).

Kinetic methods and techniques have been applied especially in the soft parts:

- relaxing massage to combat muscle spasms in temporal, masseter, medial and lateral pterigoid (fig. 1), suprahioid, infrahioid, digastrics muscles (5,6);

Figure 1 - Massage in the lateral pterigoid

- techniques for detecting and treating trigger points on the face (fig. 2), head and neck (7);
- passive and active stretching by making mandible movements of descent, lateral, protrusion and retraction (active stretching on patient is made to the limit of the pain);
- active exercises to maintain and increase the range of motion (ROM) in temporo-mandibular joint (caudal traction movements (fig. 3), medial-lateral sliding movements inside and outside the mouth (fig. 4), sliding movements ventral)(8);
- strengthening resistive exercises for temporo-mandibular movements (in patients with osteoarthritis have been applied more unilateral maneuvers and maneuvers for patients with rheumatoid arthritis were applied bilaterally) (fig. 5);
- exercises for prevention of joint noises;
- corrective exercises for position of the head, neck and trunk (body right attitude and a normal position of the head, neck and torso favors combating of temporo-mandibular dysfunctions)(9);
- proprioceptive exercises of temporomandibular joint (isometric exercises coordination with mouth closed, with mouth slightly open, with mouth open, exercises to control certain joint and muscle

Figure 2 - The detection and treatment of painful points of the face

Figure 3 - Downward movement

Figure 4 - Lateral movements

asymmetry applied by manual control at the cranio-mandibular level, mouth opening exercises with the trunk inverted) (8,10).

The kinetic treatment was performed individually for 6 months according to the diagnosis, treatment final solution was chosen after detailed study of the case and after completing preliminary stages kinetic treatment itself. It is also very important to apply a kinetic treatment of the basic rheumatic diseases, degenerative or inflammatory.

All patients were initially evaluated and re-evaluated at 3 months and 6 months.

Statistical analysis

The data were systematized and processed in a centralized database using SPSS 13.0 confidence intervals at 95% significance threshold.

Results and Discussion

There was a significantly higher proportion of women in the two groups investigated RA 29 (90.6%) and OA 17 (50.0%) ($p = 0.001$).

The study groups, monitored the patients' age had the following characteristics: RA aged between 27 and 74 years (mean 52.50 ± 15.01); OA aged 35 to 79 years (mean 56.32 ± 12.70).

On the studied cases, the average of temporo-mandibular joint involvement was 3.04 (± 2.20) in RA patients and 3.37 (± 2.69) in patients with OA (table 1).

Statistical processing of data from clinical examination parameters emphasized significant changes in pain. The average values are higher VAS scores in patients with RA 6.53 (± 1.61) compared with patients with OA 4.65 (± 1.18) ($p = 0.001$) and developments revealed significant decreases in both groups ($p = 0.001$).

Regardless of the time of the study, the mean VAS scores were significantly higher in patients with RA ($p = 0.001$) (fig. 6).

Figure 5 - Exercises with bilateral resistance

Plotting the VAS score specificity ROC curve highlights the evolution of RA matter that is not noticed in patients with OA (fig. 7).

During monitoring, the mean index TMJ between groups did not differ significantly ($p > 0,05$), but developments TMJ index showed significant decreases both in groups RA ($p = 0.001$) and in the group with OA ($p = 0.001$).

TMJ Index showed similar values to the study onset RA 15.41 (± 3.74), OA 13.88 (± 3.40) ($p > 0,01$), showing significant decreases evolution in both groups ($p = 0.001$) (fig. 8).

TMJ Index shows a high specificity to the onset of osteoarthritis (fig. 9).

Table 1 - Characteristics of patients with rheumatic temporo-mandibular disorders

Parameters	Diagnosis		Tests significance	
	RA (N = 32)	OA (N = 34)	p value	IC95%
Gender Female n (%)	29 (90.6)	17 (50.0)	0001	1.81 * (1.27-2.58)
Age mean (± SD)	52.50 (15.0)	56.32 (12.70)	0267	51-58
Mean duration of involvement (± SD)	10.08 (6.25)	10.38 (5.87)	0839	8.76-11.71
TMJ lasting damage mean (± SD)	3.04 (2.20)	3.37 (2.69)	0591	2.60-3.81
Pain VAS mean (± SD)	6.53 (1.61)	4.65 (1.18)	0001	5.15-5.97
Algo-dysfunctional index mean (± SD)	15.41 (3.74)	13.88 (3.40)	0088	13.73-15.51

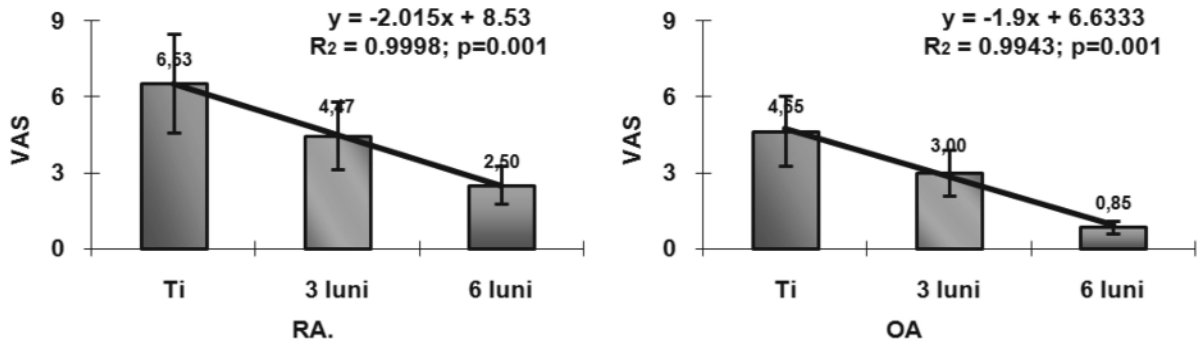

Figure 6 - Evolution of the average values of VAS scale by study groups

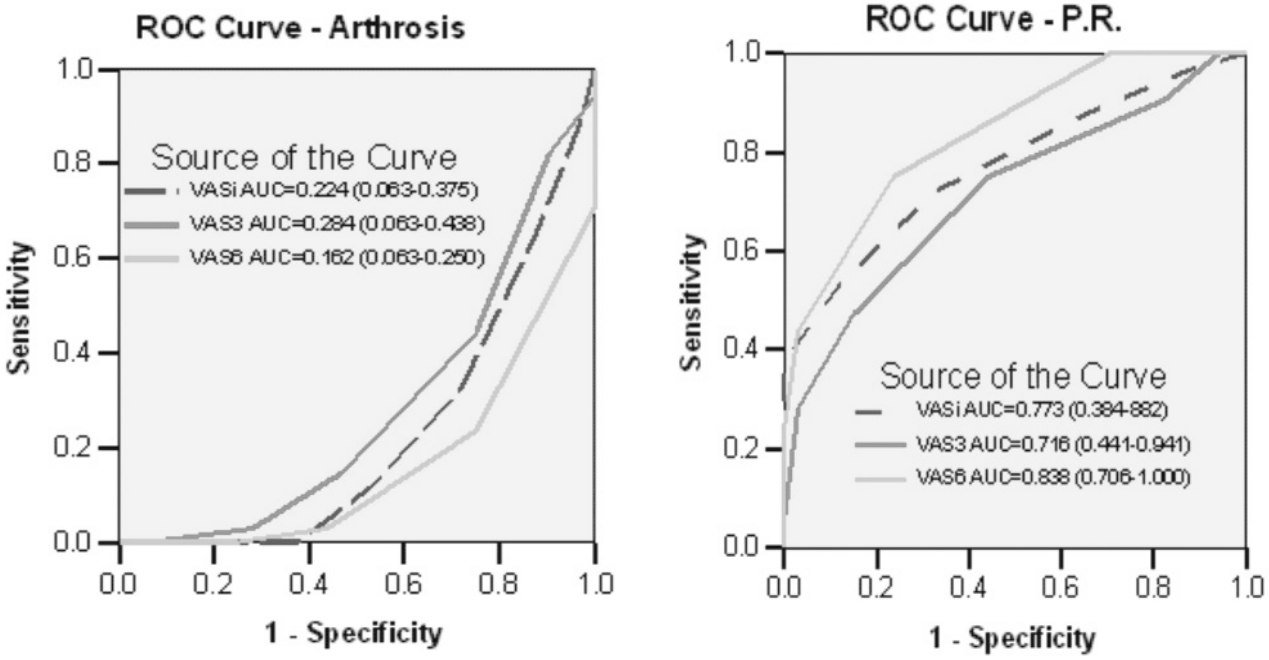

Figure 7 - Specificity and sensitivity of VAS score in RA and OA diseases

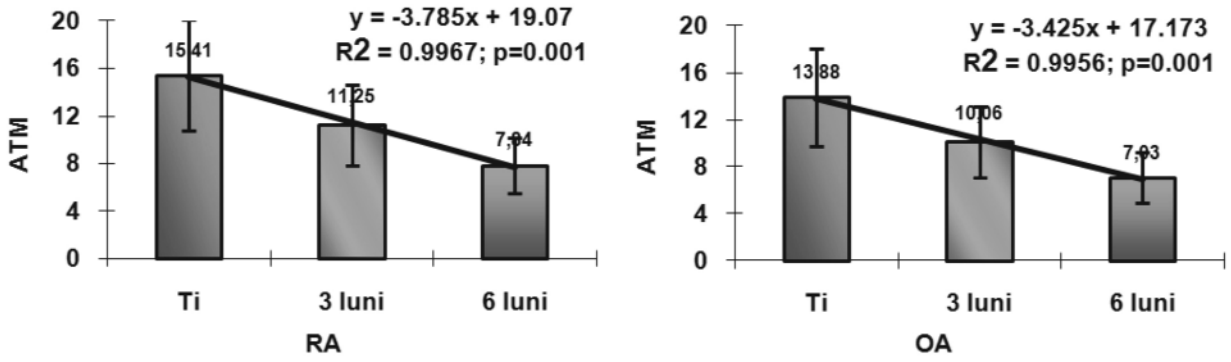

Figure 8 - Dynamics of the average values of the index TMJ by study groups

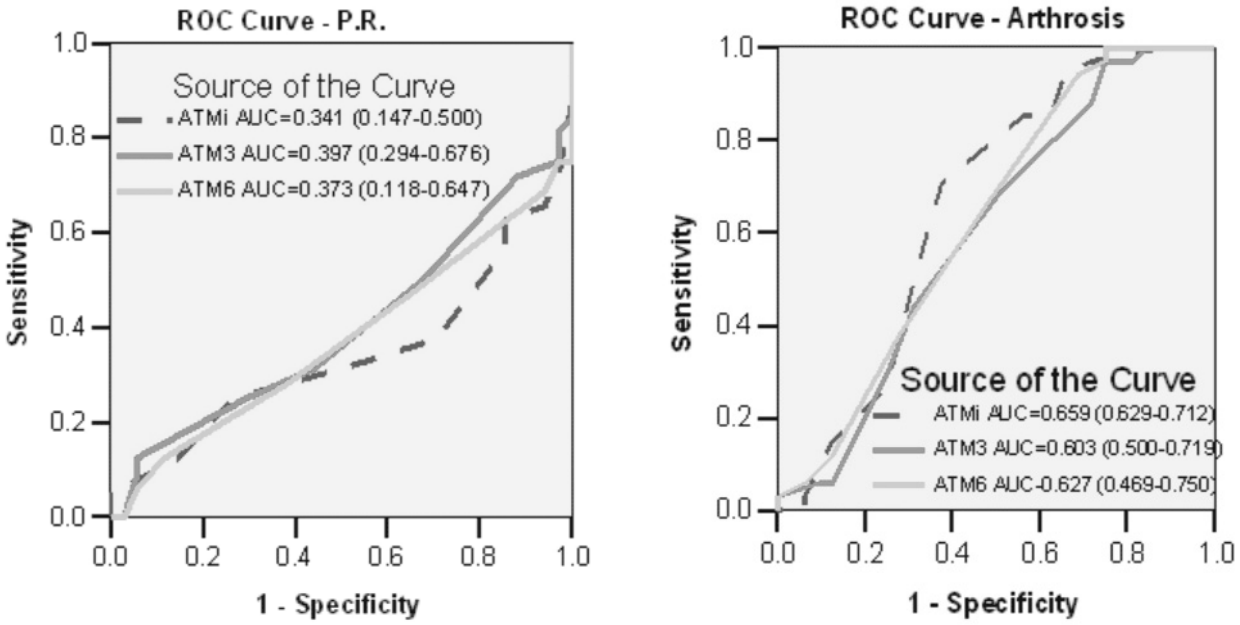

Figure 9 - Specificity and Sensitivity of TMJ index in RA and OA Diseases

Discussion

Patients with rheumatoid arthritis have an average of lower age and are mainly women; the data obtained is consistent with the literature data (1, 11).

Pain intensity is influenced by the type of rheumatic disease seen in the medium to high intensity values in patients with arthritis and mild to moderate values in patients with osteoarthritis.

In arthritis pain occurs in the early stage due to the existence of the inflammation process, compared with the osteoarthritis pain which occurs in the late stages being generated by altering joint elements and muscle dysfunction. In people with arthritis pain complains are longer and need more intense treatment, specific anti-inflammatory treatment is therefore very important. (2, 12)

Duration of pain can influence the estimation of pain intensity on VAS scale, being overrated when pain persists for shorter period or underrated when the pain duration is longer (13).

After the first weeks of treatment pain score decreases but needed lengthy treatment for controlling symptoms. In patients with osteoarthritis pain decreased significantly but remains the clicking and joint noises that are specific degenerative process (14).

The applied cranial and intraoral manual techniques aim to improve oral-facial dysfunction (15) evaluated using TMJ index, which centralizes data on the intensity and nature of pain, joint noise, amplitude of movement joints, masticators muscles tone, bad habits. Initially TMJ index was higher in patients with rheumatoid arthritis but development index decreased both in patients with rheumatoid

arthritis as well as in patients with osteoarthritis, failure is below 25% at the end of treatment.

Conclusions

Through a sustained and adapted kinetic treatment the clinical situation is obtained reducing painful symptoms, increasing the local functionality and quality of life of patients with temporo-mandibular rheumatic disorders.

Kinetic reeducation in patients included in the study favored obtaining a good posture of the head, neck and torso, achieving chewing, swallowing, and normal breaths, increase joint mobility, combat neuromuscular imbalances;

TMJ index showed a decrease of malfunction after kinetic treatment leading to an increase in physical and psychological comfort of patients.

The kinetic treatment stimulates proprioception, prevents the formation of adhesions process, prevents osteoporosis, stimulates the secretion of synovial fluid, relieves pain and increases functionality at the local orofacial level.

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ORIGINAL PAPER

STATISTICAL STUDY OF PRIMITIVE MALIGNANT LUNG TUMORS AT THE EMERGENCY UNIVERSITY HOSPITAL BUCHAREST

Ionela Hulea[1], Maria Sajin[2]

[1]*Micomi Clinic, Bucharest, Romania*
[2]*The University Emergency Hospital Bucharest, Romania*

Summary

Lung cancer is one of the most common malignancies worldwide, with a growing incidence. If at first incidence was more common in men, now report men - women tend to equalize, mainly due to the increasing number of women who smoke (1,2). In the developed, industrialized countries, the percentage of deaths from lung cancer is higher than in developing countries (22% versus 14.6%). 5-year survival rate of stage I patients is approximately 70% and 90% with IA (4). In terms of cancer deaths, lung cancer ranks first in men and fourth in women, the most common cause of cancer death in the US (1). This study is based on the clinic's practice of Thoracic Surgery and Department of Pathology of Bucharest University Emergency Hospital between January 2006 - February 2009. Were included in the study all patients with pneumonectomy, lobectomy or segmentectomie. It was followed: tumor distribution by age, sex, the area of origin, the main symptoms, histology and tumor stage.
Key words: lung cancer, age, gender, provenance, tumor stage, histology

Résumé

Etude statistique des tumeurs pulmonaires malignes primaires faite à l'Hôpital Universitaire d'Urgence de Bucarest

Le cancer du poumon est l'une des tumeurs malignes les plus courantes dans le monde entier, avec une incidence croissante. Si à première incidence il était plus fréquent chez les hommes, à présent le rapport entre les hommes et les femmes tend à s'égaliser principalement en raison de l'augmentation du nombre de femmes qui fument (1.2). Dans les pays développés et industrialisés, le pourcentage de décès par cancer du poumon est plus élevé que dans les pays en développement (22% contre 14,6%). Le taux de survie à 5 ans des patients à un stade I est d'environ 70% et 90% avec des IA (4). En termes de décès par cancer, le cancer du poumon occupe la première place chez les hommes et la quatrième chez les femmes, la cause la plus fréquente de décès par cancer aux États-Unis (1). Cette étude est basée sur la pratique de la clinique de chirurgie thoracique et du département de pathologie de l'hôpital d'urgence Université de Bucarest entre Janvier 2006 - Février 2009. Ont été inclus dans l'étude tous les patients avec une pneumonectomie, lobectomie ou segmentectomie. Ils ont suivi: la distribution de la tumeur par l'âge, le sexe, la région d'origine, les principaux symptômes, l'histologie et le stade de la tumeur.
Mots-clés: cancer du poumon, l'âge, le sexe, la provenance, le stade de la tumeur, l'histologie

Introduction

Lung cancer is a global health problem. The main etiologic factor is smoking (3,4,5). Non-smoking lung cancer is about 15% of all malignant lung tumors, and it is caused by exposure to asbestos, radon, air pollutants, viruses - Human papilloma virus, genetic factors (1). Diagnosis is based on clinical examination in conjunction with X-ray examination, bronchoscopy, CT and histopathology exam. Cytological

Correspondence address: *Ionela Hulea, MD*
Micomi Clinic, Bucharest, Romania
e-mail: dr.ionelahulea@yahoo.com

examination of sputum may have important role in early diagnosis of malignant pulmonary lesions. The treatment is surgical along with chemotherapy and / or radiotherapy (1).

Material and Method

Were analyzed in the study the malignant lung tumors from January 2006 to February 2009 using information obtained from observation sheets of Thoracic Surgery Clinic and the database of the Department of Pathology University Emergency Hospital Bucharest.

Distribution of cases were followed depending on age, gender, main symptoms, living and working conditions (smoking, toxic,radiation),tumor stage, tumor location and histological appearance.

Lung biopsies were excluded from the study.

After macroscopic examination of the surgical resection piece fragments were collected from different parts of the tumor, the limit bronchial resection and whole lymphatic tissue identified. Subsequently, by the proper processing, specimens were made 3 micron sections which were stained with standard hematoxylin-eosin (HE).

Histopathological classification was made according to WHO 2004 (1).

Results

The analysis of observation sheets and stained histopathological Hematoxylin - Eosin preparations have revealed the following:

- of the 42 patients operated in Department of Thoracic Surgery of University Emergency Hospital in Bucharest from January 2006 to February 2009 most were from sixth decade (fig. 1) and from urban areas (86%) (fig. 2).

Regarding patient distribution by sex it showed that 90% were men (fig. 3), smokers 64% (25 men and 2 women) and 11% were former smokers. 9.5% had a history of pulmonary tuberculosis and 7% worked in a toxic environment.

In what concerns the symptomatology at the moment of hospitalization the most presented symptoms were expectoration cough, thoracic discomfort and fatigue. 9.5% upon admission showed symptoms of pneumonia (fig. 4).

From the point of view of the tumoral stage most of the tumors were diagnosed in stage I (43%) and II (43%). Only 3 tumors were diagnosed in stage III (7%), and three in stage IV (7%). The three tumors stage IV were identified in three and second decade of age. The most common tumors were in the V-th decade (48%).

In terms of histological type, using the WHO classification 2004, were identified the following tumor types (fig. 5):

- squamous cell carcinoma;
- adenocarcinomas;
- neuroendocrine carcinomas;
- sarcomatoid carcinoma;
- adenosquamous carcinoma;

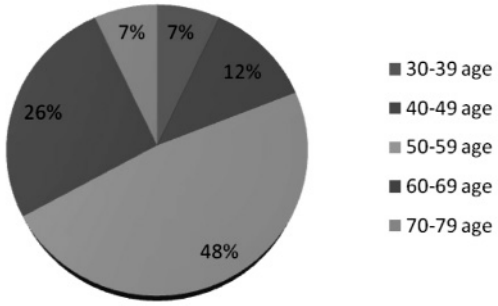

Figure 1 - Distribution of cases by age

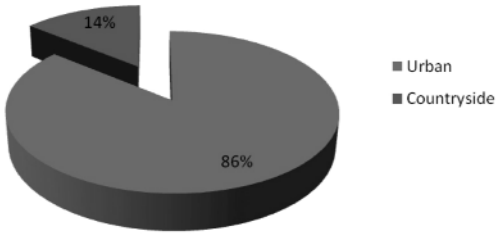

Figure 2 - Distribution of cases by area of origin

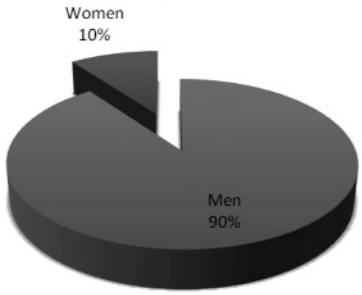

Figure 3 - Distribution of cases by sex

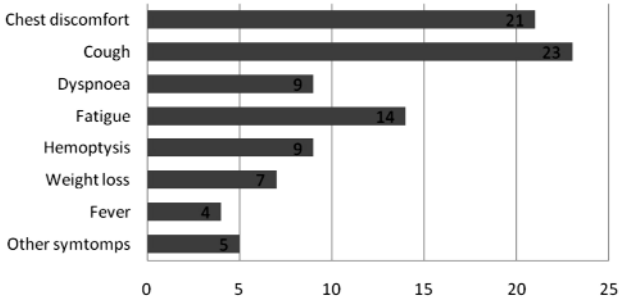

Figure 4 - Distribution of cases by hospitalization reasons

- adenoid cystic carcinoma.

Tumor size ranged between 1.8 cm and 13 cm.

The analysis of the data reveals that the most frequent malignant lung tumors is in the decade VI, here being the most squamous cell carcinomas. Regarding tumor stage most tumors were diagnosed in the early stages (I and II), and 4.7% were in stage IV.

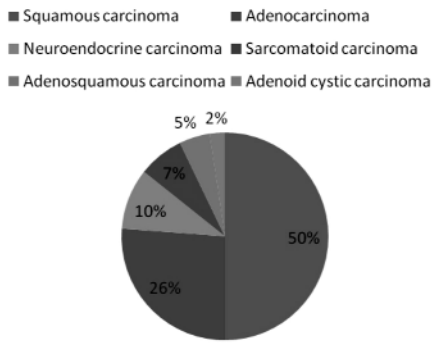

Figure 5 - The distribution of tumors according to the histopathological type

DISCUSSIONS

The analysis of these data shows that most lung tumors occurred in sixth decade of age, is more common in men and in urban areas. Most symptoms were cough with expectoration, chest discomfort and fatigue. Four patients were hospitalized for another disease (diabetes mellitus, menometrorrhagia), and were subsequently transferred to the Department of Thoracic Surgery for thoracic surgery. Of these 2 patients were diagnosed with lung cancer stage II B, one patient in stage IA and one in IB; the histopathologic type these patients had sarcomatoid carcinoma, moderately differentiated squamous cell carcinoma, lung carcinoid and pleomorphic carcinoma. Regarding histological type and age the most common tumors are moderately differentiated squamous carcinomas (the decade IV, V, VI and VII).

At the age group 30-39 years all the tumors were well differentiated, including squamous cell carcinoma, adenocarcinoma and typical carcinoid, as histological type. In decade V were identified two moderately differentiated squamous carcinomas, one poorly differentiated adenocarcinoma, an adenosquamous carcinoma and a typical carcinoid.

For the 50-59 years group age: 3 sarcomatoid carcinomas, 7 squamous carcinomas (6 moderately differentiated and one well differentiated squamous cell carcinoma), adenoid cystic carcinoma, large cell carcinoma, 7 adeno-carcinoma (of which 2 well-differentiated) and 2 sarcomatoid carcinomas. For VII-th decade: 6 squamous carcinomas, 2 adenocarcinomas and 2 large cell carcinomas; in the decade VIII were diagnosed only squamous cell carcinoma. Regarding the degree of differentiation 2 were moderately differentiated and one poorly differentiated.

It is known that tumor stage is an important prognostic factor; the survival rate is influenced by histopathological type and sex (6).

CONCLUSIONS

Identifying the factors contributing to lung cancer appearence and its diagnosis in early stages is one mean of decreasing mortality. Physical examination, as well as an adequate communication between specialists may contribute to the decresing of mortality.

Patients with long survival rate are diagnosed in the early stages, indicating the need of diagnosis in early stages, preclinical and treating neoplastic lesions.

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ORIGINAL PAPER

LIPID PROFILE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Georgiana Damache[1], Adina Petcu[2], Mihaela Başa[3], Natalia Roşoiu[4]

[1]*Ovidius University, I.O.S.U.D (Organizing Institution of Doctoral Studies), Constanța, Romania*
[2]*Ovidius University, Faculty of Pharmacy, Department of Biophysics and Biostatistics, Constanța, Romania*
[3]*Emergency Military Hospital, Clinical Laboratory, Constanța, Romania*
[4]*Ovidius University, Faculty of Medicine, Department of Biochemistry, Constanța, Romania*
Academy of Romanian Scientists, Bucharest, Romania

Summary

Background: Dyslipidemia is the primary risk factor for cardiovascular disease in diabetes mellitus. The impact of clinical factors that may coexist with diabetes such as hyperglycemia, hyperlipidemia and obesity favors the development of cardiovascular disease (CVD), the most prevalent cause of mortality among people with type 2 diabetes mellitus (T2DM). This study was conducted to detect the lipid profile abnormality of diabetic patients and compare them with healthy controls in order to demonstrate the increased prevalence of diabetics for atherogenic cardiovascular disorder.
Methods: Monitoring of lipid profile was performed by analyzing serum total cholesterol (TC), high density lipoprotein - cholesterol (HDL-C), low density lipoprotein - cholesterol (LDL-C) and triglycerides (TG). Atherogenic index (AI) has also been used to predict the risk of atherosclerosis. We examined for dyslipidemia a total of 116 diabetic patients and randomly selected 24 healthy subjects with no history of diabetes used as controls. The aim of the study was explained to the subjects and those who gave their consent were included in it.
Results: There were statistically significant increases ($p < 0.000$) in TC, LDL-C, TG and AI and a statistically significant decrease ($p < 0.000$) in HDL-C in T2DM patients when compared with healthy subjects. Correlation studies indicated a positive correlation of atherogenic index and age.
Conclusions: The results of this study highlight the strong correlation between atherogenic cardiovascular disorder and diabetes, suggesting the increased prevalence of diabetics to develop a CVD. The management of diabetic dyslipidemia is a key approach in preventing CVD in individuals with T2DM.
Key words: atherogenic index, dyslipidemia, lipid profile, type 2 diabetes mellitus

Résumé

Le profil lipidique chez les patients avec du diabète sucré de type 2

Contexte: La dyslipidémie est le principal facteur de risque pour les maladies cardiovasculaires dans le diabète sucré. L'impact des facteurs cliniques coexistent avec le diabète tels que l'hyperglycémie, l'hyperlipidémie et l'obésité favorisant le développement des maladies cardiovasculaires (MCV), la cause la plus fréquente de mortalité chez les personnes atteintes de diabète de type 2 (DT2). Cette étude a été réalisée pour détecter des anomalies du profil lipidique des patients diabétiques et les comparer avec des témoins sains afin de démontrer la prévalence accrue des diabétiques pour des troubles cardiovasculaires athérogènes.
Méthodes: La surveillance du profil lipidique a été réalisée en analysant le cholestérol total (CT), dans le sérum, le choléstérol (HDL-C) des lipoprotéines de haute densité, le cholestérol (LDL-C) des lipoprotéines de faible densité et les triglycérides (TG). L'indice athérogène (AI) a également été utilisé afin de prédire le risque d'athérosclérose. Nous avons examiné pour la dyslipidémie un total de 116 patients diabétiques et choisi au hasard 24 sujets sains sans antécédents de diabète utilisés comme témoins. L'objectif de l'étude a été expliqué aux sujets et ceux qui ont donné leur accord y ont été inclus.
Résultats: Il avait des augmentations statistiquement significatives ($p < 0{,}000$) du TC, LDL-C, TG et AI et une diminution statistiquement significative ($p < 0{,}000$) du taux de HDL-C chez les patients avec DT2 en comparaison avec les sujets sains. Les études de corrélation révèlent une corrélation positive de l'indice athérogène et l'âge.
Conclusions: Les résultats de cette étude soulignent la corrélation forte entre la maladie cardiovasculaire et le diabète, suggérant la prévalence accrue des adultes atteints de diabète à développer une maladie cardiovasculaire. La gestion de la dyslipidémie diabétique est une approche clé dans la prévention de MCV chez les individus atteints de DT2.
Mots clés: indice athérogène, la dyslipidémie, le profil lipidique, diabète de type 2

Correspondence address: *Georgiana Damache PhD*
Ovidius University, I.O.S.U.D (Organizing Institution of Doctoral Studies)
Doctoral School of Applied Sciences, Department of Biochemistry
Blvd Mamaia 124, Constanța, Romania e-mail: damache.geo@gmail.com

INTRODUCTION

The chronic hyperglycemia resulting from defects in insulin secretion or action is in diabetes associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. We demonstrated in our previously published article (1) that blood glucose concentration increases with age, as a result of developing metabolic complications (vascular disease, peripheral neuropathy, retinopathy, nephropathy, and predisposition to infection). Moreover hyperglycemia, is not only a risk factor which favors the development of cardiovascular disease, it also contributes to myocardial damage after ischemic events (2).

Patients with type 2 diabetes have also increased risk of cardiovascular disease associated with atherogenic dyslipidemia (3). Clinically, dyslipidemia increases the risk of atherosclerosis which in turn increases the risk of cardiovascular disease, and up to 97% of patients with diabetes are dyslipidemic (4). Dyslipidemia is characterized by elevation of plasma cholesterol, triglycerides, or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis of which causes may be primary (genetic) or secondary.

Atherosclerosis is the cause of death in 75-80% of adults with type 2 diabetes (5). At diagnosis, 30% of the patients have already some evidence of established coronary heart disease (6).

The most typical lipoprotein pattern in diabetes, also known as diabetic dyslipidemia or atherogenic dyslipidemia consists of moderate elevation in triglyceride levels, low HDL cholesterol values, and small dense LDL particles (7). A main cause of the elevated TG concentration is overproduction of very-low-density lipoprotein (VLD L) in the liver, provoked by an increased flow of glucose and free fatty acids (FFA) (8). Additionally, there may be reduced catabolism of the triglyceride rich lipoproteins, including VLDL and chylomicrons, due to the altered activity of lipoprotein lipase (LPL). LPL in adipose tissue is controlled by insulin and its activity may be reduced by prolonged insulin deficiency or decrease in insulin action (9).

The predominant form of LDL cholesterol in diabetics is the small, dense form. These small dense LDL particles are more atherogenic than the larger, more susceptible to oxidation, and with an increased affinity for the arterial wall because they can more easily penetrate and form stronger attachments (10). Oxidized LDL produces attract leukocytes to the intima of the vessel, improving the ability of the leukocytes to ingest lipids and differentiate into foam cells, stimulating the proliferation of leukocytes, endothelial cells, and smooth muscle cells, all of which are steps in the formation of atherosclerotic plaque (11).

Hyperinsulinemia is also associated with low HDL cholesterol levels (12, 13). The increased number of VLDL cholesterol particles and increased plasma triglyceride levels decrease the level of HDL cholesterol and increase the concentration of small dense LDL- cholesterol particles via several processes (14).

The alteration of lipid metabolism in type 2 diabetics has raised a serious medical concern with respect to vascular complications like coronary artery disease and cerebro vascular diseases. The recommendation of greater routine evaluation of serum lipid profile, its treatment and good glycemic control in patients with type 2 diabetes mellitus is strongly suggested (15).

The present study was designed to evaluate atherogenic lipid profile (serum TC, HDL-C, LDL-C and TG levels) and the pattern of dyslipidemia in type 2 diabetics in order to demonstrate the increased prevalence of diabetics for atherogenic cardiovascular disorder.

MATERIALS AND METHODS

The study was performed in collaboration with Constanța Emergency Military Hospital. We examined for dyslipidemia a total of 116 diabetic patients (57 females and 59 males) with age ranging between 35 and 75 years and with history of diabetes for more than 3 years (table 1). Were randomly selected 24 (10 females and 10 males) healthy subjects with no history of diabetes and used as controls. The aim of the study was explained to the subjects and those who gave their consent were included in it.

Blood samples were collected from all the subjects after at least 8 hours fasting using venous blood collection tubes without anticoagulant. It was allowed to clot and then centrifuged at 3400 rpm for 10 min at 4°C.

Table 1 - Baseline characteristics of all study groups

			Gender		Total
			Masculine	Feminine	
Group	T2DM	Count	59	57	116
		Age range (years)			
		(34-55]	26	24	50
		[55-76)	33	33	66
	Control	Count	12	12	24
		Age range (years)			
		(34-55]	6	5	11
		[55-76)	6	7	13
Total	Count	71	69	140	
	% of Total	50.7%	49.3%	100.0%	

Total cholesterol

Cholesterol is a steroid synthesized in many types of tissue, but particularly in the liver and intestinal wall. Approximately three quarters of cholesterol is newly synthesized and a quarter originates from dietary intake. Cholesterol assays are used for screening for atherosclerotic risk and in the diagnosis and treatment of dyslipidemias.

Serum cholesterol level was measured using an enzymatic and colorimetric method. Cholesterol esters are hydrolyzed by cholesterol esterase. Cholesterol oxidase then catalyzes the oxidation of cholesterol to cholest-4-en-3-one and hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide formed effects the oxidative coupling of phenol and 4-aminophenazone to form a red quinine-imine dye. The color intensity of the dye formed is directly proportional to the cholesterol concentration. It is determined by measuring the increase in absorbance between 500–550 nm.

HDL-cholesterol

High density lipoproteins (HDL) are responsible for the reverse transport of cholesterol from the peripheral cells to the liver. Here, cholesterol is transformed to bile acids which are excreted into the intestine via the biliary tract. Monitoring of HDL-cholesterol in serum is of clinical importance considering that elevated HDL-cholesterol concentrations are inversely correlated with risk of atherosclerotic disease.

HDL-cholesterol concentration was determined following a homogeneous enzymatic colorimetric test. The cholesterol concentration of HDL-cholesterol is determined enzymatically by cholesterol esterase and cholesterol oxidase coupled with polyethylene glycol (PEG) to the amino groups (approx. 40%). Cholesterol esters are broken down quantitatively into free cholesterol and fatty acids by cholesterol esterase. In the presence of oxygen, cholesterol is oxidized by cholesterol oxidase to Δ4-cholestenone and hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide generated reacts with 4-amino-antipyrine and HSDA (Sodium N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline) to form a purple-blue dye. The color intensity of this dye is directly proportional to the cholesterol concentration and is measured photometrically at 600 nm.

LDL-cholesterol

Low Density Lipoproteins (LDL) plays a key role in causing and influencing the progression of atherosclerosis and, in particular, coronary sclerosis. The LDLs are derived from VLDLs (very low density lipoproteins) rich in triglycerides by the action of various lipolytic enzymes and are synthesized in the liver.

LDL-Cholesterol was estimated by using Friedewald's formula (16) as it has been shown below:

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - (\text{TG}/5).$$

Triglycerides

Triglycerides are esters of the trihydric alcohol glycerol with 3 long-chain fatty acids. They are partly synthesized in the liver and partly ingested in food. The determination of triglycerides is utilized in the diagnosis and treatment of patients having diabetes mellitus, liver obstruction, lipid metabolism disorders and numerous other endocrine diseases.

This method is based on enzymatic colorimetric test. Triglycerides in the serum sample are hydrolyzed enzymatically by the action of lipase to glycerol and fatty acids. The glycerol formed is converted to glycerol phosphate by glycerol kinase (GK). Glycerol phosphate is then oxidized to dihydroxyacetone phosphate by glycerol phosphate oxidase (GPO). The librated hydrogen peroxide is detected by a chromogenic acceptor, chlorophenol-4-aminoantipyrine, in the presence of peroxidase (POD). The red quinone formed is proportional to the amount of triglycerides present in the sample and is measured at 546 nm.

Atherogenic index

Atherogenic index (AI) is calculated in an attempt to predict cardiovascular risk. AI is based on the ratio of the values of triglycerides to high-density lipoprotein levels (AI—the ratio TG/HDL-C) (17). AI is a surrogate of small LDL particle size, reflects obesity and hyperinsulinemia. It predicts coronary heart disease independently, type 2 diabetes mediated by obesity in men and women, high blood pressure, and metabolic syndrome (18).

Tests were performed with Cobas Hitachi c 501 (Roche) automated analyzer, based on assays and reagent system (Roche Diagnostics).

Statistical methods

The values of all the parameters were given in mg/dL and they were expressed as mean ± standard deviation (SD). The statistical significance of the difference between the Control and the study groups were evaluated by the Student's t-test. Pearson's correlation test was performed to examine various correlations.

Independent samples t-test (2-tailed) was used to compare means of different parameters. The results were considered non-significant when $p > 0.05$ and significant when $p < 0.05$. Statistical analyses were performed by using SPSS statistical package software version 17.0.

Results and Discussions

During the study period, a total of 140 subjects (69 females and 71 males) were evaluated for lipid profile. Subjects were grouped: 116 patients with diabetes mellitus (82,9%) and 24 controls (17,1%). The mean age ± SD for the subjects was 57,22 ± 9,67 years (female 58,51 ± 10,03 / male 55,98 ± 9,23) and 53,75 ± 8,48 years (female 54,08 ± 8,57 / male 53,42 ± 8,75) for type 2 diabetes mellitus (T2DM) and Control groups respectively. Gender distribution showed an approximately equal number of males and females in all the groups.

In the present study were used as maximum and minimum biological limits reference values according to the

National Cholesterol Education Program, Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) in order to make comparisons between individuals with type 2 diabetes and healthy people.

The mean values for all biochemical variables (TC, HDL-C, LDL-C, TG and AI) were compared between Control and T2DM group for both genders (table 2). Results revealed that mean values for diabetics were extremely significantly increased ($p < 0.000$) as compared to Control for all studied parameters in both genders. Exception made HDL-C that significantly decreases ($p < 0.000$) in diabetics compared with Control group.

Considering that no statistically significant differences were observed in the studied parameters between the two genders, we attempted to analyze biochemical variables according to age groups for each gender separately.

Total cholesterol (TC) level for masculine gender was significantly increased ($p < 0.000$) in 55-76 age group compared to the younger 34-55 group (fig. 1). Similar findings were observed also in case of feminine gender ($p < 0.009$) (fig. 2). Therefore the total cholesterol levels were statistically extremely significant elevated ($p < 0.000$) in both genders and age groups compared to maximum biological limit reference (200 mg/dL).

Figures 3 and 4 reveal comparison of mean values for high density lipoprotein cholesterol (HDL-C) among age groups in masculine and feminine gender respectively. The results revealed that mean HDL-C values were not significantly decreased in older diabetics patients compared with younger ones. The differences in the mean values of HDL-C for 55-76 and 34-55 age groups and minimum biological limit reference (40 mg/dL) were statistically significant decreased in males ($p < 0.000$) and slightly significant in second age group of females ($p < 0.004$) but not significant in females 34-55 age group.

Low density lipoprotein cholesterol (LDL-C) levels are presented in figures 5 and 6 for both genders and age

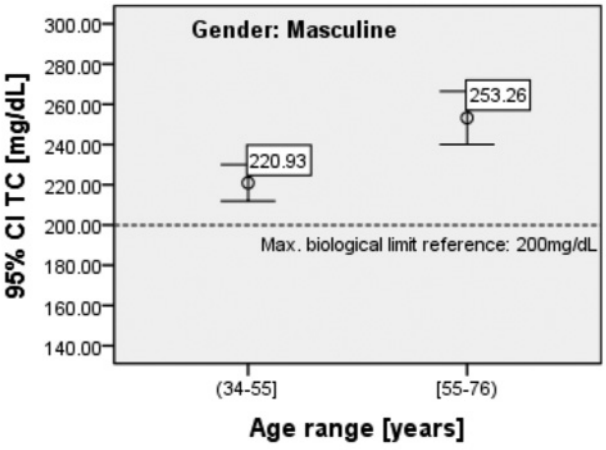

Figure 1 - Distribution of total cholesterol by age groups in the masculine gender. Data are calculated as means ± SD (n = 59) and expressed as mg/dL from controls (n = 12)

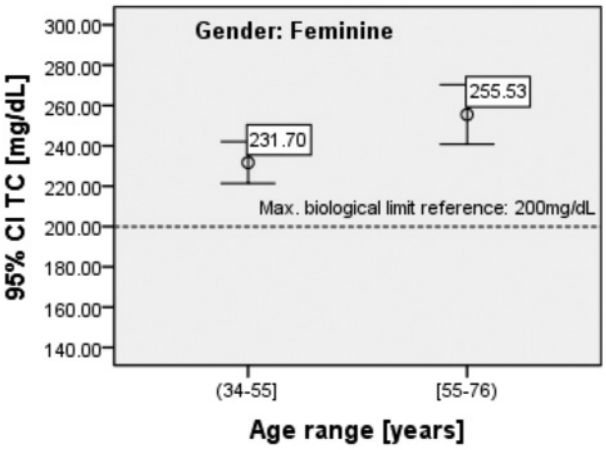

Figure 2 - Distribution of total cholesterol by age groups in the feminine gender. Data are calculated as means ± SD (n = 57) and expressed as mg/dL from controls (n = 12)

Table 2 - Comparison of the Biochemical Parameters between Control and T2DM group in both studied genders

		Group			
		Control		T2DM	
Parameters	**Gender**	**Mean**	**Std. Deviation**	**Mean and p-value**	**Std. Deviation**
TC (mg/dL)	Masculine	170.88	13.97	239.01 ($p < 0,000$)	35.28
	Feminine	172.34	16.56	245.49 ($p < 0,000$)	37.09
HDL-C (mg/dL)	Masculine	57.46	12.018	36.44 ($p < 0,000$)	4.33
	Feminine	54.76	10.75	38.42 ($p < 0,000$)	4.53
LDL-C (mg/dL)	Masculine	104.65	13.57	158.65 ($p < 0,000$)	31.96
	Feminine	107.75	14.78	163.75 ($p < 0,000$)	36.69
TG (mg/dL)	Masculine	82.75	25.84	265.21 ($p < 0,000$)	83.71
	Feminine	86.78	36.47	255.09 ($p < 0,000$)	89.29
AI	Masculine	3.08	0.60	6.64 ($p < 0,000$)	1.25
	Feminine	3.23	0.52	6.49 ($p < 0,000$)	1.36

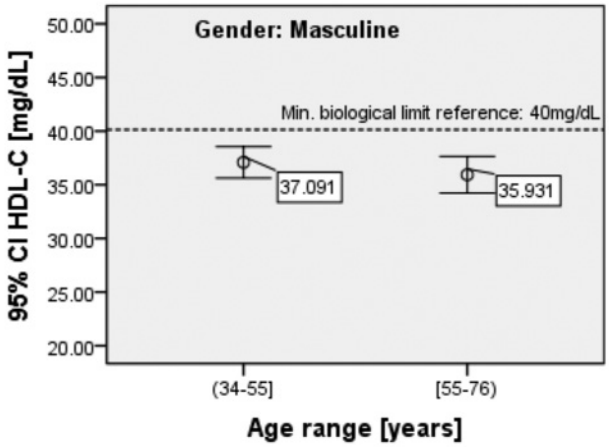

Figure 3 - Distribution of high density lipoprotein - cholesterol by age groups in the masculine gender. Data are calculated as means ± SD (n = 59) and expressed as mg/dL from controls (n = 12)

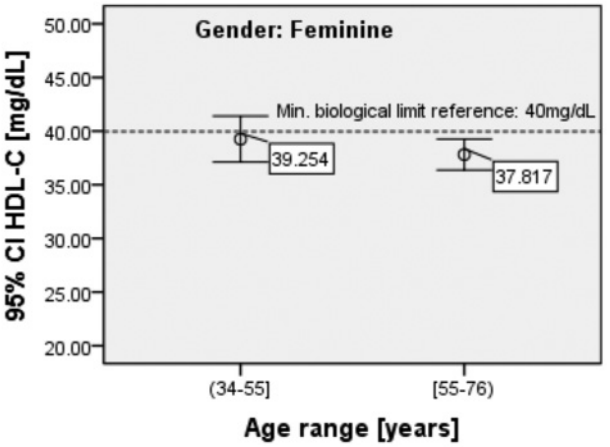

Figure 4 - Distribution of high density lipoprotein - cholesterol by age groups in the feminine gender. Data are calculated as means ± SD (n = 57) and expressed as mg/dL from controls (n = 12)

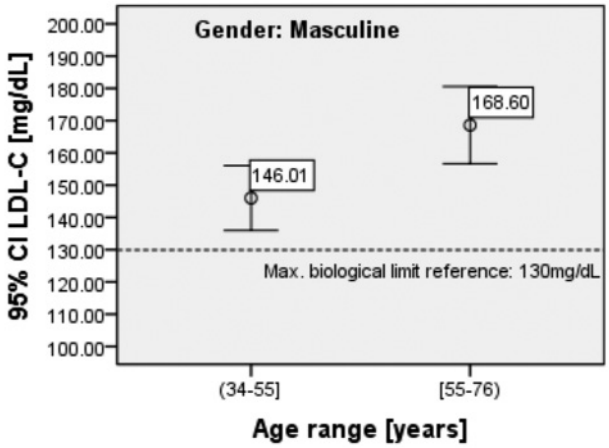

Figure 5 - Distribution of low density lipoprotein - cholesterol by age groups in the masculine gender. Data are calculated as means ± SD (n = 59) and expressed as mg/dL from controls (n = 12)

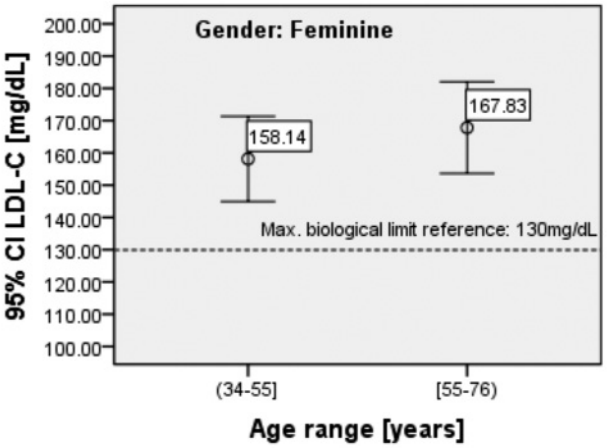

Figure 6 - Distribution of low density lipoprotein - cholesterol by age groups in the feminine gender. Data are calculated as means ± SD (n = 57) and expressed as mg/dL from controls (n = 12)

groups. In case of males LDL-C mean values were significantly increased ($p < 0.004$) in 55-76 years than in 35-55 years for T2DM group. In females results were not considered statistically significant ($p < 0.310$). Elevations in the levels of LDL-C were considered extremely significant ($p < 0.000$) compared to maximum biological limit reference (130 mg/dL) in both studied genders and age groups.

We observed significant increased triglycerides levels for masculine ($p < 0.007$) and feminine ($p < 0.002$) genders in 55-76 age group compared to the 34-55 group (fig. 7 and 8). It was observed that the difference in the mean values of TG for males and females in all age groups were statistically extremely significant ($p < 0.000$) increased compared to maximum biological limit reference (150 mg/dL).

Comparison results for atherogenic index mean values among age groups in masculine ($p < 0.000$) and feminine

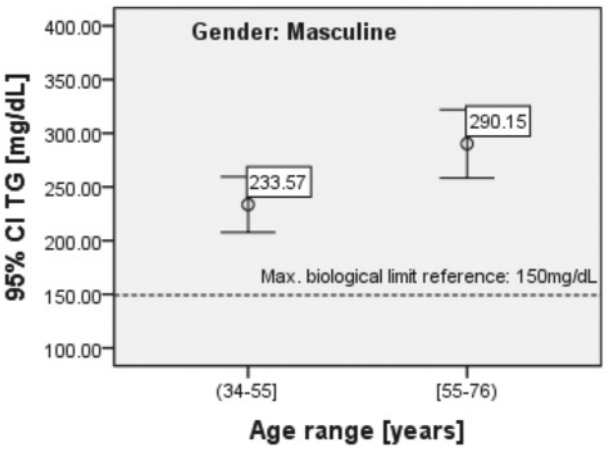

Figure 7 - Distribution of triglycerides by age groups in the masculine gender. Data are calculated as means ± SD (n = 59) and expressed as mg/dL from controls (n = 12)

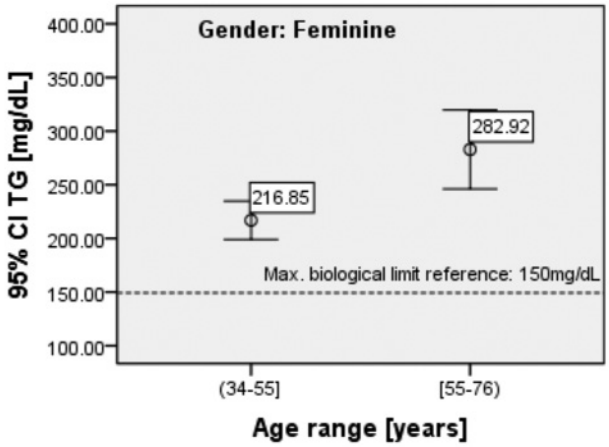

Figure 8 - Distribution of triglycerides by age groups in the feminine gender. Data are calculated as means ± SD (n = 57) and expressed as mg/dL from controls (n = 12)

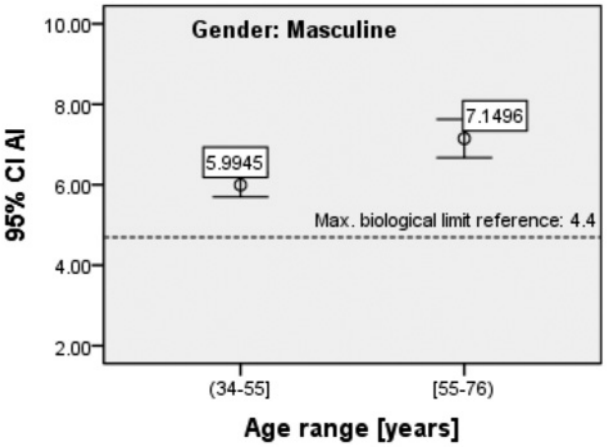

Figure 9 - Distribution of atherogenic index by age groups in the masculine gender. Data are calculated as means ± SD (n = 59) and expressed from controls (n = 12)

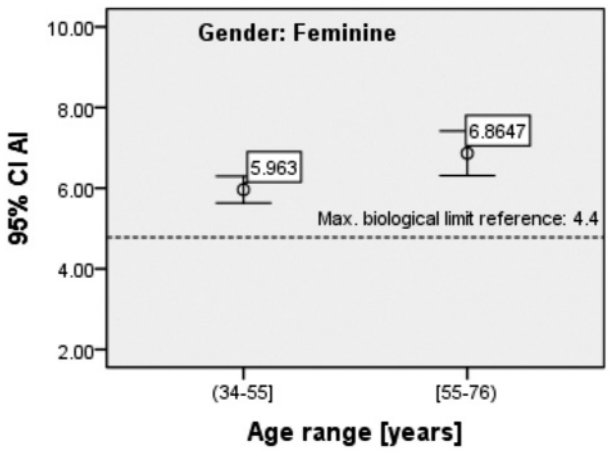

Figure 10 - Distribution of atherogenic index by age groups in the feminine gender. Data are calculated as means ± SD (n = 57) and expressed from controls (n = 12)

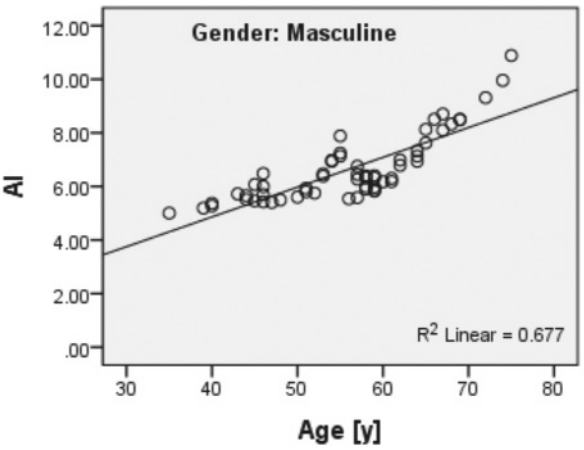

Figure 11 - Correlation coefficient of the studied variables atherogenic index and age in the masculine gender

($p < 0.006$) genders revealed highly significant elevated levels of AI (fig. 9 and 10). The differences in the mean values of AI for 55-76 and 34-55 age groups and maximum biological limit reference (4.4) were statistically significant increased in males ($p < 0.000$) and females ($p < 0.000$).

Regarding the correlation studies (fig. 11 and 12) it was proved that atherogenic index (dependent variable) is correlated with age (independent variable) by establishing a correlation coefficient $R = 0.823$ and $R = 0.726$ in masculine and feminine gender respectively, with an associated probability of $p < 0.000 < \alpha = 0.05$, a value that indicates a strong positive correlation between the studied variables.

The coefficient of determination (R2) obtained in males $R2 = 0.677$ and females $R2 = 0.527$ indicated that 67.7% and 52.7% respectively, of the variation in the dependent variable atherogenic index is determined by the variation of independent variable age. Or otherwise, the two variables shared 67.7% and 52.7% respectively, of

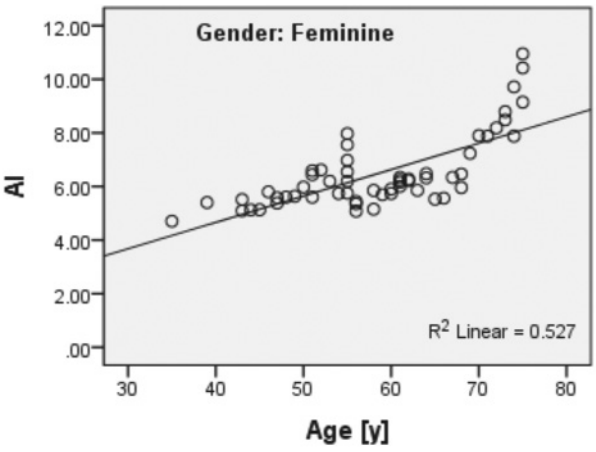

Figure 12 - Correlation coefficient of the studied variables atherogenic index and age in the feminine gender

the variation that characterizes them; the remaining 32.3% and 47.3% respectively, of the variation, probably is due to other variables, measurement errors or chance.

Testing regression model (linear model), it has been demonstrated that F = 119.536 in males and F = 61.255 in females, but also a probability associated with this value is p $<0.000 < \alpha = 0.05$ that confirms that the regression coefficient is statistically significant, a significant linear relationship respectively, between considered variables; the independent variable explains the variation of the dependent variable.

In the present study, we have evaluated the pattern of lipid profile biochemical parameters in diabetics and healthy subjects and correlation between genders, age groups and maximum or minimum biological limit references. Results suggested extremely significant increases in serum total cholesterol, low density lipoprotein - cholesterol and triglycerides along with significant decrease in serum high density lipoprotein - cholesterol among diabetics as compared with healthy subjects. Levels of TC, LDL-C and TG increased and levels of HDL-C decreased compared with the biological limit references, as the age advances and the duration of diabetes increases. Our results are consistent with the recent studies regarding dyslipidemia and cardiovascular diseases in patients with diabetes (3, 15 and 19)

The correlation between atherogenic index and age was performed considering the fact that diabetes mellitus is characterized by accelerated atherosclerosis and increased risk for cardiovascular diseases as the age advances and the duration of diabetes increases (20). Persistent hyperglycaemia causes glycosylation of all proteins, especially collagen cross linking and matrix proteins of arterial wall. This eventually causes endothelial cell dysfunction, contributing further to atherosclerosis.

The obtained results for correlation studies indicate a strong positive correlation between atherogenic index and age groups. This reveals the influence of type 2 diabetes mellitus on abnormal lipid profile and associated risk of patients for cardiovascular complications considering aging.

Conclusion

In conclusion, our results reveal common lipid abnormalities during diabetes induced dyslipidemia such as hypercholesterolemia, hypertriglyceridemia, increased LDL-C and decreased HDL-C levels which are well known risk factors for cardiovascular diseases. Hyperlipidemia is the commonest complication of diabetes mellitus and it predisposes to premature atherosclerosis and macrovascular complications. Therefore good glycaemic control, weight reduction, physical exercise can prevent development and progression of lipid-abnormalities among patients with diabetes mellitus.

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ORIGINAL PAPER

STUDY OF BIRTHRATE AND ABORTION BETWEEN 1965-2013 IN "DR. I. A. SBARCEA" CLINIC HOSPITAL OF OBSTETRICS AND GYNECOLOGY OF BRASOV

N. Bîgiu[1], Cristiana Suzana Glavce[2], M. A. Moga[1], I. Stancu[1]

[1]*Transilvania University of Braşov, Faculty of Medicine, Romania*
[2]*"Francisc I. Rainer" Anthropology Institute of Romanian Academy*

Summary

Background: The aim of this paper is to study the number of births, abortions and perinatal mortality in "Dr. I.A. Sbarcea" Clinic Hospital of Obstetrics and Gynecology in Braşov between 1965-2013.
Methods: The results registered were structured according to time periods correlated to specific political and social changes that took place in Romania. Moreover, the results obtained were compared with the data available for the entire country for those specific time periods.
Results: In 1966 before the abortion law introduced by the communist regimen, a number of 3020 births was registered. This number reached 9593 (more with 317%) births in 1979 and then decreased to 7857 (in 1989). After the abolition of the abortion law and the liberalization of the abortion, in 2013, the births reached a number of 4133 per year.
Conclusion: The only hypothetical method that influences favorably the evolution of births is the economic growth. Thus, the total fertility rate would rise above the minimum value of 2.1 providing in this way social and economic stability in the future.
Key words: fertility, abortion, second demographic transition

Résumé

Etude sur le taux de naissances et d'avortements pendant la période 1965-2013 dans l'Hôpital Clinique d'Obstétrique-Gynécologie "Dr. I. A. Sbarcea"

Contexte: Le but de cette étude est d'obtenir de précieuses informations sur le nombre de naissances, d'avortements et la mortalité périnatale dans Hôpital Clinique d'obstétrique-gynécologie "Dr. IA Sbarcea" à Brasov entre 1965-2013.
Méthodes: Les résultats enregistrés ont été structurés en fonction des périodes de temps corrélés aux changements politiques et sociaux spécifiques qui ont eu lieu en Roumanie. En outre, les résultats obtenus ont été comparés avec les données disponibles pour l'ensemble du pays pour ces périodes de temps spécifiques.
Résultats: En 1966, avant la loi sur l'avortement introduite par le régime communiste, un certain nombre de 3020 naissances a été enregistré. Ce nombre a atteint 9593 (plus de 317%) des naissances en 1979, puis a diminué à 7857 (en 1989). Après l'abolition de la loi sur l'avortement et la libéralisation de l'avortement, en 2013, les naissances ont atteint un nombre de 4133 par an.
Conclusion: La seule méthode hypothétique qui influence favorablement l'évolution des naissances est la croissance économique. Ainsi, le taux de fécondité serait élever au-dessus de la valeur minimale de 2,1 assurant de cette façon la stabilité sociale et économique à l'avenir.
Mots clefs: fertilité, avortement, transition démographique secondaires

Introduction / Background

The growth rate of the population influences the economic and social evolution which also has impacts on the sustenance level. All aspects correlated to the growth rate must be well balanced. Therefore, the components that favor or not the growth rhythm must be studied: natality and mortality. By understanding the role of these factors one can favor the growth rate of the population.

Correspondence address: *Marius Alexandru Moga, MD*
Nicolae Balcescu Bvd., 56, 500019, Brasov, Romania *e-mail : moga.og@gmail.com*

This process requires time and not impetuous, coercive measures thus assuring that the density of the population does not surpasses the resources and the economical possibilities of that nation. Moreover, by all means the situations that raise mortality, decrease natality or fertility must be counteracted.

Among these indicators, theoretically, is easier to influence natality as for mortality there are already measures taken worldwide against diseases as well as preventing measures against diseases that lead to death.

The aim of this study is to highlight the evolution of birth rate, abortion rate and perinatal mortality in " Dr I. A. Sbârcea" Hospital of Obstetrics and Gynaecology, Brașov through observational retrospective statistical study between 1965-2013.

The main goals of this study are: archiving data collected from the hospital, statistical analysis of the phenomenon, data comparison with the information revealed at a national level, predictions establishment related to the studied area (Brașov).

Methods

The information was collected from the archives of "Dr. I. A. Sbârcea" Hospital of Obstetrics and Gynecology" Brasov. The obtained data base were analyzed and the results correlated to each element of the studied given situation bordered by political and economic factors.

The results obtained were compared with other relevant information. In order to identify data key words or combination of words were used: statistics, births, cesarean section, abortions, miscarriage, and neonatal mortality.

The data were compared to other similar data from Romania or other countries within the limits of the available information.

Results

According to European Social Statistics there is a descending trend at European level, tendency that started in 1961 with 7.5 million births until 5.2 million in 2010. [1]

Most of the available statistics report situations starting with 1960-1966 because before this period there were two distinct periods: before 1950 and after 1960. After the Second World War a raise in the natality was registered. [2] The growth rate was probably determined by both peace and a natural "rebound" determined by the deaths caused in war.

This period removed the concern related to the decimation of Europe between the two world wars. [3]

This period could contradict the theory of demographic transition formulated by Warren Thompson (1929) and Frank Notestein (1954) that predicted declining birthrates either through a raised fertility counteracted by a raised mortality (agricultural society) or by low mortality unopposed by a low fertility (industrial society).[2]

Concerns start to appear when fertility drops below the level of generation replacement, meaning 2.1 children. This kind of concern started to appear at the end of 1966 then the natality decline started in 1960. [2]

This decline could be explained by the theory of Kaa, the theory of the second demographic transition that claims the change of the family model centered on children with the individualist model where the child stands on a less important place in the family, the most important being the career of the partners. [4]

Precisely because of this decrease in 1966 in Romania the pronatalist law was adopted against abortions, law that writes a black page in the history of our country because of the number of lost lives caused by desperate abortions made in inappropriate conditions. Because of this law the demographic transition lasted until 1990 when this law was repealed. At that moment a boost of the abortions was registered.

In Eastern Europe the 90's were a hectic period of time because of the political changes in Romania, the problem in Kosovo, the war in Yugoslavia and so on. These things determined this area to be called "a transition area" both from a political and economic points of view. The demographic changes that happened in this area were attributed to the behavioral transition caused by the installation of anomie and poorly understood freedom. [5]

In order to highlight the evolution of births after the establishment of the 770 Decree (The abortion law) we have decided to study the births after 1965.

In 1965 in Brașov there was a low number of births (2726) followed by a raise of approximately 10% in the next year, raise influenced probably only by the growing interest of having a baby.

The abortion law determines a raise of 123.7 % of the number of births, fact that leads to a vertical evolution of the chart. (fig. 1)

Next, between 1968 and 1973, as an adaptive measure to the abortion law the birthrate decreased constantly by 3.5% per year. This decrease can also be attributed, besides the adaptive reaction, to the harsh living condition in the communist time. Starting 1973 a raise of the birthrate began and lasts roughly 8 years until 1981 (from 5500 births in 1973 to 9503 births in 1981). The year 1979 marks a record in Brasov as the biggest birthrate between 1965-2013 registered that year. (fig. 1)

In 1979 the increase of the birthrate compared to the one in 1966 is of 9593/3020, meaning a 317% rise. Although the increase was significant, Nicolae Ceaușescu was not satisfied, thus toughening the abortion law. Despite this, starting 1981 the birthrate decreased constantly until 1989 with about 2% per year.

As expected, December 1989 determines a decrease of the birthrate until 1996, from 7857 births registered in 1989 to 3921 registered in 1996, a drop of 7.15 % meaning a decrease of 3.5 time more than in the communist period. Moreover 1989 also brings the lowest birthrate from 1967 and until 2013.

Next, there is a period of slight raise, constant, until

Figure 1 - Total of births

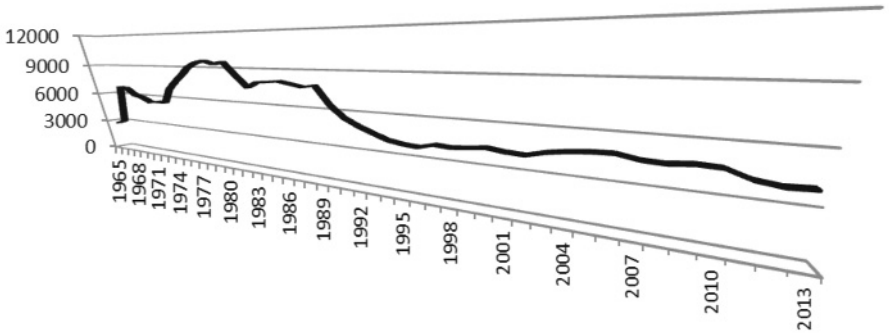
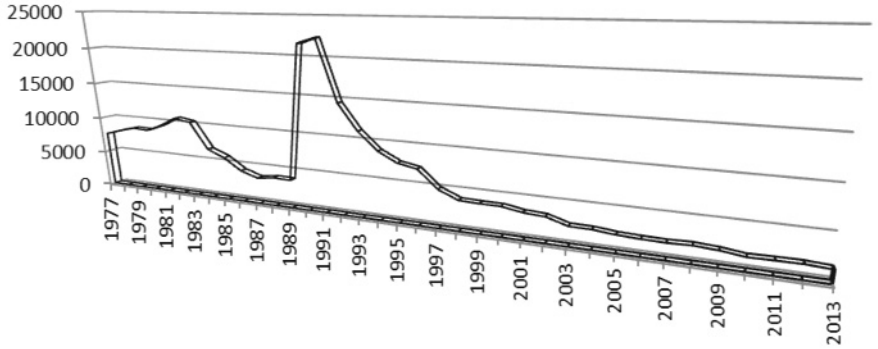


Figure 2 - Abortion evolution



2006 by 2.4% per year, following then a new decrease until 2013 reaching 4133 births.

Summing up, in 1966 there was a birthrate of 3020 per year, birthrate that reached 9593 in 1979 then dropping despite the measures taken by the communists, to 7857 births in 1989. After the Abortion law has been repealed, and the abortion legalized, the birthrate registered 4133 in 2013. (fig. 2)

As it can be noticed from fig. 2, in the communist period (1977- 1983) there is a raise from 7577 to 10748, meaning 41.8% in 7 years, resulting in a raise of 6% per year.

This raise can be explained by the party requirement of "raising the baby production for each woman", requirement applied as a coercive measure, not as a stimulant.

Because the decree application did not have the intended effect, the law toughened in 1984, doctors being responsible for this situation. The toughening consisted of very rigorous controls, the doctors not being able to start any intervention until the notice that the abortion "was legal" was not received by the officials.

These measures explain the decrease of the number of abortion registered in 1984 compared to 1983, from 10403 to 6827, meaning a drop of 34% in one year, below the level in 1977.

The total number of abortions decreases on gradually until 1989 when reaches 3824. The repeal of the decree leads to a dramatic raise of the abortions that reach 21601 in 1990, number that increases to 22403 in the following year.

From 1991 a continuous drop is registered until present time, the chart presenting an upward concavity. Initially, there is an upward slope until 1999 (3838 abortions) representing a decrease by 82.2%, then following a period of 14 years with a slower decline until 2013 (1578 abortions), meaning an average of 4.2% per year.

The 1966 decree mentioned clearly: The pregnancy interruption is forbidden. [6]

Exceptionally, the abortion was allowed only in a few situations like:

- endangering the life of the mother
- hereditary diseases or serious illness
- mother age > 45 years
- pregnancy following incest or rape [6]

Conducting an abortion in other circumstances was considered crime and punished under the criminal law.

Using these exceptions, in the communist period, women and doctors managed to give a "legal" form to the abortion, as one can clearly be seen in fig. 3.

The evolution and the chart of abortions is similar to the situation of the total abortions (fig. 2) being part of it, but the slope described for the 1977-1989 period is flatter.

During 1977-1982 the abortion number was raising by 36% (in 6 years, meaning 6% per year). Starting with 1983, the number starts to decrease, but more obvious is noticeable in 1986 (a drop by 63.8 % compared to 1985).

This fact is the proof of the controls taken to extremes, making sure that all abortions obey the law.

The important fact that between 1986 and 1989 there was a slight increase of the abortions means that ways were found in order to be able to perform an abortion.

Figure 3 - Evolution of demand abortions

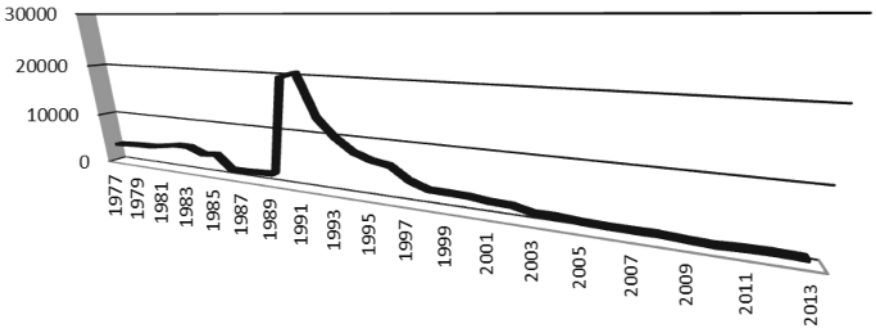
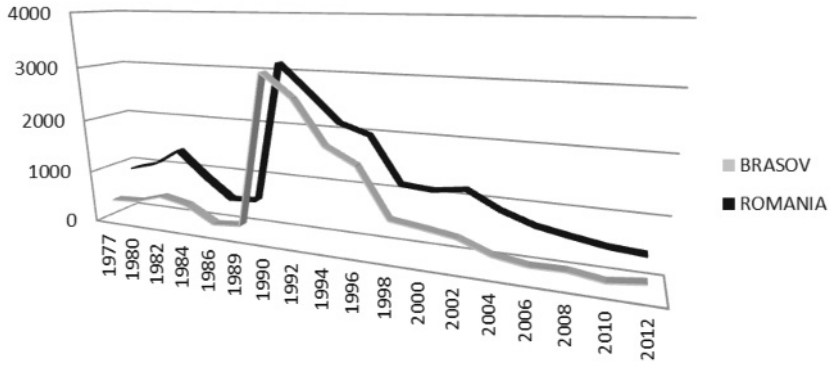


Figure 4 - Comparison between the abortion rate in Brasov and Romania



The repealing of the abortion law and the liberalization of the abortions bring a marked evolution, the chart registering almost a verticalization of the slope, respectively a raise from 1983 to 19588 and respectively to 20512 in the following year (1991).

This unprecedented situation (1990, 1991) can be interpreted as a total lack of interest for contraception, the abortion becoming a sort of "contraception". Also, this situation can be caused by lack of education or through misunderstanding of the liberalization of the abortion.

It seems that the liberalization of the abortion had an impact in the liberalization of intercourses and especially of those unprotected, the fear of an unwanted pregnancy disappearing.

In 1992 the number of abortions decreases by about 30% until 1993, moment after the chart looks like a slope with the concavity facing up, which means the number of abortions decreases progressively and constantly until 2013 when it reaches 841.

The extreme situations are highlighted: in 1991 when the peak was registered: 20512 and the minimum 841 in 2013. This represents a normal decrease related to the degree of civilization that we aim to.

Discussions

The abortion rate is calculated as being the ratio of the abortions per 1000 live births. In order to make a comparative analysis, we compared the data obtained in Brașov to those available for the entire country (Romania).

As noticed from fig. 4, the abortion rate in Brașov represented 37-50% of the entire abortion rate performed in Romania between 1977-1989.

Between 1990 and 1991, the two rates are roughly equal, later on the abortion rate in Brașov decreasing in the communist period. These results state either the fact that in Brașov the women used less the abortion compared to births or that in Brasov there was a stricter control of the officials regarding the abortions.

Still, after December 1989 the results seem to favor the second hypothesis because the differences are comparable to those registered in 1989.

Between 1990 and 1996 (fig. 5) the abortion rate is higher than the birthrate, thus confirming that in this period the abortions were used as "contraception".

The abortion rate evolution is inversely proportional to the birthrate, which means that the measures applied to favor births also affect abortions, but inversely.

This inverse proportion correlated to the political regimen that existed in Romania at that moment makes very clear the important role that politics had upon fertility. [7]

Furthermore, besides the clear connection between abortion and birthrate the health of the mother must be highlighted. As Prof. Dr. David A Grimes et al state in their study, being able to perform abortions assures women health. [8]

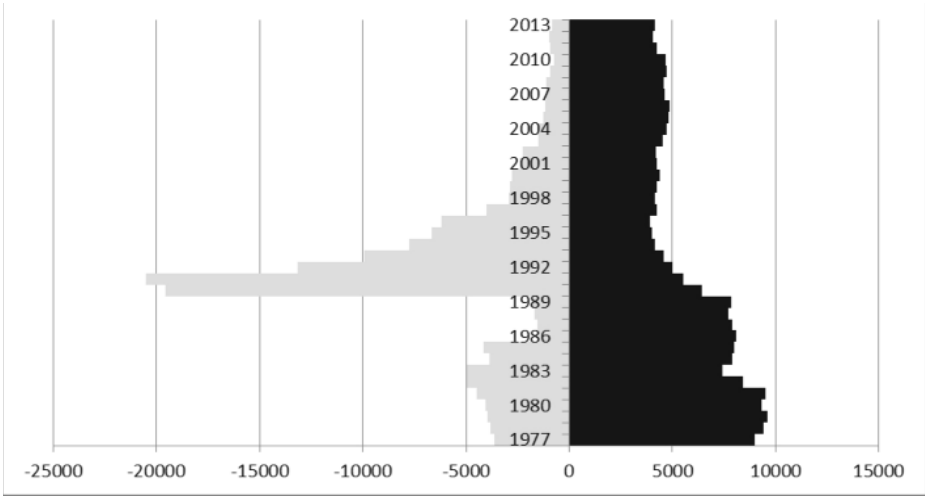


Figure 5 - Pyramid type comparative evolution of births and abortions

Moreover the educational measures supporting contraception must be well applied and also the effects of not using contraception must be well understood, not to mention the possibility of obstetrical disasters when facing multiple abortions.

This complex problem caused by banning abortions has traumatizing effects on the mother (approximately 150 maternal deaths per 100000 live births- 1989), on the child (thousands of unwanted children in institutions) and on the society that has to assure the economic conditions and the social environment so that the integration in the population be effective. [9]

The benefits of the repeal of the abortion law are obvious for all parts involved in the process, but maybe the most important is the fact that numerous women were saved (in 1990 the maternal deaths registered 83 deaths per 100000 live births, meaning almost half the ratio in 1989). [10]

CONCLUSIONS

The evolution of birthrate in the period studied starts from 3020 births per year in 1966, birthrate that reached 9593 in 1979 then dropping despite the measures taken by the communists to 7857 births in 1989. After the Abortion law was repealed, and the abortion legalized, the birthrate registers 4133 in 2013

Our results state the fact that during communism time, abortion in Brasov was under strict control meaning that the abortion rate in Brasov represented 37-50% of the entire abortion rate performed in Romania in the period 1977 – 1989.

In the period 1990 – 1996 abortion rate was higher than the birthrate confirming the fact that abortions were used as contraceptive measures.

The only hypothetical method that influences favorable the evolution of births is the economic growth. Thus, the total fertility rate would rise above the minimum value of 2.1 this way providing social and economic stability in the future.

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ORIGINAL PAPER

INVOLVEMENT OF PHYSICAL THERAPY AND SPIRITUAL CARE IN CANCER-RELATED SYMPTOMS MANAGEMENT

Gabriela Rahnea Niță[1], M. Slăvilă, D.E. Frâncu, Anca-Mirona Mocanu, Roxana-Andreea Rahnea Niță[2], Mihaela Popescu[3], Anda-Natalia Ciuhu[1]

[1] *"Sf. Luca" Chronic Diseases Hospital, Bucharest Romania*
[2] *"Dr. Constantin Gorgos" Titan Psychiatric Hospital, Bucharest, Romania*
[3] *Colentina Hospital Bucharest, Romania*

SUMMARY

Background: Physical therapy in the field of Oncology and Palliative Care is a continuously evolving and developing specialty.
Materials and methods: The study was conducted in the Physical Therapy department of the hospital "St. Luke" Bucharest, on a total of 30 patients with oncological diseases. Each patient received individualized physical therapy programs and have benefited of physical therapy program, occupational therapy and music therapy.
Results: Depression, anxiety decreased significantly while feelings of well being increased significantly after 10 days of physical therapy program, at patients with moderate or severe fatigue.
Discussions and conclusions: Physical therapy was shown to have positive influence on quality of life and perceived well-being in patients with cancer requiring palliative care. Also, our study indicates that patients consider that spiritual care can be complementary to medical treatment, having a role in support them during the illness
Key words: symptoms, physical therapy, spiritual care, quality of life

RÉSUMÉ

Implication de la physiothérapie et des soins spirituels dans l'approche des symptômes liés au cancer

Fond: La physiothérapie dans le domaine de l'oncologie et de soins palliatifs est une spécialité en constante évolution et développement.
Matériels et méthodes: L'étude a été menée dans le département de physiothérapie de l'hôpital «Saint-Luc» Bucarest, sur un total de 30 patients atteints de cancer. Chaque patient a reçu des programmes de thérapie physique individualisés et bénéficié du programme de physiothérapie, d'ergothérapie et de la musique.
Résultats: La dépression, l'anxiété ont diminué significativement tandis que des sentiments de bien-être ont augmenté de manière significative après 10 jours de programme de thérapie physique, chez les patients avec fatigue modérée ou sévère.
Discussions et conclusions: La physiothérapie s' montré d'avoir une influence positive sur la qualité de vie et bien-être perçu chez les patients cancéreux nécessitant des soins palliatifs. De plus, notre étude indique que les patients considèrent que les soins spirituels peuvent être complémentaires à un traitement médical, ayant un rôle dans leur soutien au cours de la maladie.
Mots clés: symptômes, la thérapie physique, les soins spirituels, la qualité de vie

BACKGROUND

The number of patients diagnosed with cancer has increased significantly in the last years due to improved diagnosis techniques and treatments.

Cancer treatments like chemotherapy, radiation and surgery often result in side effects like fatigue, joint pain and stiffness, nerve damage, limb swelling (lymph edema), skin issues and nausea which require supportive care (1,2, 3, 5).

Cancer-related fatigue is recognized as one of the most common and distressing symptoms of cancer affecting 70-100% of patients during and post anti-cancer treatments

Correspondence address: *Mircea Slăvilă, PhD*
"St. Luke" Hospital, 12 Berceni Street, Bucharest Romania *e-mail: mirceaslavila@yahoo.com*

(5). Cancer-related fatigue impacts on the functional ability of the patients; it is the number one cause of reduced activities of daily living leading to depression, irritability and total inactivity of the patient and is the most common in patients with persistent or advanced disease (3,4,5).

Fatigue is partially caused by a decline in neuromuscular efficiency resulting from metabolic and cellular mechanisms altered by cancer and its treatment (4,5).

It is proved that physical activity and strengthening exercises can significantly reduce cancer-related fatigue, joint pain and increase overall strength and well-being. Exercises are known to improve neuromuscular tone and efficiency and can be beneficial for individuals with cancer-related fatigue during and post treatment (1,3,4).

Physical therapy in the field of Oncology and Palliative Care is a continuously evolving and developing specialty. Rehabilitation for cancer patients is recognized as an essential part of the clinical pathway and they should have access to an appropriate level of rehabilitation, so that they can function at a minimum level of dependency and optimize their quality of life (1, 4, 5, 6).

Physical therapy has an important role in management of cancer-related fatigue. Physical therapists have a key role in screening patients for fatigue, assessing current activity levels and providing exercise advice and initiating exercise programs with patients based on patients' unique medical and demographic characteristics and associated anticancer treatments and side effects.

Also, physical therapy can have an important role in other symptoms like depression, anxiety and feelings of well being at patients with cancer-related fatigue.

Physical therapist, as experts in human movement, have an important role in advising patients on suitable exercise programs and monitoring their progress at all stages in the "patient pathway" (1, 4).

Patients with advanced disease have questions regarding their mortality and the meaning and purpose of life. Most of cancer patients are seeking spiritual support therefore it is important for them to develop and maintain their spirituality which plays an important role and maintains dignity, confidence and self-esteem in patients with an advanced illness, a greater spiritual well-being has been associated with fewer symptoms.

Objectives

Evaluation the role of physical therapy and spiritual care in the management of cancer- related symptoms (anxiety, depression and feelings of well being) at patients with cancer-related fatigue.

Materials and Methods

The study was conducted in the Physical Therapy Department of the hospital "St. Luke" Bucharest, on a total of 30 patients with oncological diseases. Each patient received individualized physical therapy programs and have benefited of physical therapy program, occupational therapy and music therapy.

In the year 2014, 30 patients with advanced cancer, with performance status – ECOG between 1 and 3, with moderate or high level of fatigue participated to a program which involved physical therapy and spiritual care, during 10 days. Patients inclusion was made according to their choice, after meeting with the oncologist, physical therapist and priest and accurate information about treatment goals and expectations. The participants were explained about the importance and the purpose of the study and patients signed a written informed consent, in which they freely agreed to join this study. The approval of the Medical Ethical Commission of the "St. Luke" Hospital has been previously obtained. Patients presented a moderate or high level of fatigue, and, also, other cancer-induced symptoms. The level of principal symptoms (fatigue, anxiety, depression and feelings of well being) was evaluated at baseline, after admission to the Oncology Palliative Care Department and after 10 days of physical therapy, using, "The Edmonton Symptom Assessment System" (7,8).

Physical therapy was represented by daily exercises, having the goal to improve symptoms.

The duration of a session of physical therapy is 40-45 minutes and includes: 10 minutes warming, 25 minutes fundamental basis and 10 minutes closure

The programs have an individual character and include exercises adapted to each case.

Programs have numerous breathing exercises.

Also, patients performed occupational therapy and music therapy.

Blood pressure and pulse were measured at the beginning and at the end of the exercises, every day.

The role of spirituality was identified through interviews with open questions at the beginning and at the end of the program (day 1 and day 10).

Data obtained were analyzed using Microsoft Office Excel 2007.

Results

Out of 30 cancer patients with cancer – related symptoms, hospitalized on the Palliative Oncology Department, in the last 3 months of 2014, 20 patients (66,67%) were male and 10 patients (33,33%) were female (fig. 1), 14 patients (46,67%) were from urban area and 16 patients (53,33%) were from rural area (fig. 2). Average age was 62,4 years.

Patients distribution according to the disease diagnosis is : 16 (53,33%) patients have lung cancer, 4 (13,33%) patients have head and neck cancer, 2 (6,67%) patients have breast cancer, 2 (6,67%) patients have cervix cancer, 2 (6,67%) patients have gastric cancer, 2 (6,67%) patients have bowel cancer and 2 (6,67%) patients have renal cancer (fig. 3).

It was evaluated the impact of physical therapy on symptoms like anxiety, depression and feelings of well being at patients who presented moderate and severe intensity of fatigue.

The results indicated:

Depression:

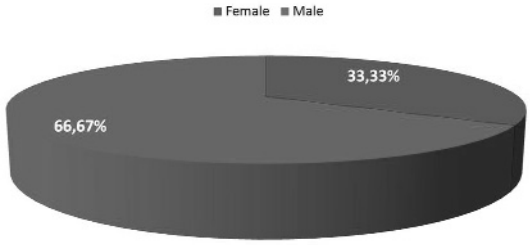

Figure 1 - Patients distribution according to the gender

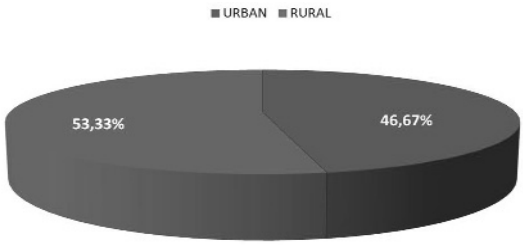

Figure 2 - Patients distribution according to the life environment

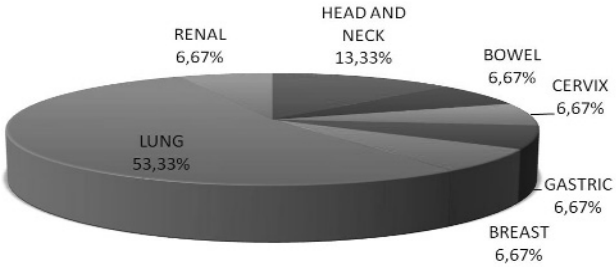

Figure 3 - Patients distribution according to the disease diagnosis

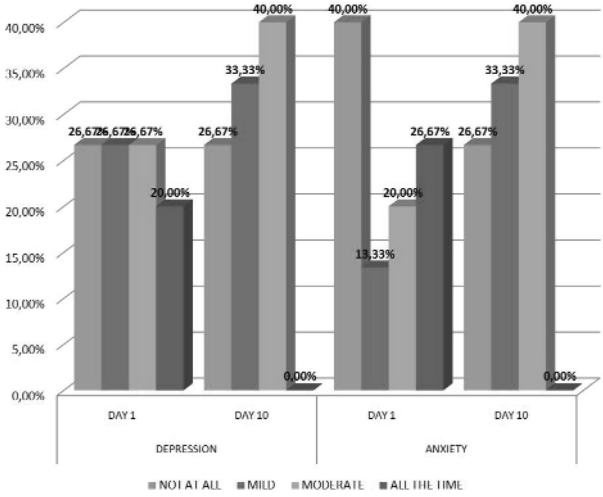

Figure 4 - Evaluation of symptoms (depression, anxiety)

- day 1: all the time at 6 patients (20,00%), moderate, at 8 patients (26,67%), mild for 8 patients (26,67%) and not at all for 8 patients (26,67%).
- day 10: all the time at 0 patients (0,00%), moderate, at 12 patients (40%), mild for 10 patients (33,33%) and not at all for 8 patients (26,67%). (fig. 4)

Anxiety:

- day 1: all the time at 8 patients (26,67%), moderate, at 6 patients (20%), mild for 4 patients (13,33%) and not at all for 12 patients (40%).
- day 10: all the time at 0 patients (0,00%), moderate, at 12 patients (40%), mild for 10 patients (33,33%) and not at all for 8 patients (26,67%). (fig. 4)

Feelings of well being:

- day 1: very good at 4 patients (13,33%), moderate, at 6 patients (20%), mild for 16 patients (53,33%) and not at all for 4 patients (13,33%).
- day 10: very good at 8 patients (26,67%), moderate, at 12 patients (40%), mild for 8 patients (26,67%) and not at all for 2 patients (6,67%). (fig. 5)

Spiritual support during the treatment was high for 20 patients (66,67%), moderate for 6 patients (20 %), and mild for 4 patients (13,33%) and not at all for 0 patients (0%). (fig. 6)

Patients considered that spiritual care can be complementary to medical treatment as following: very important for 20 patients (60%), important for 4 patients (13,33%), not so important for 6 patients (20%), and not at all for 2 patients (6,67%) (fig. 7).

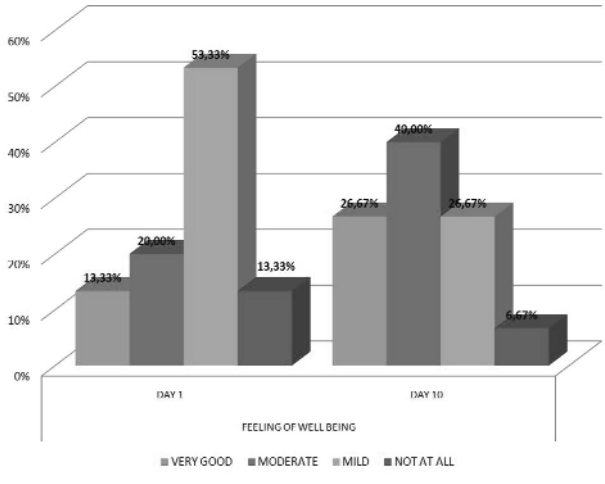

Figure 5 - Evaluation of feelings of well being

DISCUSSION

Within rehabilitations a medical and social complex process, physical therapy is an important therapeutic method.

The goals of physical therapy are: improving the overall capacity of walking, preventing faulty compensatory

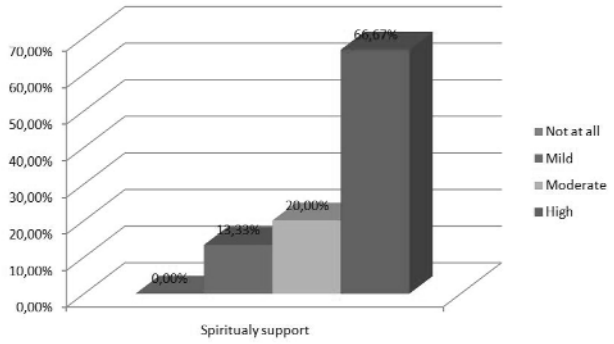

Figure 6 - Spiritual support during the treatment

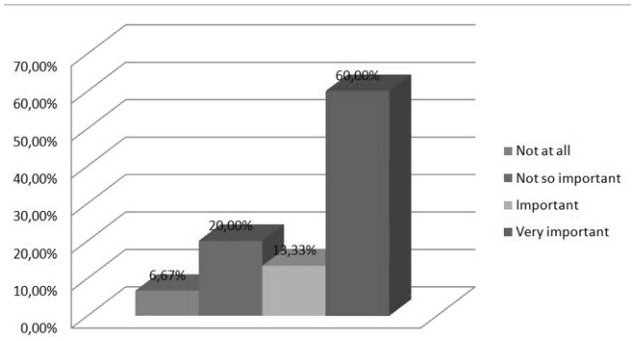

Figure 7 - Do you consider that spiritual care can be complementary to medical treatment?

Figure 8

Figure 9

Figure 10

skills installation and stimulate mental state.

The primary means of recovery is exercise, under its multiple forms (fig. 8, 9).

Occupational therapy is part of the complex rehabilitation and integrated recovery therapy of a person with disability. The goal of occupational therapy is to restore the patient's independence, either by giving him the ability to adapt to his disability or to participate in improving his condition. (fig. 10).

Also, the effects of music therapy are multiple: relaxing, analgesic effects, pain relief.

The results of our study indicates that symptoms like, depression, anxiety, and feelings of well being had a significant improvement at the end of the physical therapy program, increasing the quality of life.

Also, our study indicates that patients consider that spiritual care can be complementary to medical treatment, having a role in support them during the illness.

CONCLUSIONS

Physical therapy has shown to have positive influence

on quality of life and perceived well-being in patients with cancer requiring palliative care. (9)

Management of cancer-related symptoms includes physical therapy, by recommending and using exercise for patients with a variety types of cancer, also during advanced stages of the disease, with performance status ECOG: 1-3.

Physical therapy can be recommended for improving symptoms like , depression, anxiety and feelings of well being at patients with cancer-related fatigue.

Also, a greater spiritual well being is being associated with fewer symptoms.

The results of this study show that physical therapy and spirituality have an important role in improving cancer - related symptoms and patients quality of life.

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ORIGINAL PAPER

MODIFIED BUNNELL SUTURE IN ACHILLES TENDON INJURIES

I. Șamotă, R. Necula, F. Sabou, R. Vaidahazan, I. Szava, Alina Pascu

Transilvania University of Brașov, Romania

Summary

The treatment of Achilles tendon lesions is still controversial. Though the usual Bunnell technique of suture is appreciated to be a good one, it is still associated with a low rate of reruptures. In order to improve the suture strength, we modified the original Bunnell suture by using two sutures in Bunnell manner, one starting from the superior and the other from the inferior tendon stumps. The manner of fixing the knots is in double points and realizes a superior tight fitting than the usual Bunnell suture. We used this suture in four cases of accidental section and in 11 cases of acute rupture, with no reruptures. Based on our own experience, we consider that this modification of Bunnell sutures increases the strength of the sutured tendon and generates a low rate of reruptures.

Key words: Achilles tendon injuries, surgical repair, modified Bunnell suture, no major complications, good results

Résumé

Modification suture Bunnell en lésions du tendon d'Achilles

Le traitement des lésions du tendon d'Achille est encore controversé. Bien que la technique de suture normale de Bunnell, soit appréciée comme très bonne, elle est encore associée à un taux de récidive. Pour un meilleure résultat, nous avons modifié la suture originale Bunnell par deux suture séparées, une qui commence au niveau du tendon proximal et l'autre au niveau du tendon distal. Les nœuds sont faits en points doubles. Nous utilisons cette technique pour les lésions accidentelles et dans les cas d'une lésion aiguë, sans récidive. Suite à notre expérience, nous considérons que la suture modifiée de Bunnell augmente la force du tendon suturé et détermine un faible taux de récidive.

Mots clefs: lésions du tendon d'Achille, traitement chirurgical, suture modifiée de Bunnell aucune complication majeure, bons résultats

Background

The Achilles tendon is the largest and the most frequently injured tendon of the human body (1, 2, 3). In cases with accidental section, the only surgical treatment is accepted.

Treatment protocols for patients with acute Achilles tendon rupture include surgical and nonsurgical management, but they are constantly being modified (4, 5). The rerupture following acute lesion is the most frequent major complication and it is higher in nonsurgical treatment than in surgical one (6). In surgery the rates is lower, but it is still up to 3% (7, 5). Various surgical methods have been described including open, minimally invasive and percutaneous repair (8, 9).

In chronic ruptures of Achilles tendon, most authors consider the surgical treatment to be the only satisfactory one (12, 13, 14). In chronic ruptures, we never used any type of suture but the augmentation only.

Each surgeon chooses one surgical technique because considers it to be associated with a low rate of complication. Based on our experience, we consider, in the acute Achilles tendon ruptures, the surgical treatment has some advantages. We present our experience with Bunnell modified surgical suture of Achilles tendon lesions and discuss on the used techniques in accidental sections and acute ruptures. We believe our modified Bunnell suture to be associated with a lower level of reruptures than the original one.

Materials and Methods

This study is a retrospective evaluation of patients with accidental section or acute Achilles tendon ruptures treated by a modified Bunnell suture. Every patient who underwent a modified Bunnell suture of an Achilles tendon between January 2010 and December 2014, was identified and information was abstracted from the

Correspondence address: *Iosif Șamotă, MD*
Transilvania University of Brașov, Romania *e-mail: samota.iosif@gmail.com*

medical records. All the patients with Achille lesions operated in this period by a modified Bunnell suture were included. It was a number of four patients with section and 11 with acute rupture.

In cases with accidental sections the diagnosis was established by clinical examination, and in all cases an immediate surgical repair was performed. There were three males and one female, between 37 and 42 years old. In all of them an end-to-end modified Bunnell suture was done.

In acute ruptures cases the diagnosis was based on history and physical examination. In some cases, an ultrasound or MRI examination were added. All the patients accepted for surgery had to present a palpable depression on the tendon, a positive Thompson test and disability to stand on their tiptoes on the injured side. The duration of ruptures from injury to surgery was from a couple of days to five weeks. The patients group comprised 11 men and two women ranging in age from 24 to 59 years. The majority of the ruptures were at about 4 to 6 cm proximal to the calcaneal insertion. All the patients were treated by the same technique, a modified Bunnell suture.

Surgical techniques

With the patient under anesthesia, tourniquet control and in prone position, the surgery started by a posteromedial incision from 4 cm. up to 4 cm. down to the rupture site. The incision is without dissection, sharply through the skin, subcutaneous tissue and fibrous tendon sheath. Then, the synovial sheath is carefully dissected and then longitudinally incised on both sides of tendon section or rupture, and protected in order to be easy sutured at the end of tendon repair. The ragged ends of the ruptured tendon are limited excised and with the ankle plantarflexed up to 35° a direct modified Bunnell suture is done.

In our technique, instead of one centrally running suture as in original Bunnell (fig. 1), two laterally sutures on both sides of each stump, were used (fig. 3 and fig. 4). One of the sutures starts from the superior and the other from the inferior tendon stumps. Each of the two sutures is passed through the level of section or rupture and then is fixed in the opposite tendon stump. This fixation is by four knots, two in the end of the proximal stump and two in the end of the distal stump in the manner described in fig. 2. In some cases, especially in cases of tendon sections, the tendon repairing was supplemented with interrupted circumferential sutures. After tendon repairing, we pay special attention to the synovial sheath suture. It is carefully sutured to cover as long as possible the repaired tendon.

Postoperatively, a series of three casts is used. First it is a long cast with the knee in 20 degree of flexion and the ankle in 30 degree of plantar flexion is applied. After three weeks another below-knee with the ankle in 15-20 degree of plantar flexion is applied. The patient is encouraged to move his knee. Five weeks after surgery the third below-knee walking cast with the ankle in neutral position or slight flexion is applied. The last cast is for another two weeks and the progressive weight-bearing is commenced.

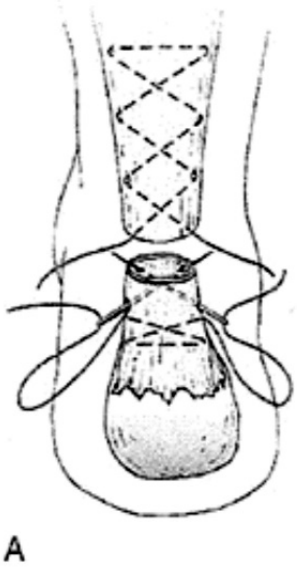

Figure 1 - Original Bunnell suture (from Coughlin MJ, Schon LC. Disorders of Tendons. In: Surgery of the Foot and Ankle. Eighth edition, Mosby, Inc. 2007.)

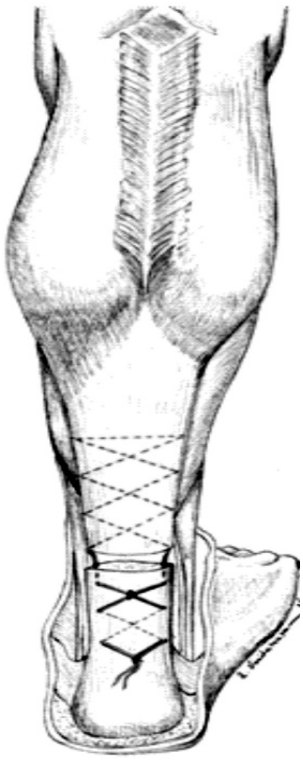

Figure 2 - Modified centrally running Bunnell suture with two distal knots fixation. This initial variant was not used in cases included in this study

After cast removal the patient is advised to wear shoe with high heel for another three months and increased activity and physical therapy are initiated.

RESULTS

In the cases of section the average follow-up was 6 months and ll of them have had the evolutions with no major or minor complications.

In the cases of acute ruptures the average follow-up was 12 months. In all cases, no surgery related major compli

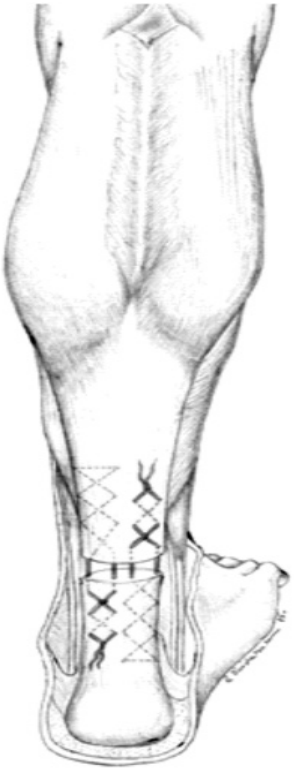

Figure 3 - Modified Bunnell with two laterally sutures. This is our technique which was used in all cases of the study

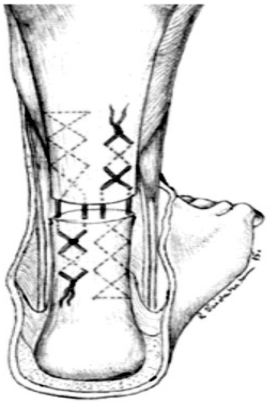

Figure 4 - Our technique - detail

cations, such as tendon rerupture or necroses, sural nerve injury, skin necrosis, wound infection, or deep infection. As minor complications, there were two tendon contractures and one superficial wound infection which was conservatively treated. In all patients with minor complications, no supplementary surgical treatment was done. None of them had tendon adhesion to the skin and the skin over the tendon was movable. Two patients had cosmetic complaints concerning the scar but without affecting the ankle function.

All patients were able to stand on their tiptoes and single affected side leg hopping was possible one year postoperatively. Active range of motion was found to be reduced with limited dorsiflexion in two cases with acute rupture, and the difference was less than 10°. At the last follow-up, there had been no cases of rerupture and the subjective satisfaction was excellent or good in all the patients.

DISCUSSION

In accidental section of Achilles tendon, an end-to-end tendon suture is usually done but simple interrupted suture is not sufficient. In these cases, we consider Bunnell suture to be the method of choice. Initially, we modified centrally running Bunnell suture in the manner shown in fig. 2. This initial variant was not used in cases included in this study. Then, in order to improve the suture strength we used two running suture of the original Bunnell, in the manner shown in fig. 2. This surgical variant was used in all patients of this study.

In acute ruptures of the Achilles tendon the treatment options include nonsurgical and surgical variants. The nonsurgical one avoids the surgical risks but it is associated with a high risk of rerupture (15). Despite the surgical risks, a number of authors consider surgery as a common treatment of Achilles acute ruptures (16, 17, 7).

Although, in acute cases, percutaneous procedure increases in popularity, surgery is commonly performed as an open technique (16). The most usual techniques for primary open repair are Bunnel, Kessler and Krackow sutures (6, 19). Although there were reported reruptures after a Bunnell suture, we consider this method and used a modified Bunnell one in the majority of our patients with direct primary sutures. This modified Bunnell is a preference of the main author (IS).

Our manner of fixing the knots realizes a superior tight fitting than the usual Bunnell suture. In this variant, instead of two knots both of them placed at the level of section or rupture, there are four knots, two in the end of the proximal stump and two in the end of the distal stump. These four knots are not at the level of section, but two up and two down, proximal to the level of section. Our results suggest that this modified Bunnell suture improves the suture strength and is associated with a low rate of reruptures.

We consider to be important the protection and dissection of the synovial sheath. At the end of the tendon repairing, a carefully synovial sheath suture has the advantage to create good biological conditions for tendon healing. Based on this special attention to the synovial sheath, in our series none of them had tendon adhesion to the skin.

CONCLUSIONS

The results of this study suggest the modified Bunnell suture in our manner has some advantages. In Achilles tendon section or acute ruptures, it is associated with good functional results and a low rate of complications. We consider that this type of suture increases the strength of the sutured tendon and generates a low rate of reruptures.

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REVIEW

LIVER DISEASE IN PREGNANCY

Corina Silvia Pop[1,2], Petruța Jantea[1], Denisa Dobrin[1], Alina Tomescu[1], Roxana Maria Nemeș[3], Floarea Mimi Nițu[4], Paraschiva Postolache[5]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[2]*Medical Clinic and Gastroenterology, University Emergency Hospital, Bucharest*
[3]*Marius Nasta National Institute of Pneumology, Bucharest, Romania*
[4]*University of Medicine and Pharmacy, Craiova, Romania*
[5]*Grigore T. Popa, University of Medicine and Pharmacy, Iași, Romania*

Summary

The liver diseases during pregnancy represent a challenge of both the hepatologist and the obstetrician. The abnormal hepatic test appears in 3% of the cases. They represent the expression of three categories of liver diseases: liver disease specific in pregnancy of which the most severe one being the acute fatty liver of pregnancy, chronic liver previous to pregnancy such as chronic viral hepatitis, cirrhosis and liver diseases coincidentally with the pregnancy of which the most frequent ones are the acute viral hepatitis. The evolution and prognosis of these liver affections as well as the treatment of these depend to some extent on the trimester of the pregnancy, as the affections tend to be more severe in the third one. However it also depends on the possible occurrence of the hepatic failure with major consequences for the mother and her child. The main objectives when managing the mentioned diseases are to diminish the risk of affecting the fetus and last but not least to decrease the maternal distress.
Key words: liver, hepatitis, pregnancy, fetal, maternal

Résumé

Les maladies du foie pendant la grossesse

Les maladies du foie pendant la grossesse représentent un défi pour l'hépatologue et pour le obstétricien. Les tests hépatiques anormaux pendant la grossesse surviennent dans 3% des cas et représentent une expression de trois types de maladie du foie: maladies du foie spécifiques à la grossesse, dont la plus grave est la stéatose hépatique aiguë de la grossesse, maladies chroniques du foie avant de grossesse telles que l'hépatite chronique, la cirrhose et les maladies du foie qui coïncident avec la grossesse dont les plus courantes sont l'hépatite virale aiguë. L'évolution et le pronostic de ces maladies du foie et leur traitement dépendent dans une certaine mesure du trimestre de la grossesse, devencent au troisième trimester, mais aussi de la possibilité de l'apparition de l' insuffisance hépatique aux conséquences majeures pour la mère et le fœtus. L'amélioration de la souffrance maternelle et la réduction du risque de nuire au foetus sont des objectifs importants de la gestion de ces maladies.
Mots clés: foie, hépatite, grossesse, fœtus, maternelle

Introduction

Abnormal liver test occurs in 3% of pregnancies being caused by many potential causes [7]. Liver diseases during pregnancy can be divided in three category. The first group of liver affections are that of liver disease specific or unique with pregnancy: hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, hepatic disorders associated with preeclampsia. [8] The second group is that of coincidentally acute liver disease such as acute viral hepatites that are usually benign, such as hepatitis E and herpes simplex, but are more likely to lead to fulminant hepatic failure during pregnancy [7]. The third group comprises chronic liver disease and includes autoimmune hepatitis, chronic viral hepatitis B and C, cirrhosis. The evolution and prognosis of these liver affections as well as the treatment of these depend to some extent on the trimester of the pregnancy, as the affections tend to be more severe in the third one [7,9]. However it also depends on the possible occurrence of the

Correspondence address: *Roxana Maria Nemeș, MD, PhD, FCCP*
Marius Nasta National Institute of Pneumology, Bucharest
Head of Pulmonary Function Tests Department
e-mail: roxa.nemes@gmail.com

hepatic failure with major consequences for the mother and her child. [8,9]

The main objectives when managing the mentioned diseases are to diminish the risk of affecting the fetus and last but not least to decrease the maternal distress.[7,8,9]

Physiological change in pregnancy

Biochemical and hematological tests in normal pregnancy show little difference in non-pregnant women [7]. The transaminases remain unchanged. Serum alkaline phosphatase increases two to four fold in the last trimester. Serum bilirubin is normal or slightly lower, γ-glutamyl transpeptidase remains within normal limits. Fall in serum albumin is related to haemodilution, known the blood volume is increased by 40% [8].

Liver diseses unique to pregnancy

Hyperemesis Gravidarum

Hyperemesis gravidarum (HG) occuring in 0,4% of pregnancies, is not a really liver disease. Nevertheless, HG should be considered in the differential diagnosis of elevated aminotransferase level presenting in the first trimester, liver dysfunction occuring in one-quarter of cases[1]. This condition, named also extreme morning sickness, consists of an intractable nausea and vomiting with dehydration and ketosis, that necessitates intravenous rehydration and nutritional support [1,2]. Unnecessary upper endoscopy is performed frequently to rule out other gastroduodenal diseases. HG resolves by about 20 week but in some patients it may persist, especially during a first pregnancy, with no increase in prematurity or birth defects [2].

Intrahepatic Cholestasis of Pregnancy (ICP)

Represents a type of cholestasis of unknown cause that shows up in the second or third trimester of pregnancy [3]. It is characterised by a severe pruritus in more than 70% of the cases and an increase in the level of serum bile acids. The prevalence in Europe is 1% and the family history is present in more than 50% of the cases [4].

Etiology and Pathogenesis

Etiology and Pathogenesis are unknown. Genetical, hormonal and metabolic factors are involved: genetic mutation at the MDR3 gene, oestrogen and progesterone can determine the appearance of cholestasis, dysfunction of lipid metabolism respectively [4].

Clinical Manifestation

Initial pruritus is in palms and soles and then becomes generalised and can determine insomnia and fatigue. 20% presents jaundice at 1-4 weeks after the appearance of pruritus together with nausea and vague pain in the right upper quadrant [4,5].

Laboratory findings

Hepatic Cytolysis and Cholestasis are relatively frequent; ten faults increased level of aminotransferase are present in almost half of the cases [3,4]. Total bilirubin and GGT are slightly increased in almost half of the patients. High levels of serum Alkaline phosphatase is difficult to interpret knowing that this enzyme is already present in high levels at the placental membrane site [3,5].

The most distinct characteristic is the 10 and 100 times increase of bile acids in the serum [3,4,5]. This increase can be sometimes the only change together with the pruritus in pregnant women with Intrahepatic Cholestasis.

Differencial Diagnosis of the pruritus [4,5]

In pregnant women the DD is done with acute fatty liver of pregnancy at which jaundice is always present and the general state is profoundly distorted [4].

Treatment

The objectives are represented by the diminishing of the pruritus and the decrease of fetal risk [3]. Some studies have shown that ursodeoxycholic acid can improve the mother's itch and the fetal outcome [4]. Giving Dexamethasone for ten days has been used for emergency treatment. We can also use Cholestiramine or Phenobarbital [4]. Women with this condition will have an induced delivery at 38 weeks to decrease the fetal risk [5].

Course and Prognosis

ICP is a rare, benign disease with a favorable evolution. In most cases at a future pregnancy the women show a moderate cholestasis and the administration of contraception will determine the reappearance of the syndrome [3,4]. The fetal injury is shown in 40-60% of the cases but perinatal mortality does not exceed 10%[4,5].

Acute fatty liver of pregnancy

Acute Fatty Liver of Pregnancy represents a rare disease with potential mortality risk that could appear in third trimester of pregnancy [7].

The Etiology and Pathology are not known. Impairment of mitochondrial fatty acid oxidation in generally prone women is thought to cause microvesicular steatosis [9].

Clinical Manifestation

Some of the symptoms are vomiting, malaise, abdominal pain and polydipsia followed by jaundice not together with pruritus. In severe cases hepatic failure occurs up to hepatic coma [10].

Laboratory Findings

Cytolysis is always present and moderate, together with minimal cholestasis. ALT and AST are <1000 U/l. Hyperuricemia is present up to 20 mg/dl [7,11]. Signs of hepatic failure can be present: increased prothrombin time and especially hypoglycemia [8,9].

Prognosis and Treatment

AFLP represents a medical and obstetrical emergency.

The diagnostic suspicion based on the clinical and paraclinical data is sufficient for hospitalization in the Intensive Supportive Care Center and also to initiate the emergency treatment [7,8].

There is no specific treatment of AFLP. The therapeutic decision, the treatment of hepatic failure and immediate termination of pregnancy, need to be done in absence of the pathological confirmation [9,10].

In order to save a patient suffering from AFLP and the hospital can provide this, the emergency hepatic transplant represents an option [10,11].

The fetal and maternal mortality is up to 90%. However this can be decreased if AFLP is recongnised early and the birth is induced[9,11].

Hellp syndrome and pre-eclampsia (HS and PE)

HELLP syndrome and Pre-eclampsia represents a syndrome occuring in more than 20 weeks pregnant women characterized by arterial hypertension, proteinuria, and edema [6]. Although the hepatic involvement in pre-eclampsia is rare, it indicates a severe evolution with fetal and maternal morbidity and mortality. The criteria of severe PE: BP > 160/100 mmHg; proteinuria > 5g/24h; oliguria < 400 ml/ 24h; Seizure, Pulmonary Edema and HELLP syndrome [12].

HELLP syndrome occurs at 10% of the pregnancies with PE, more frequent in older women [12,13].

Etiology and Pathology

The Etiology is not known however the pathology is characterized by endothelial injury and platelet activation and fibrin deposition in vessels [13]. There are areas of hemorrhage and necrosis involving even the entire liver lobule which may lead to intraperitoneal bleeding[13].

Clinical Manifestations

Most women present themselves with abdominal pain, nausea, headache, vomiting and visual disturbances. Jaundice occurs only in 5% of cases[12,13].

Laboratory Findings

- Microangiopathic hemolytic anemia
- hyperbilirubinemia with indirect bilirubin
- decreased serum haptoglobin
- slight cytolysis with ASTx2N
- low platelets > 150,000/mm^3 [14]

The complications of the HELLP can be: abruption of placenta, disseminated intravascular coagulation and seldom acute liver failure [14].

Treatment and Prognosis

HS and PE could threat the child and the mothers' life. Maternal mortality is 35% but could reach 50% in case of a liver rupture. However it can reoccur in future pregnancies [6].The initial treatment must focus on the stabilization of the hemodynamic parameters of the patient for the induced delivery [12].

Chronic liver disease in pregnancy

Viral hepatitis

Viral Hepatitis represents the frequent cause of jaundice during the pregnancy [21]. The evolution of the several types of hepatitis e.g. Hepatitis A, B,C is not affected by pregnancy. However Virus E hepatitis can occur with severe evolution during pregnancy. Acute viral hepatitis presents a fetal and maternal morbidity and mortality risk: the infection of the fetus, pregnancy complications and death [21].

Hepatitis B

Flares of hepatitis B are more common in post-partum due to immune tolerant state of pregnancy [21]. HBV infection presents a high risk of vertical transmission causing fetal and newbornhepatitis The materno-fetal vertical transmission of the B virus predisposes to cirrhosis and hepatocarcinoma in young adults [15].The perinatal vertical transmission of the B virus occurs if the mother shows acute virus B hepatitis in the last few months of pregnancy or shows one of the forms of chronic hepatitis B: HBe positive/negative, HBs carrier, virus B occulted infection[15].The risk of transmission of the virus B during the pregnancy is increased especially if

- The mother presents AgHBe positive- risk of transmission based on maternal serologic status > 90% in the absence of immunoprophylaxis [21];
- Viral load is high (HVB-DNA)-risk of transmission based on maternal viral load as low as 106 copies/ mL (200 U/mL)[21];
- Prolonged delivery [15].

Goals for antiviral therapy during pregnancy consisted in treatment of chronic disease in the pregnant woman and treatment to decrease risk of perinatal transmission [21].

Pregnant women with high risk of exposure to HVB (multiple partners, IV drugs) must be vaccinated even during the pregnancy with rappel at 1 and 6 months [21].

When the child is born from an infected mother infected with B Virus must receive the HBIG-immunoglobulin for B Virus 0.5ml IM and anti-HVB vaccination in less than 12h after birth with a repeat at 1-2 and 6-12 months [21].

The efficiency of this treatment is 95% with the exception of the cases when the mother presents an increase level of HVB-DNA [21].

Breast feeding is possible however there is a transmission risk through milk especially in high viral load cases [15].

The pregnant women with chronic hepatitis B can be treated with Telbivudin and in the last trimester Tenofovir is efficient and safe [21].

Hepatitis C

The risk of transmission during pregnancy of HCV is low. Acute hepatitis with C virus is extremely rare and does not interfere with the evolution of pregnancy. [15,16] In developed countries prenatal consultation consists of Virus B and C markers. Breast feeding is not recommended as the HCV can be passed on especially in high viral load cases. [15,19] Interferon and Ribavirin are contra-indicated

during pregnancy. [15,16] A new generation of antiviral treatment for HCV Ledipasvirand/or Sofosbuvir are considered category B, studies in progress in 2015 with good preliminary results.

Liver diseases coincidentally with pregnancy

Hepatitis E

Hepatitis E represents an acute liver affection with oral-fecal transmission and similar evolution with the other types of hepatitis with the exception of the appearance during the pregnancy when the evolution can be fatal in >25% of the cases [22]. Other complications determined by HVE complications during the pregnancy are the following: fetal-maternal transmission, abortion, premature delivery, infection, and death of the newborn [22].

Acute viral hepatitis E represents the most frequent cause of hepatic failure during pregnancy, associated with high mortality [15,22]. Differential diagnosis is made especially with acute fatty liver of pregnancy due to similarity of the clinical picture [15].

Herpetic Hepatitis(HH)

Herpetic Hepatitis represents an acute liver disease determined by the simplex HSV1 and HSV2 virus [17] that represents a potential fatal disease if it occurs during a pregnancy. Genital Herpes represents an important risk factor for the occurrence of this disease. Herpetic Hepatitis presents general unspecific manifestations such as fatigue, inappetence, nausea, vomiting, and fever together with laboratory suggestive changes: Marked cytolysis up to 5000U/L, minimal cholestasis, hyperbilirubinemia, low platelets, hepatic liver failure manifestations[18].The most severe complication of HH occurred during the pregnancy represents acute liver failure with fetal and maternal mortality risk up to 80-90%[17,18].

The Hepatic biopsy performed in most cases when doing the autopsy, highlights viral inclusions within the nucleus situated in the areas with dispersed necrosis [17,18]. The clinical suspicion for HH is sufficient in order to start the emergency treatment with Acyclovir together with the measures of sustaining the hepatic function [17,18].

The urgent administration of acyclovir both to the mother and the child straight after birth represents the only solution of decreasing the high mortality in this disease [17,18].

Conclusions

It is important to put the correct diagnostic of the cause of liver disease in pregnancy-as difficult as it may be not only because it can cause a high mortality and morbidity of the mother, but also because of the complication to her fetus.

The gynecologist has to know not only the normal physiology of the pregnancy, but also certain disorder that appear only during the pregnancy or that are exarcerbated by it. Moreover it has to exist a great collaboration between the gastroenterologist and gynecologist, to work as a team so they can prevent any unfavorable evolution of the pregnancy and deliver a healthy child.

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REVIEW

URIC ACID IN PREGNANCY - INDUCED HYPERTENSION / PREECLAMPSIA - PATHOGENIC FACTOR OR PROGRESSION MARKER DURING PREGNANCY AND AT A DISTANCE?

Carmen Gabriela Predoi[1], Corina Grigoriu[2], Andreea Elena Mihart[3]

[1]*PhD candidate, "Carol Davila" University of Medicine and Pharmacy, Bucharest*
[2]*"Carol Davila" University of Medicine and Pharmacy, Bucharest*
[3]*Obstetrics-Gynaecology Department, Bucharest Emergency University Hospital*

Summary

Pregnancy-induced hypertension / preeclampsia (PIHT / PE) is a complex condition, which develops in the first weeks of pregnancy, involving the placenta and vascular endothelium as key tissues, with remote pathological response of the cardiovascular system, both in the mother, and the child. Uric acid levels increase more in pregnancies complicated by PIHT and preeclampsia, the values possibly signalling severe progress of the condition. It is also considered that hyperuricemia is very often associated with intrauterine growth restriction. The studies published to date have tried to highlight a possible role of uric acid as early marker for PE, but the results were inconsistent. We do know, on the other hand, that later in pregnancy, after the 34th WA, significant increases in serum uric acid can act as a severe warning sign for severe maternal, as well as foetal, progression. Exceeding the values outside pregnancy is always a sign of aggravation, which requires close monitoring of the pregnant woman and foetus. The most interesting results were obtained determining the levels of serum uric acid after 20 WA, in primiparae presenting with elevated BP (PIHT). Serial determinations of serum uric acid, especially values above 5.2mg / dl suggest a high risk of progression to PE or risk of intrauterine growth restriction, making uric acid a valuable element of prognostic and supervision for a specific group of pregnant women at risk.
Key words: pregnancy-induced hypertension, preeclampsia, uric acid, hyperuricemia

Résumé

L'acide urique dans l'hypertension artérielle gravidique / pré-éclampsie - facteur pathogène ou marqueur évolutif dans la grossesse ou à la distance?

L'hypertension artérielle gravidique / pré-éclampsie (HTA / PE) est une maladie complexe, qui est constituée dans les premières semaines de la grossesse, ayant le placenta et l'endothélium vasculaire comme tissus clé, avec un tintement pathologique à distance sur le système cardio-vasculaire, pour la mère et pour l'enfant. L'acide urique est plus élevé dans les grossesses qui se compliquent avec HTA et pré-éclampsie, et il est possible que ses valeurs signalent l'évolution sévère de la maladie. Il est également considéré que l'hyperuricémie est très souvent associée à un retard de croissance intra-utérin. Les études publiées à ce jour ont essayé de mettre en évidence un possible rôle de l'acide urique marqueur précoce pour la PE, mais les résultats ont été discordants. D'autre part, nous savons que plus tard dans la grossesse, après 34 semaines, les augmentations significatives de l'uricémie peuvent agir comme une alerte sur une évolution maternelle et fœtale grave. Surmonter les valeurs hors de la grossesse est toujours un signe d'aggravation, qui exige une surveillance approfondie de la femme enceinte et du fœtus. Les résultats les plus intéressants ont été obtenus avec la détermination d'uricémie après 20 semaines de grossesse, chez les primipares avec la tension artérielle élevée (HTA). Les déterminations en série de l'uricémie, en particulier les valeurs en dessus de 5,2 mg / dl, suggèrent un risque élevé d'évolution vers la PE ou le risque de retard de croissance intra-utérin, ce qui fait de l'acide urique un élément précieux pour le pronostic et la surveillance d'un groupe spécifique des femmes enceintes à risque.
Mots-clés: hypertension gravidique, la pré-éclampsie, l'acide urique, l'hyperuricémie

Correspondence address: *Corina Grigoriu, MD*
Lecturer at "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
e-mail: corigri@gmail.com

Pregnancy-induced hypertension / preeclampsia (PIHT / PE) is a complex condition, which develops in the first weeks of pregnancy, with the placenta and vascular endothelium as key tissues, with remote pathological response of the cardiovascular system, in both the mother, and child. Current studies worldwide are trying to bring the opportunities of screening, early prediction and prevention of this disease closer to daily practice.

Poor invasion of spiral arterioles by the foetal trophoblast is a histopathological certainty, resulting in placental ischemia and reperfusion. This creates a hypoxic environment that promotes oxidative attack and generalized endothelial inflammation.

The hallmark of the disease is hypertension, which occurs after 20 weeks of amenorrhea (WA) also associating signs that signal endothelial involvement: proteinuria, possibly oedema, damage in the foetal territory - intrauterine growth restriction, oligoamnios, chronic foetal suffering. HELLP syndrome (an acronym derived from English - haemolysis, elevated liver enzymes and thrombocytopenia) may complicate the progression of a pregnancy, with or without preeclampsia, being considered one of the major complications of this generalized endothelial impairment.

Considered a "first pregnancy disease", PIHT / PE recognizes the following risk factors: extreme ends of the reproductive age interval, chronic arterial hypertension, renal disease, obesity and insulin resistance, diabetes mellitus, hereditary thrombophilia, family history of preeclampsia. Patients who develop HELLP syndrome are more often multiparous, over 35 years of age, with possible history of hypertensive disease during pregnancy.

The main cause of pregnancy-induced hypertension / preeclampsia, primum movens of the pathophysiological processes, is low placental perfusion. Trophoblastic invasion of the spiral arterioles is poor, and their modelling is insufficient.The release of factors with widespread endothelial damage potential is initialized at placenta level, both in the maternal, and in the foetal compartment.

Biochemistry of Uric Acid

Uric acid is a breakdown product of purines, by a process catalysed by enzymes xanthine dehydrogenase / xanthine oxidase. Xanthine dehydrogenase is converted to xanthine oxidase by various stimuli, of which ischemia has an important role to play. At the same time of the production of uric acid, the free radical superoxide is also produced, so that the purine metabolism contributes to oxidative stress. Xanthine oxidase is found in most tissues, but the maximum concentrations are recorded in the liver and bowels. (fig. 1)

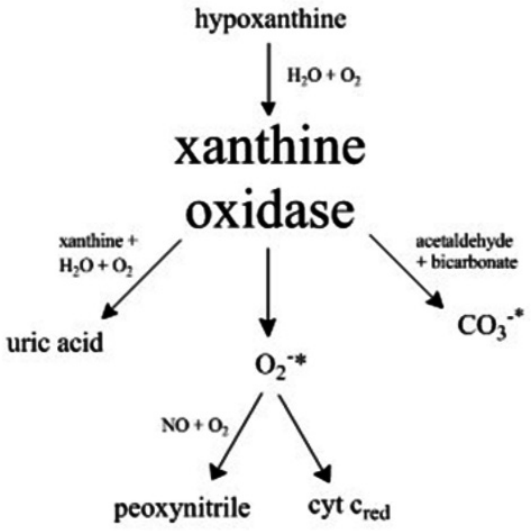
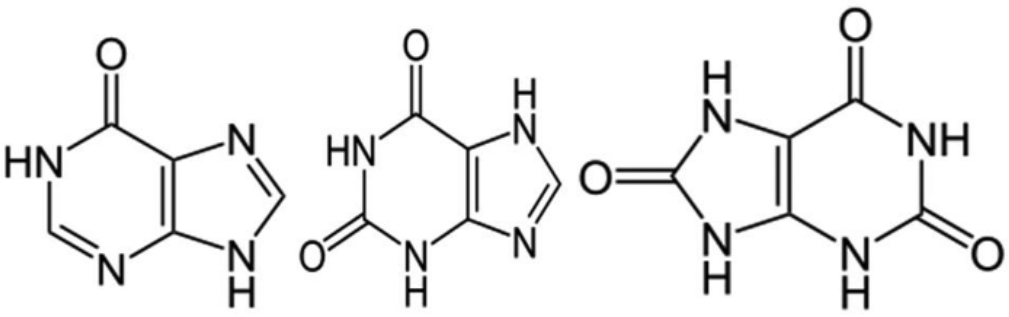


Figure 1

It has been demonstrated that after an ischemic aggression, both the xanthine oxidase concentration and that of uric acid increase, supporting the hypothesis that free xanthine oxidase is involved in the endothelial oxidative attack. (fig. 2)

One should take note of the fact that man and great apes, unlike other mammals (possessing the enzyme uricase, that breaks down uric acid into allantoin, a totally non-toxic compound that is excreted by the kidneys), must eliminate uric acid by renal excretion. The levels of uric acid in healthy adults involve low circulating concentrations (below 6 mg / dl).

Uric acid presents some specific and important biological functions:



HYPOXANTHINE XANTHINE URIC ACID

- it is an important antioxidant, antagonizing the superoxide ion, free oxygen and hydroxyl radicals;
- reduces tyrosine residue nitrosylation by peroxynitrite;
- maintains the activity of superoxide dismutase;
- when there are not enough antioxidants (ascorbate in deficit), it becomes a pro-oxidant itself (urate radical);
- it is a mediator of inflammation, stimulating production of monocyte attracting proteins -1, IL-1beta, IL -6 and TNF alpha.

The levels of uric acid are influenced by diet (increased amounts of proteins, fructose), alcohol, intense cellular metabolism, purine metabolism enzyme defects, or kidney disease.

Uric acid in pregnancy

Oestrogens stimulate the renal excretion of uric acid (which is why serum uric acid levels are higher in men, and in women who have reached menopause). In pregnancy, although under the direct influence of oestrogens there is an increased protein anabolism (to support the function of the maternal body and new syntheses in the foetal territory), and increased production of uric acid, given the increasing volume of circulating plasma and glomerular ultrafiltration, serum uric acid values decrease by 25-30% below those outside pregnancy. The values will slowly increase toward the end of pregnancy, never going beyond the values of non-pregnant women (4-6 mg / dl) however.

Uric acid increases more in pregnancies complicated by PIHT and preeclampsia, its values possibly signalling the progress towards a more severe condition. Uric acid may be elevated as early as the 10th WA, its role as possible early marker of the disease being still under discussion. It has been seen that uric acid levels can be increased even before the appearance of proteinuria. It is also considered that very often hyperuricemia is associated with intrauterine growth restriction.

One should remember that hyperuricemia is considered a predictive factor for cardiovascular and renal disease (in the non-pregnant population, both the general and in chronic hypertensives). Uric acid is accepted as a marker of progression in patients with established cardiovascular disease. On the other hand, experimental studies have shown that uric acid can have a directly pathogenic effect (endothelial and kidney impairment). Thus the discussions regarding the possible pathogenic effect of hyperuricemia in the maternal placental bed and on the maternal vessels.

From recent research, several potential mechanisms by which uric acid could (also) have pathogenic effect in preeclampsia result:

- in the placenta: it inhibits trophoblasts migration (in vitro studies), increases oxidative stress and stimulates the inflammatory response;
- in the maternal territory: inhibits normal function at endothelium level, induces oxidative stress, increases systemic and glomerular pressure (animal studies), induces insulin resistance (animal studies);
- in the foetal territory: inhibits foetal angiogenesis (blocking VEGF-induced endothelial proliferation), with intrauterine growth delay as a possible effect.

The causes of hyperuricemia in preeclampsia are not yet clearly established. The most important mechanism seems to be reduced glomerular filtration rate. However, serum uric acid levels are too high to not involve other mechanisms as well, either decreased secretion or increased renal reabsorption. There is a possible parallelism to the effect of the injection of a vasoconstrictor (norepinephrine), which is followed by decreased renal clearance of uric acid or low clearance in glomerulonephritis. Given these observations, it can be concluded that an increase in serum uric acid may be considered an early marker for the development of PE.

On the other hand, an increased placental production of uric acid, due to placental ischemia and trophoblasts' degradation is also plausible, with increased release of purines. Also, a foetus exposed to chronic hypoxia presents high levels of purine metabolites, that cross the placenta into the maternal territory to be degraded by xanthine oxidase. This latter mechanism seems to be the best explanation for the association of hyperuricemia and foetuses with intrauterine growth retardation.

Latest studies show that uric acid can induce the production of interleukin 1 in the trophoblasts, by activating a specific receptor (Nod-like receptor Nalp3), stimulating the expression of imflammasone components.

The initiating element of hyperuricemia in preeclampsia is not yet well characterized. Uric acid is increased before hypovolemia and decreased glomerular flow become detectable. This phenomenon can be explained by two mechanisms: women who develop PE begin their pregnancy with already established metabolic syndrome, or increased uric acid occurs very early in pregnancy. Possible sources of increase in uric acid in preeclamptic patients are multiple: the foetus, placenta, maternal and vascular territories.

Trophoblastic invasion is inhibited by elevated serum uric acid, so vascular modelling is flawed at placental level. Ischemia, post-ischemic placental reperfusion and increased oxidative stress result. In the maternal territory, consecutive to endothelial dysfunction (induced by uric acid), vasospasm and ischemia also occur. The ischemia and oxidative stress maintain the vicious circle of uric acid hyperproduction. Tissue injuries cause the release of purines, while hypoxia stimulates the activity of xanthine oxidase. Thus, both the substrate and the enzyme required to increase the production of uric acid present elevated levels. Vasospasm and endothelial dysfunction stimulate renal reabsorption of uric acid, reducing its excretion.

Clinical applicability

The studies published to date have tried to highlight a possible role of uric acid as early marker for PE, but the results were inconsistent. We do know, on the other hand, that later in pregnancy, after the 34th WA, significant increases in serum uric acid can act as a warning sign for severe maternal, as well as foetal, development. Exceeding values outside pregnancy are always a sign of aggravation, which require close monitoring of the pregnant woman and of the foetus.

The most interesting results were obtained by determining serum uric acid levels after 20 WA, primiparae presenting with elevated BP (PIHT). Serial determinations of serum uric acid levels, especially values above 5.2 mg / dl suggest a high risk of evolution towards PE, or risk of intrauterine growth restriction, making uric acid a valuable element of prognosis and monitoring for a specific group of pregnant women at risk.

Cardiovascular risk in pregnant women with PIHT / PE

Preeclampsia with early onset exposes the patient to increased risk of developing metabolic syndrome over their lifetime, compared with late-onset PE. CHAMPS study (Cardiovascular Health After Maternal Placental Syndromes), conducted on an impressive number of women - 1.03 million- concluded that in women with a history of PE and metabolic syndrome the risk of developing cardiovascular disease is 12 times higher than in patients without such a history. The cardiovascular risk was assessed based on the occurrence in women with no heart or vascular disease or manifestation before a pregnancy complicated by hypertensive / preeclampsia / eclampsia pathology of the following conditions: coronary obstruction, cerebrovascular or peripheral artery obstruction, heart attack, severe arrhythmias or thromboembolic accidents, for which hospitalization and interventions such as thrombolysis, coronary bypass, revascularization, implanting a cardiac defibrillator etc. were required.

The American Heart Association considers a history of PIHT / PE and gestational diabetes as major cardiovascular risk factors, of equal importance with hypertension, hypercholesterolemia, smoking, sedentary lifestyle, obesity or family history of cardiovascular disease. In the UK, there is a recommendation to reassess patients who had PE, at 8 weeks postpartum (National Institute of Clinical Excellence). It is the proper time for a reassessment and for patient education regarding the future risk of PE, as well as of cardiovascular disease, constant (annual) cardiovascular evaluation being indicated, as well as any preventive measures required. Thus, weight loss and maintaining a low body mass index, taking control over a sedentary lifestyle and avoiding smoking, proper nutrition, medical control of diabetes, hyperuricemia, of dyslipidemia and hypertension become essential.

From a practical standpoint, the clinical development of preeclampsia in a pregnant woman can be treated as a pressor test in vivo, indicating an increased risk for subsequent pregnancies, but also for the cardiovascular health of the patient for the rest of her life.

Conclusions

Hyperuricemia in pregnancy is associated with PE / E, with effects both in the maternal and foetal (intrauterine growth restriction) territories. In the non-pregnant population, elevated serum uric acid levels indicate increased risk of cardiovascular and kidney disease. Given that among pregnant women with PE / E, women with cardiovascular pathology will be recruited over the years, it is particularly important to identify biochemical data early and precisely, to ensure proper prevention. Since most frequently it is the gynaecologist who has a chance of meeting a woman at risk, his role in pointing out risk factors becomes very important.

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REVIEW

ELECTROMYOGRAPHIC RECORDING OF THE ABDOMINO-THORACIC WALL IN THE STUDY OF THE ABDOMINAL ACCOMMODATION

L. L. Pop, Iulia Antonia Mureșan, D. L. Dumitrașcu

2nd Medical Department, University of Medicine and Pharmacy Iuliu Haţieganu, Cluj Napoca

Summary

Functional patients are often complaining of postprandial fullness as a disturbing feeling of increased pressure within the abdomen, most of the time accompanied by an acute increase in girth. The shape of the abdomen is determined by the disposition of the walls of the abdominal cavity, mostly by the anterior abdominal wall and the diaphragm. Monitorization by electromyography of the anterior abdominal wall muscles and intercostal muscles, using surface electrodes, and diaphragmatic activity through an intra-esophageal electrode mounted over a probe, led to the conclusion that activity of abdominal musculature adapt to intra-abdominal content. This modulatory mechanism fails in functional patients complaining of postprandial fullness. This abdomino-phrenic incoordination should be corrected with behavioral techniques. The electromyographic activity recording of the abdominal wall will provide an objective diagnosis for postprandial fullness and a good monitorization of the treatment.

Key words: abdominal accommodation, postprandial fullness, EMG, biofeedback treatment

Résumé

Enregistrement électromyographique de la paroi abdomino-thoracique dans l'étude de l'accomodation abdominale.

Les patients fonctionnels qui aux souffrent de gonflement post-prandial, décrivent une sensation de pression accrue dans l'abdomen, frequemment accompagnée de l'ellargissement de la ceinture. La forme de l' abdomen est determinée par la disposition de la paroi de la cavité abdominale, premièrement de l'abdomen antérieur et du diaphragme. La monitorisation par électromyographie des muscles abdominaux antérieurs et intercostaux, en usant des électrodes de surface, et de l'activité diaphragmatique mésurée par un électrode intra-esophage monté par une sonde, a conduit à la conclusion que l'activité de la musculature abdominale antérieure s'adapte au contenu intraabdominal. Ce mechanism modulateur est un échec restéche ant chez les patients fonctionaux qui accusent des gonflements post-prandiaux. Cette incoordination abdomino-phreniquedoit être correctée par des techniques comportamentales. L'enrégistrement de l'activité électromyographique de la paroi abdominale permet un diagnostic objectif du gonflement post-prandial et une bonne monitorisation de la thérapie.

Mots clefs: adaptation, abdominale, plénitude post-prandiale, EMG, traitement bio rétroactif

Introduction

Postprandial fullness and distension are common complains in functional patients (1). Post-prandial fullness is an ambiguous term that defines both, the subjective sensation and the objective abdominal distension. The term should cover the feeling of increased pressure within the abdomen, but when this sensation is accompanied by an actual increase in girth, the term distension might be better used (2). There are four factors included in the pathophysiology of postprandial fullness: subjective sensation, objective girth changes, volume of intra-abdominal contents and muscular activity of the abdominal walls (3).

The shape of the abdomen is determined by the disposition of the walls of the abdominal cavity: the vertebral column and paravertebral muscles which give the shape of the posterior abdominal wall, the diaphragm,

Correspondence address: *Prof. Dan L Dumitrașcu*
2nd Medical Dept., University of Medicine and Pharmacy Iuliu Haţieganu Cluj-Napoca
Clinicilor Str. , no. 2-4, RO 400 003 Cluj, Romania e-mail: ddumitrascu@umfcluj.ro

the anterovertebral muscles and the pelvic floor – with its limited mobility.

Application of new technologies such as abdominal inductance, computerized tomography scanning, gas challenge technique or electromyography of the diaphragm and anterior abdominal wall can lead to a better understanding of the physiologic conditions and pathogenesis of various conditions related to intra-abdominal volume changes.

Electromyography

Electromyography (EMG) is a technique that uses electrodes to detect electrical currents created by muscles contraction. The EMG signal is a complex and noisy signal that generally should be filtered. The signal is described by its amplitude, frequency and phase as a function of time, amongst other parameters. There are two methods that can be used to acquire EMG signal: an invasive method using needle electrodes and a non-invasive method that requires placement of patch electrodes on the surface of the skin – the surface EMG (sEMG) (4). sEMG may provide valuable information from a large mass of muscle tissue and would be more directly correlated to mechanical effect (5), but electrode placement is critical in ensuring reliable and repeatable results.

EMG of the abdomino-thoracic walls

The anterolateral wall of the abdomen is formed by deep layers of muscles, but due to their particular anatomic position it makes possible a selective study of 4 of the most superficial: internal oblique, external oblique, upper rectus and lower rectus. In a study lead by Ng JK et al (6) they were intended to establish best position of the surface electrodes in respect to the abdominal wall muscles. They standardized that for optimal pick-up of EMG signals surface electrodes are best aligned in parallel with the fiber orientation. Results showed that the fibers of external oblique muscle are about 4 degrees more vertical that the lower edge of the eighth rib and 5 degrees closer to vertical than a reference line between the most inferior point of the costal margin and the contralateral pubic tubercle. At the level of anterior superior iliac spine, fibers of the internal oblique muscle are almost horizontally orientated, but at 2 cm below superior iliac spine are aligned about 6 degrees inferomedially to the horizontal. Muscle fibers of upper rectus muscle are 2 degrees inferolateral to the midline while the lower rectus fibers deviated inferomedially from the midline by about 8 degrees. Hence, the appropriate surface electrode placements must follow the muscle fiber orientation described above.

The intercostal muscles activity is recorded at the second intercostals space in the right midclavicular line using a monopolar electrode and a ground electrode placed over the center of the sternum (7,8). (fig. 1)

There are different types of surface electrodes that can be used for the sEMG recording but the most common used are the bipolar Ag-AgCl surface electrodes. These electrodes have a good signal transmission with low interference level, they are easily available and economical.

The surface electrodes are placed on the skin surface that was previously prepared with an abrasive paste to reduce skin impedance. Cutaneous impedance is defined as the resistance of the skin at the pass of an electrical current. Low impedance provides a stable EMG register with low levels of interference.

In case of using sEMG recording with bipolar electrodes, the inter-electrode distance is not yet standardized, so every laboratory is using different positions. In a study of Zedka et al (1), the Canadian group concluded that information about muscle activity is independent from inter-electrode distance or electrode orientation. Recommendations for these electrodes are to make sure that they are well set on skin surface to avoid displacement and thus limiting interference levels.

The appropriate location of abdominal electrodes is checked by recording EMG response to a Valsalva maneuver – global activation of all muscular components or responses

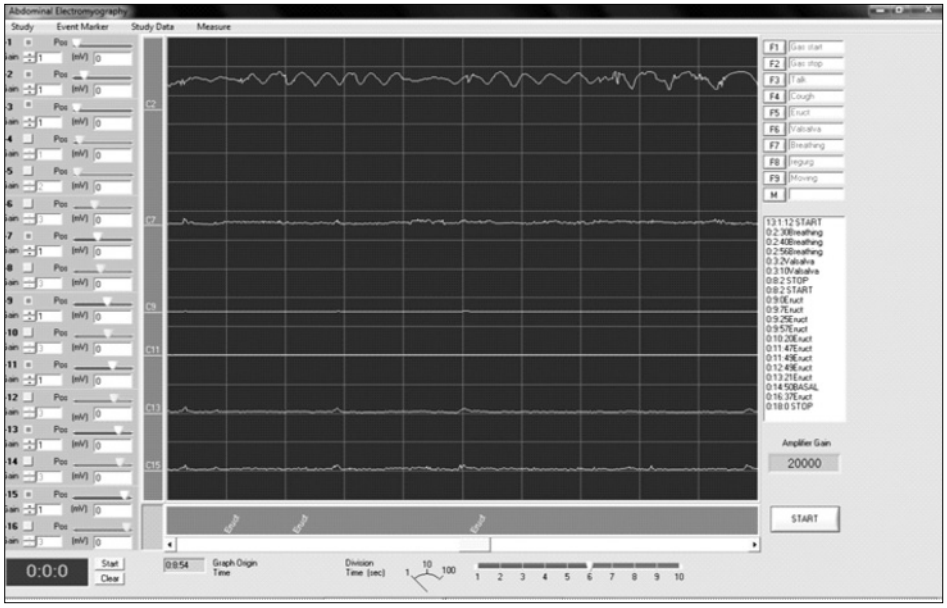

Figure 1

to sit-ups (preferential activation of upper and lower rectus) and responses to rotation of the trunk (activation of ipsilateral internal and contralateral external oblique) (2,3). Intercostals electrode location is checked by recording EMG response to deep inspiration muscle contraction (4).

The amplitude of the EMG signal is used as a parameter to estimate muscular contraction force. The amplitude of the EMG signal is estimated by the root mean square (RMS). The RMS represents the square root of the average power of the EMG signal for a given period of time. It is known as a time domain variable because the amplitude of the signal is measured as a function of time. It is expressed in microvolt (μV). Therefore an increase in the contractile activity of a muscle can be estimated as an increase in RMS respect to its initial values.

Diaphragmatic EMG

There are three methods described in the literature that can be used to record EMG activity of the diaphragm: using

$$\mathrm{RMS} = \sqrt{\frac{1}{T_2 - T_1}\int_{T_1}^{T_2}[f(t)]^2 dt}$$

needle electrodes placed in the diaphragm (5), using surface electrodes (6) or intra-esophageal electrodes mounted over a probe (7). The use of the needle electrode EMG technique has been applied in humans in small physiological studies because of its invasivity, discomfort inducing, technical difficulty and its increase risk of a pneumothorax. Chest wall surface electrodes provide a non-invasive technique, easily applied and more acceptable to patients. Although several possible sites have been proposed, there is not a standardized method for placing the chest wall electrodes. Most commonly it was suggested the collocation close to the anterior axillary line, the midclavicular line, or between the xyphoid process and the costal margin (8, 9, 10). This easy-to-perform method has also its disadvantages: it has a high level of signal contamination from adjacent muscles (11, 12), RMS can be unreliable because of "cross-talk" signals-contamination from intercostals and abdominal muscles activity (13). Subcutaneous fat which significantly reduces signal strength due to its muscle-to electrode filtering effect it's also a drawback for the sEMG measuring of the diaphragm (14).

The diaphragmatic EMG using an intra-esophageal electrode mounted over a probe is by far the technique of choice. This technique is less affected by the "cross-talk" signals and electrodes position has a good standardization. The diaphragmatic muscle is composed by two portions, the crural and the costal portion, that can be anatomically and functionally distinguished. It has been proved that the muscular activity of the crural portion can be correlated with the global diaphragmatic activity (15). Given this fact, the intra-esophageal EMG recording of the crural portion of the diaphragm reflects the entire muscle activity.

Diaphragmatic EMG activity is measured via intra-esophageal ring electrodes mounted over a probe. Number of electrodes per probe, its size and the distance between them are different for every laboratory.

The probe can be inserted via the mouth or the nose and positioned across the diaphragmatic hiatus under fluoroscopic control.

The diaphragm EMG recorded from the esophageal electrode can be contaminated by esophageal peristaltic movements and cardiac activity (recorded by ECG). This inconvenient can be exceeded by using high-pass filters setted at 20-30 Hz (16, 17). (fig. 2)

Pathophysiology of the abdominal thoracic walls

Using an experimental model of colonic gas infusion, the Barcelona groups led by Azpiroz have showed that in healthy controls the colonic gas load is associated with significant increment in EMG activity of all abdominal muscles but the internal oblique which is already contracted due to its antigravitational function (9). In further studies (10)

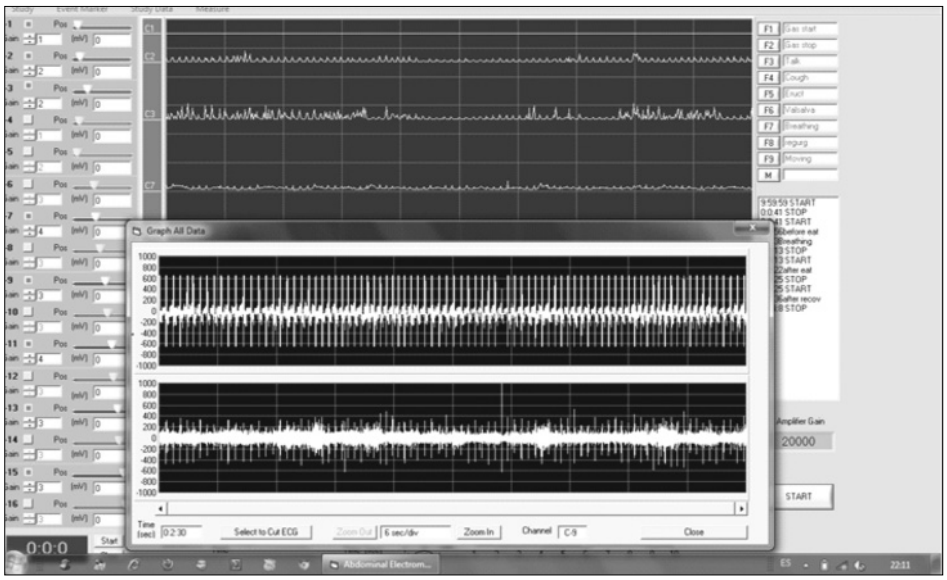

Figure 2 - Filtered EMG registration of the diaphragm and abdomino-thoracic walls

they showed that the abdominal walls actively accommodate to intra-abdominal contents by a coordinated muscular response consisting in a diaphragmatic relaxation completed with compensatory anterior abdominal wall contraction. In the same study Villoria et al (10) have concluded that in healthy subjects the degree of abdominal distension induced by colonic gas infusion results from posture-related abdomino-phrenic muscular response. Hence, in the erect position, the diaphragm relaxed while muscular activity of the anterior abdominal wall increased. The changes in EMG activity occurred progressively during gas infusion period, and diaphragmatic inhibition was correlated with anterior abdominal wall contraction ($R=0.89$; $P< 0.05$). In the supine position, activity of the diaphragm progressively increased (by $15 \pm 6\%$; $P<0.05$); basal activity of anterior abdominal wall was low and there was no relaxation in response to colonic gas infusion.

In functional patients, the abdominal accommodation reflex is abnormal (18,19). This functional patients complaining of abdominal postprandial fullness develop paradoxical contraction of the diaphragm and relaxation of the anterior abdominal muscles in response to intra-abdominal volume increments (10,20). This abdomino-phrenic incoordination is associated with abdominal distension.

In a further study Burri et al (11) have investigated the thorax contribution to abdominal accommodation. Using surface EMG recording of the intercostal muscles in addition to EMG activity of the diaphragm and the abdominal anterior wall muscles, it has been showed that in healthy subjects, accommodation of intra-abdominal loads involves an integrated abdomino-thoracic response. In response to colonic gas load EMG activity increased in abdominal anterior wall muscles with a progressive inhibition of diaphragmatic activity and progressive intercostal muscle contraction. It was reported an increment by 2.0 ± 0.5 mm of the thoracic perimeter which was correlated with diaphragmatic ascent ($R= 0.824$; $P = 0.044$). The normal abdomino-thoracic response maintains intra-abdominal pressure constant. Due to these results, the authors conclude that abdomino-phrenic incoordination in functional patients may be a behavioral response triggered by the uncomfortable postprandial fullness sensation. Given this fact, abdominal postprandial fullness and other functional symptoms may perhaps be treated with behavioral techniques, such as biofeedback techniques to correct abdomino-phrenic incoordination (21).

Conclusions

Data resulting from the EMG recording studies in respect to the muscular activity of the abdominal and thoracic walls have shown that the activity of the abdominal musculature adapts to intra-abdominal content. This modulatory mechanism that involves anterior abdominal wall muscles, diaphragm and the thoracic cage fails in functional patients complaining of postprandial fullness.

In analogy to the idea of behavioral techniques to correct abdomino-phrenic incoordination in functional patients, the EMG recording technique will allow an objective diagnosis for postprandial fullness and a good monitoring of the biofeedback treatment response.

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REVIEW

RELATIONSHIP OF HEPCIDIN LEVELS TO PARAMETERS OF IRON METABOLISM DURING PREGNANCY

Tsvetelina Petkova-Marinova, Boryana Ruseva

Department of Physiology, Medical University, Pleven, Bulgaria

Summary

Pregnancy as a physiological condition in women is associated with elevated requirements of macro- and microelements. Regulation of iron homeostasis is crucial to the mother and developing foetus, because both deficiency and excess of iron are associated with alteration of cellular functions. It has been recently described that a small peptide hormone - hepcidin, acts as a key regulator of iron metabolism. Hepcidin inhibits duodenal iron absorption, the release of iron from macrophages recycling senescent red blood cells, and iron-storing hepatocytes, as well as materno-foetal iron transfer across the placenta. The aim of this review is to examine contemporary conception for the changes in hepcidin secretion and their relationships to parameters of iron metabolism during pregnancy. Results of the literature review indicate that during normal pregnancy, hepcidin exhibits lower serum concentrations compared to non-pregnant women. In high-risk pregnancies - associated with inflammatory processes, hepcidin levels are higher compared to healthy controls. Limited and conflicting data are available on the relationship between hepcidin levels in biological fluids and markers of iron metabolism in pregnancy. Due to the relatively scarce studies on hepcidin levels during pregnancy, and contradictory data on the relationships of hepcidin to parameters of iron metabolism, further research is needed to fully explore the interactions between hepcidin and factors regulating iron homeostasis during pregnancy. Assessment of serum hepcidin concentrations has diagnostic, differential-diagnostic and therapeutic applications. Determination and monitoring serum hepcidin levels is a modern, useful biomarker for early diagnostic evaluation and dynamical assessment of iron bioavailability.

Abbreviations: DCT1 - Divalent cation transporter 1, Dcytb - Duodenal cytochrome b, DMT1 - Divalent metal transporter 1, FPN1 - Ferroportin 1, ID - Iron deficiency, IDA - Iron deficiency anaemia, IL-6 - Interleukin-6, Ireg1 - Iron regulatory protein 1, SatTf - Transferrin saturation, sTfR - Soluble transferrin receptor

Key words: hepcidin, iron, pregnancy

Résumé

La relation des niveaux de l'hepcidine aux paramètres du métabolisme du fer pendant la grossesse

La grossesse comme un état physiologique chez les femmes est associée aux exigences élevées de macro et oligo-éléments. Régulation de l'homéostasie du fer est cruciale pour la mère et le développement du foetus parce que les deux - lacune et excès de fer sont associés à une altération des fonctions cellulaires. Il a été décrit récemment qu'une petite hormone peptidique - hepcidine, agit comme un régulateur clé de métabolisme du fer. L'hepcidine inhibe l'absorption duodénale de fer, la libération du fer par les macrophages recyclage des globules rouges sénescents et les hépatocytes de fer-stockage, ainsi que le transfert de fer materno-fœtale à travers le placenta. Le but de cette revue est d'examiner la conception contemporaine pour les changements dans la sécrétion d'hepcidine et leurs relations aux paramètres de métabolisme du fer pendant la grossesse. Résultats de l'examen de la littérature indiquent que pendant la grossesse normale, l'hepcidine présente des concentrations sériques plus faibles par rapport aux femmes non-enceintes. Dans les grossesses à haut risque - associées aux processus inflammatoires, les niveaux de l'hepcidine sont plus élevés par rapport aux témoins sains. Des données limitées et contradictoires sont disponibles sur la relation entre les niveaux de l'hepcidine dans les fluides biologiques et les marqueurs de métabolisme du fer pendant la grossesse. Grâce aux études relativement rares sur les niveaux d'hepcidine pendant la grossesse, et les données contradictoires sur les relations de l'hepcidine aux paramètres du métabolisme du fer, d'autres recherches sont nécessaires pour explorer pleinement les interactions entre l'hepcidine et les facteurs régulant l'homéostasie du fer pendant la grossesse. Évaluation des concentrations sériques de l'hepcidine a des applications diagnostiques, différentielles diagnostiques et thérapeutiques. La détermination et la surveillance des niveaux de l'hepcidine dans le sérum sont un biomarqueur utile et moderne pour évaluation diagnostique précoce et l'évaluation dynamique de la biodisponibilité du fer.

Mots-clés: l'hepcidine, le fer, la grossesse

Correspondence address: *Tsvetelina Petkova-Marinova, MD*
Department of Physiology, Medical University, Pleven
1 St. Kliment Ohridski Str., 5800 Pleven, Bulgaria *e-mail: cveti_doc@abv.bg*

INTRODUCTION

Essential significance of iron for the human organism has been known since the XIXth century. Nowadays, it is the most intensively studied trace element (1). Due to its properties of redox-active ion, iron is both required for the survival of living organisms, and toxic to the cell in excess through the Fenton reaction (2, 3, 4). Maintaining normal iron homeostasis is crucial to the organism because both deficiency and excess of iron are associated with impairment of cellular functions (2).

Discovery of hepcidin - a small peptide hormone produced in the liver, has led to significant advances in the knowledge of iron homeostasis. It was first isolated and identified from human plasma ultrafiltrate in the beginning of the XXIth century as an antimicrobial peptide (5). Subsequently, a link between hepcidin and iron metabolism was found (6). Experimental in vitro studies (6, 7, 8) have shown that hepcidin inhibits duodenal iron absorption, the release of iron from macrophages recycling senescent red blood cells, and iron-storing hepatocytes, as well as materno-foetal iron transfer across the placenta. Key role of hepcidin in the regulation of iron metabolism was demonstrated by the discovery of hepcidin mutations in humans (9). At present, it is thought that hepcidin is the central regulator of iron homeostasis (3, 10), because this hormone represents a point of convergence of different regulatory mechanisms (11). Hepcidin acts by binding and inactivating the transmembrane iron exporter ferroportin (FPN1, Iron regulatory protein 1 – Ireg1) which is expressed on the cells releasing iron into the plasma and extracellular fluid. By reducing the effective iron exporters, transport of iron from the cells into plasma is suppressed (12).

Three main factors are currently considered to regulate the systemic iron homeostasis and hepcidin production: the level of body iron reflected by both the circulating transferrin-bound iron and the amount of iron stores; the erythropoietic activity of bone marrow; presence of inflammatory processes in the organism. Iron excess stimulates hepcidin synthesis, and increased levels of hepcidin inhibit intestinal iron absorption preventing iron overload. In contrast, under conditions of iron deficiency (ID), hepcidin is suppressed allowing enhanced dietary iron absorption (10). Regardless of iron levels, hepcidin production is also inhibited by increased erythropoietic activity of the bone marrow thus providing increased supply of iron for the erythropoiesis. Hepcidin synthesis is rapidly stimulated by infection and inflammation which presumably reflects the antimicrobial role of this peptide. The cytokine interleukin-6 (IL-6) has emerged as a prominent inducer of hepcidin synthesis in inflammatory conditions. Hepcidin is proposed to be a key messenger between the factors regulating iron homeostasis and different aspects of iron metabolism – intestinal iron absorption, iron release from macrophages and hepatocytes. This hormone maintains the levels of circulating iron within a relatively narrow physiological range corresponding with the requirements of erythropoiesis, while simultaneously limits the possibility of oxidative stress on the cells (2,10, 13).

Pregnancy as a physiological condition in women is associated with elevated requirements of macro- and microelements. Factors involved in the regulation of iron homeostasis during pregnancy are not sufficiently elucidated yet. Suppression of hepcidin production due to decreased iron levels during pregnancy, or existence of unknown pregnancy-specific regulators of hepcidin synthesis and secretion are presumed (14). Investigation of the relationships between hepcidin levels and biochemical parameters of iron metabolism would allow us to examine factors implicated in the regulation of iron homeostasis during pregnancy. Knowledge about changes in hepcidin secretion and their influence on iron parameters during pregnancy would optimize the period of iron supplementation and its duration for the purpose of carrying and delivering healthy children.

The aim of this review is to examine contemporary conception for the changes in hepcidin secretion and their relationships to parameters of iron metabolism during pregnancy.

METHODS

A review of the world scientific literature was conducted. Data were gathered through the databases Google Scholar and Pubmed by using the keywords: "hepcidin", "iron", and "pregnancy".

Changes in hepcidin secretion during normal pregnancies

Pregnancy is a physiological state characterized by elevated requirements of iron due to the growth of foetus, placenta, and expansion of the maternal erythroid mass (14). Maternal and foetal iron demands are compensated initially by iron mobilization from maternal iron stores but as they become depleted, intestinal iron absorption is markedly increased to a nearly ten-fold rate in the third trimester (15, 16). The rate of materno-foetal iron transfer via placenta also increases during pregnancy and is maximal just before the birth (15).

Studies on hepcidin level during pregnancy in the world scientific literature are relatively scarce. There are no data for women with multifoetal pregnancies. Results of the literature search indicate that hepcidin changes even in normal pregnancies. In general, hepcidin exhibits lower serum levels during pregnancy compared to non-pregnant women (16, 17).

Dynamical assessment of serum hepcidin concentrations shows a progressive decline throughout the gestation with the lowest levels found in the third trimester (16, 18). Similar decrease is found in animal studies investigating expression of liver hepcidin mRNA during pregnancy (15). It is known that iron demand of the foetus increases during pregnancy reaching a maximal level in the third trimester and may be responsible for observed dynamics in maternal hepcidin (14).

Data from animal studies show that decline in liver hepcidin expression throughout pregnancy was paralleled

by increase in duodenal iron transport proteins: the ferrireductase duodenal cytochrome b (Dcytb), divalent metal transporter 1 (DMT1, DCT1) on the brush border, and basolateral exporter ferroportin (FPN1, Ireg1). These findings imply that hepcidin acts as a suppressor of intestinal iron absorption during pregnancy (15). Moreover, Young et al. (2012) found that maternal hepcidin play a role in the placental transfer of maternally ingested iron to the foetus (19). Collectively, results suggest that suppression of hepcidin production during pregnancy is presumed to ensure greater iron bioavailability to the mother and foetus, as it was recently concluded in a review by Koenig et al. (14). However, the factors associated with hepcidin suppression during pregnancy still remain unknown (16).

Relationship of hepcidin levels to parameters of iron metabolism during pregnancy

Under physiological conditions the two main factors regulating iron homeostasis are the levels of circulating and stored iron, and the rate of erythropoietic activity (10). In order to examine factors implicated in the regulation of iron homeostasis during pregnancy we explored the relationship between hepcidin levels and iron biomarkers. Modern biochemical parameters characterize different aspects of iron metabolism. Serum ferritin provides an assessment of body iron stores, transferrin saturation (SatTf) is a measure of transport iron, soluble transferrin receptor (sTfR) reflects erythropoietic activity of bone marrow, and serum transferrin estimates biochemical capacity of plasma for binding and transport of iron (20, 21).

Limited data are available on the relationship between hepcidin levels in biological fluids and markers of iron metabolism in pregnancy. Results obtained from different researchers are conflicting. In a significant part of studies, positive correlations of serum hepcidin with ferritin (16, 18, 19), SatTf (16, 18), and haemoglobin concentration (18, 19), and negative correlation of serum hepcidin with sTfR (18, 19) and transferrin (16) have been observed. In contrast, some studies found no significant correlations of hepcidin levels with ferritin (17), sTfR (22), and haemoglobin (22, 23). The significant relationships between hepcidin and iron parameters imply that the functional link between hepcidin and iron metabolism is preserved and hepcidin is likely to be a key regulator of iron homeostasis during pregnancy (16). The regulatory influence on hepcidin production by the levels of iron and erythropoiesis presumably remains relatively unaltered during pregnancy (14). Results of animal studies show that maternal levels of stored and circulating iron are a potential regulator of hepcidin levels (15). Human studies found that hepcidin production during pregnancy is primarily controlled by body iron stores (16, 22).

Results of research by Gambling et al. (2009) indicate that foetal but not maternal iron stores regulate hepcidin expression in the mother (24). Therefore, the issue of interactions between hepcidin and factors regulating iron metabolism during pregnancy remains still debatable.

Changes in hepcidin secretion during problem pregnancies

In high-risk pregnancies – associated with inflammatory processes, obesity (25), and preeclampsia (26), higher hepcidin levels in serum compared to healthy controls have been found. Elevated hepcidin levels during pregnancy might cause iron restriction of mother and insufficient placental iron supply to the foetus (14, 25). Under conditions of hepcidin excess, transfer of iron into plasma is decreased (10). The so-called "functional" ID develops – relative ID in blood resulting from excess storage of iron in the form of ferritin, i.e. in the presence of adequate iron stores (20, 27). Since more than 80% of plasma iron is destined for the bone marrow, hepcidin-mediated hypoferremia results in disturbances of haemoglobin synthesis and red blood cell production (10, 20). Ultimately, persisting hepcidin-mediated iron restriction would be supposed to lead to anaemia of inflammation (10).

In contrast to elevated levels of hepcidin in inflammatory states, in pregnant women with true (actual) ID, serum levels of hepcidin are lower than in pregnant women with normal iron status. This is presumed to be due to the low levels of circulating iron and increased erythropoiesis (28). In animal studies, maternal liver hepcidin expression was significantly reduced under conditions of ID (24, 29). Hepcidin suppression in ID states would promote increased iron absorption in intestine, mobilization from stores, and, therefore, increase in iron bioavailability (14, 29).

Differentiation between true iron deficiency anaemia (IDA) and inflammation-induced iron restriction in pregnancy would allow prescribing iron supplements appropriately (14). In hepcidin excess resulting from inflammation, iron absorption from supplemental sources is markedly decreased and iron supplementation has no benefit (14, 20). A reasonable alternative in such cases may be treatment of the underlying disease (14). Proper diagnosis and treatment of ID and anaemia during pregnancy is crucial to both the mother and developing foetus because, when untreated, they may lead to adverse health outcomes – preterm delivery, low birth weight, increased infant and maternal mortality, morbidity, but also reduced work capacity of the mother, and impaired cognitive development of the child (30).

Moreover, a hypothesis exists that in chronic infections and inflammation, iron supplementation provides free iron with a pro-oxidant role, which may exacerbate the already present oxidative stress (25, 27).

CONCLUSIONS

Discovery of the hormone hepcidin gives new insight into the regulation of iron homeostasis. This small peptide regulates iron bioavailability which is crucial to both the mother and developing foetus throughout the gestation. Reduced hepcidin levels in pregnant women ensure a substantial increase in maternal dietary iron absorption

contributing to adequate iron supply to the foetus via placenta.

Assessment of serum hepcidin concentrations has diagnostic, differential-diagnostic and therapeutic applications. Determination and monitoring serum hepcidin levels is a modern, useful biomarker for early diagnostic evaluation and dynamical assessment of iron bioavailability. As a differential diagnostic tool, hepcidin provides the ability to discriminate between true ID and functional ID resulting from inflammation. This recognition may be useful in predicting the response and therapeutic effect of iron supplementation. Dynamical assessment of serum concentrations of hepcidin in women with normal and problem pregnancies would optimize trace element supplementation and its duration.

Most of the studies on the relationships of hepcidin to iron parameters imply that the regulation of hepcidin by the levels of iron and erythropoiesis remains relatively unaltered during pregnancy although the results are conflicting. The functional link between hepcidin and iron metabolism is presumably preserved and hepcidin is likely to be a key regulator of iron homeostasis in pregnancy. Due to the relatively scarce studies on hepcidin levels during pregnancy, and contradictory data on the relationships of hepcidin to iron parameters, further research is needed to fully explore the interactions between hepcidin and factors regulating iron homeostasis during this physiological state.

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REVIEW

PULMONARY REHABILITATION IN COPD

Paraschiva Postolache[1], Corina Silvia Pop[2,3], Roxana Maria Nemeș[4], Floarea Mimi Nițu[5]

[1]*„Grigore T.Popa", University of Medicine and Pharmacy, Iasi, Romania*
[2]*„Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[3]*Medical Clinic and Gastroenterology, University Emergency Hospital, Bucharest*
[4]*„Marius Nasta" National Institute of Pneumology, Bucharest, Romania*
[5]*University of Medicine and Pharmacy, Craiova, Romania*

Summary

This review aimed to present the use of pulmonary rehabilitation (PR) in different phenotypes of COPD and to highlight the impact of PR on patients with COPD (chronic obstructive pulmonary disease), focusing on the clinical usefulness of PR, which provides patients a favorable environment for optimizing therapy. The data used are of very recent update. Tailored pulmonary rehabilitation programs should be considered for COPD patients of all stages, who have respiratory symptoms and/or who have intolerance to physical effort despite optimal pharmacological treatment. PR has certainly been demonstrated to provide beneficial effects on dyspnea, improvement in muscle strength and endurance, improvement of psychological status, reduction of hospital admissions, and improvement of HRQoL in COPD patients, with a gradual increase in daily physical activity and autonomy. To achieve this, patients' skill and adherence may be facilitated if they are enrolled in longer, comprehensive programs comprising interactions with a multidisciplinary team offering support, council, encouragement, and coaching.
Key words: rehabilitation, COPD, guidelines, quality of life, management

Résumé

La réhabilitation pulmonaire dans la BPCO

Cet avis visait à présenter l'utilisation de la réhabilitation pulmonaire (RP) dans les différents phénotypes de la bronchopneumopathie chronique obstructive (BPCO) et de mettre en évidence l'impact de la RP sur les patients BPCO, mettant l'accent sur l'utilité clinique de RP, qui fournit aux patients un environnement favorable pour l'optimisation de la thérapie.
Les données utilisées sont de très récente mise à jour. Programmes de réhabilitation pulmonaire adaptées devraient être considérés pour les patients BPCO de toutes les étapes, qui ont des symptômes respiratoires et / ou qui ont une intolérance à l'effort physique malgré un traitement pharmacologique optimal. RP a certainement été démontrée à fournir des effets bénéfiques sur la dyspnée, l'amélioration de la force musculaire et l'endurance, l'amélioration de l'état psychologique, la réduction des admissions à l'hôpital, et l'amélioration de la qualité de vie chez les patients BPCO, avec une augmentation progressive de l'activité physique quotidienne et l'autonomie. Pour atteindre ces objectifs, les compétences et l'adhésion du patient peuvent être facilitées par leur inscription dans les programmes longs et complets, y compris leur interaction avec une équipe multidisciplinaire pour offrir un soutien, des conseils, des encouragements et entraînement.
Mots clés: la réhabilitation, la BPCO, les guides, la qualité de vie, le management

Introduction

The prevalence of Chronic Obstructive Pulmonary Disease (COPD) is constantly increasing (1) while its incidence is growing in old age.(2,3) COPD is also a leading cause of morbidity worldwide, particularly in developing countries.(1) Whereas COPD is an obstructive and progressive airway disease, it is also associated with a significant reduction in physical activity, and psychological problems, all of which contribute

Correspondence address: *Roxana Maria Nemeș, MD, PhD, FCCP*
„Marius Nasta" National Institute of Pneumology, Bucharest
Head of Pulmonary Function Tests Department *e-mail: roxa.nemes@gmail.com*

to the patient's disability and poor health-related quality of life (HRQoL).(3,4)

PR and pharmacological therapy are not competitive but rather, must work closely together, if they are to result in a more successful outcome. One particular study has shown that a better outcome of PR can be obtained when it is associated with long-acting anticholinergic bronchodilators.(5) The benefit of PR in patients with COPD in improving exercise capacity and HRQoL, and in reducing breathlessness and health care utilization, has been widely established by randomized studies, summarized in reviews, and by meta-analyses.(6–10) PR is now recommended in several influential guidelines.(3,11)

METHODS

This review aimed to present the use of PR in different phenotypes of COPD and to highlight the impact of PR on patients with COPD, focusing on the clinical usefulness of PR, which provides patients a favorable environment for optimizing therapy. The data used are of very recent update. We also hoped to stimulate or persuade physicians to use PR more often.

What is pulmonary rehabilitation?

The updated statement by the American Thoracic Society and the European Respiratory Society (ATS/ERS) Task Force on PR gives the following definition of PR:

"Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and emotional condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors."(12)

A PR program is not a stand-alone therapy, but rather, should be integrated into a management program in which the general practitioner as well as the patient's pulmonary specialist take an active part.

Who should attend a pulmonary rehabilitation program?

PR offers benefits for all patients suffering from a chronic respiratory disease of whatever origin, who have a decrease of pulmonary function, who are symptomatic, and who have intolerance to effort, in spite of an optimal pharmacological treatment.(6,8,9) Even candidates for lung volume reduction surgery for severe emphysema or for lung transplantation are good candidates for PR.(13) A program of PR may be proposed in stable COPD as well as immediately after COPD exacerbation.(14) All patients suffering from the systemic consequences of COPD are good candidates for PR.(8) According to the new Global initiative for Obstructive Lung Disease (GOLD) guidelines, COPD patients (groups B–D) will benefit from a PR program.(3) However, a recent evidence-based practice guideline from the American College of Physicians supports the use of PR for symptomatic severe COPD patients (FEV1 $<$50% of predicted: strong recommendation) and for symptomatic or exercise-limited patients with FEV1 $\geq$ 50% of predicted (weak recommendation). (11)

Contraindications and barriers to pulmonary rehabilitation

The main contraindications are lack of motivation and nonadherence, psychiatric illness or dementia, uncontrolled cardiovascular diseases, inability to do exercise (for orthopedic or other reasons), and unstable diseases (eg, hepatic, diabetes).(6) In some countries, active cigarette smoking is considered as a relative contraindication. While it has been proven that current smokers obtain the same benefits from PR, they will nevertheless be encouraged to undergo a smoking cessation program. However, the adherence to PR by smokers generally remains less than that of ex-smokers. (15,16,17)

Nevertheless, we believe that excluding smoking patients would deprive them of a potential opportunity to quit smoking. (18) Age (19) as well as the degree of the bronchial obstruction (20,21) do not constitute contraindications to PR; neither does continuous or intermittent noninvasive ventilation. Exertional severe hypoxemia must be corrected beforehand, by oxygen therapy.

Few studies have established the predictive factors of nonadherence to PR. A retrospective analysis has shown that COPD patients are less likely to complete a PR program if they are current smokers, attend a long-lasting program, have suffered frequent exacerbations requiring hospital admission in the preceding year, have a long journey time to reach the center, and higher Medical Research Council (MRC) dyspnea score.(22) In a more recent review, Keating et al identified travel and transport, a lack of perceived benefit of PR, being current smoker, illness, and depression as barriers to completion of a PR program.(16) For such reasons, the dropout rate from PR reported in most of these studies was within the order of 20%–30%.

Evidence of the effectiveness of pulmonary rehabilitation in COPD

Based on various published RCTs and on meta-analyses, numerous evidence-based reviews have evaluated the effect of PR programs on symptomatic COPD patients. These have demonstrated the effectiveness and utility of PR. The main outcomes, including exercise performance, dyspnea, HRQoL, psychosocial benefits, cost effectiveness, reduced health care utilization, and survival have been reported. (3,7,9,14) The benefits on many laboratory and clinical parameters associated with PR are produced without demonstrable improvements in pulmonary function. This apparent contradiction could be explained by the fact that we know that PR acts mainly on the systemic effects of the disease.

In two meta-analyses involving respectively 230 and 432 COPD patients, PR following the exacerbation of COPD significantly reduced hospital admission and mortality.(14). Griffiths et al reported that PR was found to be cost effective and resulted in financial benefits. (23)

A more recent Canadian study suggested that PR is cost effective for patients with relatively high utilization of emergency and hospital-based services. (24)

Setting and length for pulmonary rehabilitation programs

The minimum duration of an effective ambulatory PR program is currently unknown,(9) but the GOLD guidelines suggest 6 weeks.(3) It appears that a minimum of 20 sessions is needed to achieve physiological benefits,(8,9) although longer programs are associated with better results.(25,26) A recent review concluded that prolonged PR programs tend to have more favorable effects on HRQoL, but the results for exercise capacity are less clear.(27) Furthermore the limited number of RCTs comparing different lengths of PR prevents a more definitive conclusion on the optimal duration of PR.(27)

Prerehabilitation assessment program

This assessment is carried out under the direction of the pulmonary physician specialized in rehabilitation. The pulmonary physician leads and coordinates the multidisciplinary team and is responsible for the medical treatment and rehabilitation program and for investigating comorbidities that could contraindicate or interact with PR (as described previously).(6,9) The possible assessments include past medical history (including comorbidities), physical examination, cycling cardiopulmonary exercises (incremental workload), the 6-minute walk test, the shuttle walking test, pulmonary function tests, maximal expiratory and inspiratory pressure evaluations, measurement of peripheral muscle forces, disease-specific questionnaires, and nutritional and psychological evaluations.

Exercise training

Endurance training is the most common exercise modality in COPD patients. The main objective is to improve aerobic exercise capacity as aerobic activities are part of many tasks.(29) The exercise training is guided by the following three parameters: intensity, frequency, and duration.(9)

Lower extremity exercise training at a higher exercise intensity produces greater physiologic benefits than does training at a lower intensity, in patients with COPD.(9) Nonetheless, both low-intensity and high-intensity exercise training produce clinical benefits for patients with COPD. (9) Indeed, muscular functional disorders are reversible with moderate-to high-intensity rehabilitation exercise, (8,30,31) with the same magnitude changes across GOLD stages II to IV. (32) Low-intensity training results in improvements in symptoms, HRQoL, and some aspects of performance of the activities associated with daily living; (8) moreover, the long-term adherence seems to be better with low-intensity training. However, training programs should attempt to achieve maximal physiologic effects. (8) So high-intensity training is proposed in PR centers. High-intensity training targets have been defined to be at least 60% to 80% of the peak work rate achieved in an incremental maximal exercise test. (9) This intensity seems sufficient to elicit some physiologic training effects. (8) The total effective training time should ideally be over 30 minutes. (8) Endurance exercise of the leg muscles is the main focus, with walking, stationary cycling, and treadmill exercise being commonly performed. In clinical practice, symptom scores can be used to adjust the training load (eg, a Borg score of 4 to 6 for dyspnea). (8,33)

For severely breathless patients, it is not possible to achieve the above training targets. In such cases, an interval training regime may be preferred.(34) Here, the continuous exercise session is substituted by a succession of shorter high-intensity exercise periods alternated with low-to moderate-intensity exercise recovery periods.(62) This form of training may be more comfortable for patients with more severe dynamic hyperinflation,(10) and adherence to the treatment may be better.(35)

Supplementary oxygen is given in order to maintain an oxygen saturation of above 90%.(6,9,19)

For each patient, the physiotherapist chooses the optimal resistance, frequency of exercise, speed, and mode of training and also, the implementation during the PR program. The addition of the strength training component increases muscle mass and strength.(9) The combination of endurance and strength training generally has multiple beneficial effects and is well tolerated.

Neuromuscular electrical stimulation (NMES) may be an adjunctive therapy for patients with severe chronic respiratory diseases who are bedbound or suffering from extreme skeletal muscle weakness.(9) NMES can be conducted at home and is safe and relatively inexpensive.(10) NMES was shown to enhance walking performance in patients with severe COPD.(36)

Inspiratory muscle training (IMT) is not recommended as a routine component of a PR program(9) but should be considered in COPD patients with ventilatory muscle weakness.(8) Normocapnichyperpnea resistive training and threshold loading have been described as training modalities.(8) The use of a threshold loading device can be recommended for training the inspiratory muscles.(37) Moreover, a meta-analysis of 25 studies that assessed the efficacy of IMT in patients with stable COPD found significant increases in inspiratory muscle strength, exercise capacity, and one measure of quality of life, and a significant decrease in dyspnea.(38)

Education

Patient education, incorporating self-management training, remains an important component of any comprehensive PR program, despite the difficulties in measuring its direct contribution to overall outcome. (8,9) The content of the education program varies depending on local resources, but the topics commonly covered are aspects of the disease, physiotherapy skills, nutrition interventions, energy conservation, and psychosocial interventions.Patient education includes relevant topics associated with COPD (eg, anatomy, pathophysiology, nutritional advice, disease education, breathing techniques and pharmacology, oxygen

therapy, smoking cessation, inhalation techniques, symptom management, chest clearance techniques, energy conservation, daily exercise, psychological interventions, anxiety management, relaxation, goal setting, travelling with COPD, sexuality issues, prevention and early recognition/management of COPD exacerbation, end of life issues, etc). Patient education aims to equip the patient with the knowledge and skills they need to manage their disease and to change their lifestyle, which is the ultimate aim of PR. All the multidisciplinary team members participate in educational programs.

Physiotherapy skills

Chest physiotherapy represents a nonessential component of PR but proves its usefulness in patients with a marked bronchial hypersecretion. Relaxation exercises, flexibility and stretching exercises, breathing techniques (eg, pursed lip and diaphragmatic breathing) are often coupled with an exercise training session (39). These are administered for a brief period (5–10 minutes) and are recommended to maintain muscle length and to prevent injury and soreness.

Nutritional intervention

In COPD, nutritional depletion is common and has a negative impact on respiratory as well as on skeletal muscle functions, and contributes to the morbidity and mortality of COPD patients (40). The dietician's role is to establish a dietary history, evaluate the body mass index (BMI), measure the body fat percentage (eg, by impedancemetry), and ensure dietary follow-up. Underweight patients may require nutritional advice (caloric supplements may be required) prior to commencing a PR program to ensure that the extra physical activity does not lead to further weight loss. Overweight patients may also need nutritional advice regarding weight loss, but the challenge here, is to not lose fat-free mass.(10) Current scientific evidence does not support the routine use of anabolic agents in PR for patients with COPD.(9)

Psychosocial support

Anxiety and depression are important comorbidities of COPD,(3,12,13) and a significant proportion of COPD patients referred to PR centers suffer from these psychiatric disorders.(13). The psychologist can be helped to evaluate for anxiety−depression disorders by means of tools such as the Hospital Anxiety and Depression Scale (HADS), as symptoms of anxiety in COPD have been demonstrated to have a negative impact on quality of life (QoL).(41)QoL can be assessed with a disease-specific questionnaire, such as the Chronic Respiratory Disease Questionnaire (CRQ)(42) or the St George's Respiratory Questionnaire (SGRQ).(43,44). Psychological support helps in overcoming addictions, especially tobacco smoking and, along with medical treatment for smoking cessation, is an important intervention in PR programs.(10) In some instances, the social worker provides assistance to the patient in securing financial support.

Maintenance program

The benefits of a PR program tend to diminish over the months following its discontinuation. PR programs are usually not associated with sustained benefits beyond 12 months.(44,45) However, programs lasting for at least 6 months have been more successful in maintaining outcomes, even in the absence of structured maintenance programs

However, the optimal strategy to meet this aim has not yet been described. Among the available options, we find telephone contacts and monthly supervised reinforcement sessions,(46,47) home exercise training (with or without a weekly supervised outpatient session), and recurrent PR programs.(48,49)

Moreover a recent meta-analysis has suggested that post-PR exercise programs for COPD patients are superior to traditional care in maintaining exercise capacity in the medium term (6 months) but not in the long term (≥1 year) and have no sustained effect at all with regard to the HRQoL.(50) These results should be interpreted with caution, given the heterogeneity in interventions, follow-up intervals, and outcomes measures.

The best and the most effective maintenance program currently remains to be found. Beyond post-PR exercise programs, the PR center staff, as well as family members and general practitioners, should encourage and motivate the patient to follow the maintenance program and continue with a more active lifestyle, in order to retain the gains. This advice is supported by the 12-month follow-up data taken from a cohort of COPD patients who had completed a 10-week comprehensive PR program and who were invited to follow a structured home program at the end of the PR program.(50)

Pulmonary rehabilitation and effect on physical activity

Patients with COPD are typically less active in daily life than are healthy older adults. In addition, inactivity is associated with poor functional status and higher risk of hospital admissions and mortality.(51)

Cindy et al(52) recently published the first meta-analysis evaluating the effect of exercise training on measures of physical activity. This meta-analysis pointed out that supervised exercise training confers a significant but small effect on physical activity.

Two parameters appear to be crucial to enhancing physical activity in COPD patients after PR: the frequency of supervised exercise training and the duration of the program. Indeed, in the meta-analysis by Cindy et al,(52) the studies that proposed an exercise training regimen of three times per week showed a significant increase in physical activity, in contrast with those that offered exercise only two times a week. Moreover, in a study measuring physical activity with an accelerometer, Pitta et al(53) showed that a 6-month, supervised exercise training program was required to obtain a significant effect on physical activity, while three months was shown to be insufficient. This is consistent with the recent concept that 6 months are needed for most people to change behavior.(54) The recording of spontaneous daily physical activity provides a new dimension in patient assessment that goes beyond any measurement of physiological

capacity. Daily activity and the completion of domestic tasks are more important for the patient than an improvement in the 6-minute walk test, total CRQ score, or maximal load achieved during ergospirometry. Thus clinicians should take into account what people actually do (eg, walking, climbing stairs, dressing, etc), rather than what they are capable of doing since it is the natural level of physical activity that seems to best determine the prognostic benefit.(55)

As mentioned above, a study showed that a better outcome of PR can be obtained by its association with long-acting anticholinergic bronchodilators.(5) This treatment appears to amplify the effectiveness of PR, as seen by greater improvements (beyond that obtained with PR alone) in patient self-reported participation in physical activities outside of the PR program, during the 8 weeks of PR and the 12 weeks following.(56)

Conclusion

Tailored pulmonary rehabilitation programs should be considered for COPD patients of all stages, who have respiratory symptoms and/or who have intolerance to physical effort despite optimal pharmacological treatment.

PR has certainly been demonstrated to provide beneficial effects on dyspnea, improvement in muscle strength and endurance, improvement of psychological status, reduction of hospital admissions, and improvement of HRQoL in COPD patients, with a gradual increase in daily physical activity and autonomy.

Successful PR therefore requires behavioral changes. To achieve this, patients' skill and adherence may be facilitated if they are enrolled in longer, comprehensive programs comprising interactions with a multidisciplinary team offering support, council, encouragement, and coaching. These changes rest on the following: exercise training; psychosocial support; nutritional intervention; self-management; and education, as well as pacing and energy conservation strategies, all of which are intended for motivated COPD patients. Therefore, PR embodies a very important and safe therapeutic option that aims to reverse the systemic manifestations of COPD and which, along with pharmacological therapy, can be used to obtain optimal patient management, leading to a favorable change in the daily life of our COPD patients. Accordingly, with the increasing burden of COPD patients in the world, there is an urgent need for advocacy with the concerned authorities, for a more widespread reimbursement of PR programs worldwide.

All the authors have the same contribution.

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REVIEW

UPPER ABDOMINAL LYMPH NODE DISSECTION IN OVARIAN CANCER - LITERATURE REVIEW

Olivia Ionescu[1], N. Bacalbașa[2]

[1] *"Bucur" Maternity Hospital, Bucharest, Romania*
[2] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Summary

The standard management for advanced-stage epithelial ovarian cancer consists of optimum cytoreductive surgery followed by platinum based chemotherapy. However, lymph node dissection in the upper abdomen remains controversial. The multiple directions of the lymph drainage pathway in ovarian cancer have been recognized. Several published cohorts suggest the survival benefit of pelvic and para-aortic lymphadenectomy. The aim of this review is to balance the risks and benefits of the upper abdominal lymphadenectomy in advanced ovarian cancer.
Abbreviations: celiac lymph node - CLN, lymph node - LN, Society of Gynecologic Oncologists - SGO, Memorial Sloan Kettering Cancer Center - MSKCC
Key words: advanced stage ovarian cancer, upper abdomen, lymph node dissection, survival

Résumé

La lymphadénectomie abdominale supérieure dans le cancer de l'ovaire - revue de la littérature

L'abord standard pour le cancer de l'ovaire épithélial en stade avancé est composé de la chirurgie de réduction tumorale optimale suivie d'une chimiothérapie à base de platine. Cependant, le curage ganglionnaire dans l'abdomen supérieur reste controversée. De multiples directions de la voie de drainage lymphatique dans le cancer de l'ovaire ont été reconnues. Plusieurs cohortes publiées suggèrent le bénéfice de survie du curage pelvien et lombo-aortique. Le but de cette revue est d'etudier les risques et les avantages de la lymphadénectomie abdominale supérieure dans le cancer avancé de l'ovaire.
Mots-clés: cancer de l'ovaire en stade avancé, abdomen supérieur, dissection des ganglions lymphatiques, survie

Introduction

Incidence of retroperitoneal LN metastases in advanced ovarian cancer ranges from 62% to 75% in reported studies, and the paraaortic involvement is the most commonly encountered [1]. However, frequency of metastatic involvement of the porta hepatis region and celiac lymph node (CLN) involvement is not well detailed in the medical literature [2]. Among patients with advanced ovarian cancer, more than 50% of them have positive retroperitoneal nodes. Unfortunately, the nodal status can be diagnosed only by a systematic lymphadenectomy. Furthermore, 25% of patients with unsuspected lymphatic disease will show lymph nodes infiltration[3].

The surgical approach to advanced ovarian cancer involving the upper abdomen has changed in the last decades, and upper abdominal surgical procedures have been incorporated to achieve technically complete safe cytoreduction. It is commonly accepted that clinically enlarged retroperitoneal nodes must be removed as part of the cytoreductive effort. However, the role of systematic retroperitoneal lymphadenectomy in gynecologic tumors is debatable especially if they are not clinically relevant[4]

Treating upper abdominal disease increases the rate of optimal cytoreduction from 50% to 76%[5]. However, celiac lymph node (CLN) metastases, usually due to retroperitoneal spread from upper abdominal disease, are a major obstacle to achieve complete cytoreduction. Lymphadenectomies of the porta hepatis and of the celiac trunk are being attempted in order to improve optimal cytoreduction rates [6].

Upper abdominal lymphadenectomy- hepatic pedicle

Correspondence address: Nicolae Bacalbașa, MD
Dimitrie Racoviță Street, no. 2, Bucharest, Romania e-mail: nicolae_bacalbasa@yahoo.ro

and celiac trunk.

Celiac lymphadenectomy comprises all lymph nodes between the hepatic artery and the root of the left gastric artery. The resection of CLNs includes the hepatic, celiac trunk, splenic and/or gastric lymph node (LN) groups limited to the suspect ones. The meta-analysis performed by Bristow et al. demonstrated a statistically significant positive correlation between the percent of maximal cytoreduction and the median survival time. [7].

A survey of SGO (Society of Gynecologic Oncologists) members showed that tumors involving the diaphragm, bowel, mesentery, and portal triad make impossible optimal cytoreduction, the metastatic disease being technically unresectable. Consequently, extensive upper abdominal lymph nodes metastases involving the hepatic pedicle and celiac trunk are associated with suboptimal residual disease thus suggesting that the anatomic marker of unresectable disease could be a predictor of suboptimal surgical outcome [8].

Patients with extensive upper abdominal tumor and positive nodes at the celiac axis or with involvement of the porta hepatis require ultra-radical procedures [9]. Extensive surgical approach to the upper abdomen improves optimal cytoreduction rate but is associated to increased blood loss and higher peroperative complications such as vascular and bile duct injuries [5].

Because cytoreduction to no microscopic tumor nodule is crucial for the efficacy of chemotherapy and for long-term survival, grossly abnormal enlarged nodes should be removed when discovered during the procedure. Recent studies demonstrate the beneficial therapeutic effect of pelvic and paraaortic lymphadenectomy in epithelial ovarian cancer without considering the stage of the disease [6]. The combination of residual disease and clinical LN status shows a significant impact of lymphadenectomy in patients with no residual disease and clinically suspect nodes [10]. Based on previous reports which have revealed that more than 90% of patients with clinically suspect LNs had histological positive LNs , resection of the suspected LNs at the celiac axis participates in debulking by removal of the macroscopic tumor[11].

With regard of lymph node dimensions, it could not be considered as an indicator for the ovarian cancer metastasis [12]. When considering patients with diffuse upper abdominal disease and/or more than 4 metastatic aortic LNs, positivity of celiac LNs increases to 75%. Bulky metastatic disease at the porta hepatis peritoneum can also be confused with node disease at the hepatic pedicle [13].

The location of suspect lymph nodes at the celiac axis should not be considered a contraindication for surgery, except when there is diffuse lymph node dissemination to mesenteric LN or when a complex surgical procedure with unacceptable morbidity is required. It is reasonable to achieve an optimal cytoreductive outcome when metastatic disease involves celiac nodes or porta hepatis region [14].

Survival benefits and quality of life

It has been studied weather patients with bulky upper abdominal disease requiring extremely aggressive procedures obtain a survival benefit with an acceptable quality of life [15]. Reports from Memorial Sloan Kettering Cancer Center (MSKCC) have demonstrated that patients requiring extensive upper abdominal procedures have similar initial response, progression-free survival, and overall survival to patients optimally cytoreduced by standard surgery. Other studies have shown that the completeness of cytoreduction has a more significant influence on survival than the extent of metastatic disease before surgery [16].

Metastases to the celiac lymph nodes are associated to an increased risk of hepatic metastases and progression to mediastinal LN. In the study of Martinez et al, 20% of patients with metastatic celiac lymph nodes had also a suspect mediastinal LN before prior chemotherapy. One of the three cases underwent resection of the mediastinal LN by a diaphragmatic direct approach. In the other two cases, image study after neoadjuvant chemotherapy demonstrated a complete response at this level [13].

The quality of life and peroperative morbidity associated to extensive upper abdominal surgery must be balanced with oncological benefit of surgery. Lymphadenectomy, multivisceral resections, multiple anastomoses, patient medical status, and prior chemotherapy increase the risk of postoperative complications. A preoperative risk-assessment is essential at initial exploration of the abdominal cavity taking into consideration that preoperative imaging often underestimates surgical findings. The decision to undergo an aggressive cytoreductive surgery is rather based on the patient's medical comorbidities, and their potential to tolerate an extensive procedure, rather than on specific anatomic locations.

The complications specific to upper abdominal lymphadenectomy refer to increased operative time and blood loss. A blood loss >1000 ml and a surgical time >327 min increases the risk of postoperative complications [17]. Abu-Rustum et al. reported that patients with advanced ovarian cancer who require transfusion after primary cytoreduction have an increased risk of developing venous thrombosis and/or pulmonary emboli compared to those not transfused [18].

CONCLUSIONS

The prognostic value of complete macroscopic resection of primary disease has been confirmed in several publications. The resection of metastates lymph nodes of the porta hepatis and celiac trunk in patients with advanced epithelial ovarian cancer proved to be feasible with an acceptable morbidity

The decision to undergo lymphadenectomy in the superior abdomen is based on the patients characteristics such as medical comorbidities, and the tolerability of an extensive procedure, rather than on specific anatomic locations of the lymph nodes.

Conflict of interest

The authors declare no conflict of interest.

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REVIEW

UTERINE ARTERY EMBOLIZATION OF SYMPTOMATIC FIBROIDS. PRO AND CON ARGUMENTS

N. Bacalbașa[1], Olivia Ionescu[2], Irina Bălescu[3]

[1] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2] *"Bucur" Maternity Hospital, Bucharest, Romania*
[3] *"Ponderas" Hospital, Bucharest, Romania*

Summary

Uterine artery embolization(UAE) is a minimally invasive therapy used for reducing symptoms caused by uterine fibroids. It represents a well-established alternative to hormonal treatment or surgery which uses particulate emboli to occlude the uterine arteries, therefore leading to devascularization and infarction of fibroids. The evidence on the long-term effectiveness and safety of uterine fibroids embolization UFE is broad and debatable . The aim of this review is to summarize the short, mid- and long term benefits of UFE over surgery with focus on symptom reduction, complications, reinterventions, health-related quality of life and possibility of pregnancy after UAE.

Abreviations: uterine artery embolization - UAE, uterine fibroids embolization - UFE, embolization vs hysterectomy - EMMY, health-related quality of life - HRQOL, uterine fibroid symptom and quality of life - UFS-QOL, magnetic resonance guided focused ultrasound surgery - MRgFUS, embolization with surgical treatment for fibroids - REST

Key words: uterine artery embolization, fibroids, hysterectomy, myomectomy

Résumé

L'embolisation de l'artère utérine des fibromes utérins. Des arguments pour et contre

L'embolisation de l'artère utérine (EAU) est un traitement mini-invasif utilisé pour réduire les symptômes causés par des fibromes utérins. Il représente une alternative bien établie au traitement hormonal ou la chirurgie qui utilise des emboles de particules pour obstruer les artères utérines, conduisant donc à dévascularisation et l'infarctus des fibromes. La preuve sur l'efficacité et la sécurité à long terme d'EFU est vaste et discutable. L'objectif de cette revue est de résumer les avantages à court, moyen et long terme de l'UFE par rapport à la chirurgie en mettant l'accent sur la réduction des symptômes, complications, réinterventions, la qualité de vie et la possibilité de grossesse après EAU.

Mots clés: l'embolisation de l'artère utérine, les fibromes, l'hystérectomie, la myomectomie

Introduction

Leiomyomas or benign uterine fibroids are the most frequent gynecologic tumors with a cumulative incidence of over 50% by the age of 50 with a large number of women requiring treatment to manage symptoms [1]. During the last decade, UAE has been regarded as a minimally invasive treatment alternative to surgery in the reduction of symptoms of heavy menstrual bleedings caused by fibroids. Several randomized controlled trials compared UAE with hysterectomy and/or myomectomy and found similarly good results for both interventions up to 24 months of follow-up [2].

The EMbolization vs hysterectoMY (EMMY) trial and compared clinical results, health-related quality of life (HRQOL) outcomes, and menopausal symptoms between UAE and hysterectomy. After 2 years the chance to avoid a hysterectomy in the UAE group was 76.5% while menorrhagia and HRQOL improved significantly, similarly in both groups [3]. Based on these 2-year follow-up results, UAE was considered to be a good alternative to hysterectomy. Because fibroids may grow back, menorrhagia can recur, or other symptoms that warrant hysterectomy may emerge beyond the 2-years of follow-up period, long-term out-

Correspondence address: Nicolae Bacalbașa, MD
Dimitrie Racoviță Street, no. 2, Bucharest, Romania e-mail: nicolae_bacalbasa@yahoo.ro

come studies with results to 5 years and above were published.

Symptom reduction after UAE

The studies investigating the symptom control after UFE were small and showed that both heavy menstrual bleeding, pain, pressure and other symptoms related to the dimension of the fibroids responded to embolization, with subsequent reduction of the tumor and relief of symptoms in most patients [3,4]. An early, large series was published by Hutchins et al.who treated 305 patients and followed them up to 12 months posttreatment. Menorrhagia was controlled in 86% of patients at 3 months and 92% at 12 months, bulk symptoms were controlled in 64% of patients at 3 months and 92% at 12 months [5].

Spies et al reported results, including subsequent gynecologic interventions, in 200 consecutive patients with mean follow-up of 21 months. Menorrhagia was improved in 87% and bulk symptoms were improved in 93% at 3 months. Subsequent gynecologic interventions or rehospitalizations occurred in 21 patients (10.5%). Half of these occurred because of recurrence of fibroids [6]. Several larger trials showed similar promising results which were obtained in expert centers with improved menorrhagia in 83% of patiens, dysmenorrhea in 77% and urinary incontinence in 86% [7].

The Fibroid Registry for Outcomes Data developed by the Society of International Radiology is a collection of prospective data on a large number of UFE patients,which measurers symptom severity, change in symptoms, adverse events, and HRQOL for 3 years after therapy. A self-administered validated questionnaire, the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire, measures symptom status and health-related quality of life with a symptom score that ranges from 0 to 100. A reported symptom score from the UFS-QOL was 59.83 (standard deviation [SD] 20.8), and 19,87 (SD 18.6) at 6 months after UAE and 19,23 (SD 17,9) at 12 month. Therefore, patients went from very symptomatic to near-normal level of symptoms as a result of embolization[8]. The long-term results from the FIBROID Registry patients revealed mean UFS-QOL symptom scores of 18.3 at 2 years and 16.5 at 3 years, thus confirming that symptoms of uterine fibroids are controlled by embolization [9].

UAE vs. Surgery

In order to assess extent of the symptomatic improvement after embolization, a standard control procedure was needed. Hysterectomy is by far the most common intervention for symptomatic fibroids while myomectomy is the most important uterine-sparing therapy for women wishing to preserve fertility. A newer interventions such as magnetic resonance guided focused ultrasound surgery (MRgFUS) has been compared with UFE in several small, randomized trials but the available data is currently limited. An early retrospective review of a series of patients treated with UAE or myomectomy at a single medical compared 51 patients who underwent UAE and 30 myomectomy patients. The level of symptom control was similar between the two groups, but the re-intervention rate was higher for the UAE group compared with the myomectomy group (29% vs 3%)[10].

In a study examining the effectiveness of tris-acryl gelatin microspheres used or for embolization, 102 UAE and 50 hysterectomy patients were treated and outcomes compared. Patients treated with hysterectomy had at 12 months a better relief of pain but for other symptoms there was no difference. Moreover, complications were more likely after hysterectomy (50%) than after UAE (27.5%, p =0.01). At 3 years posttreatment, among patients, 8% UAE patients had additional intervention and 88% of them had continued symptom control. Re-intervention is also less likely in hysterectomy patients, as new fibroids cannot develop [11].

The first randomized trial comparing UAE to abdominal hysterectomy with focus only on the short-term outcomes revealed fewer complications and shorter hospital stay after embolization than after surgery, and a symptom control in 86% of UAE patients [12].

The EMMY trial (EMbolization versus hysterectoMY) is the first large multicenter randomized trial comparing uterine embolization and hysterectomy concentrating on the short- and mid-term outcomes to 2 years.[13,14]. The procedural failure rate of UAE was 18%, the recovery and return-to-work time was significantly faster after UAE, and there was no difference in the major complication rates. Symptom control, appreciated both as patient satisfaction and quality of life, after embolization and hysterectomy was nearly similar. Patients who underwent hysterectomy had a greater degree of satisfaction with outcome, and 24% of the UAE patients had recurrence of symptoms that led to hysterectomy over the course of the 2-year follow-up [15].

Another trial comparing Embolization with Surgical Treatment for Fibroids (REST) found that UAE patients recovered more quickly both in terms of length of hospitalization and return to work, and had less pain than surgery patients. With a median follow-up of 32 months, the likelihood of re-intervention was much higher in UAE patients (21 for UAE vs. 1 for surgery, $p < 0.001$) with 10 of these interventions occurring in the first year, presumably due to failure of symptom control and 11 during subsequent follow-up. Regarding the postprocedure complications, hysterectomy patients were more prone to urinary stress incontinence. They obtained significantly better outcomes for control of menorrhagia, but pressure symptoms were improved in a greater proportion for the UAE patients [16,17]. The embolization patients experience less pain postoperatively, have shorter hospital stays, and shorter overall recoveries. A better quality of life status in follow-up in the UAE group has also been reported [18]. Although it appears to have a higher minor complication rate and more frequent subsequent interventions than surgery, it is also less invasive and therefore has a more rapid recovery and lower procedural costs [19].

Long-Term Outcomes

The long-term effectiveness of UAE is still debatable

since 2005 when studies with results to 5 years and beyond after UAE began to be published. Long-term outcome is appreciated as symptom status and re-intervention (hysterectomy, myomectomy, dilatation and curettage, hysteroscopic resection of fibroids, endometrial ablation, or repeat of UAE). Failure of UaE is defined as any subsequent major re-intervention, including hysterectomy, definitive myomectomy, or repeat UAE for any reason, or no improvement in symptoms after embolization. The majority (73%) of patients reported improved symptom control for the full 5 years of follow-up. These rates suggest that after approximately 10 to 12% of patients not achieving symptom control at 12 months, there was a subsequent Recurrence rate of 3 to 4% per year. Re-interventions were reported in nearly 20% of the patients, with 13.7% of patients undergoing a hysterectomy [20]. Additional studies showed that between 80 and 90% of patients had long-term symptom control and hysterectomy rates were between 5 and 20% [21].

The recurrence rate in Poulsen et al study was 25% at a median of 8.9 years, with most of these patients having a hysterectomy [22]. Scheurig-Muenkler et al showed a cumulative recurrence rate of 23.3% at 10 years. If a patient did not recur in the early years after embolization then it is unlikely to have a late recurrence This may in part reflect the onset of menopause in this population. A very late recurrence may be limited by menopause, and its onset provides the large majority of patients' permanent relief from further symptoms [23].

Effects of UFE on Fertility and Pregnancy Outcome

Leyomyomas are one of the reasons for repeated abortion and infertility, and UAE could be a solution for these patients. The possibility of pregnancy after UAE is the most important consideration with many studies have reporting the case series of successful pregnancies after UAE [24,25]. According to the series of pregnancy reported after UAE, it can be concluded that some obstetrical complications are higher after UAE in comparison to normal pregnancies and myomectomy and in a especial consideration, during first two years after treatment in comparison to myomectomy [26, 27], The pregnancy is certainly possible after embolization and the newborn outcome seems normal and satisfactory [28].

Pregnancy complications are more probable in older women [29] probably because fibroma treated patients who want to be pregnant have been infertile and are older in comparison to the normal population. The time between UAE and pregnancy is also an important point in relation to the obstetrical outcome. If the pregnancy time is close to the UAE, the pregnancy complication rate could be higher. Many authors recommend a safe time of 2 years after UAE to become pregnant. Another point of debate are patients with myomatous uterus. Although the myomectomy seems the standard treatment for the fibroma patients who want to be pregnant, the UAE seems to be a better option for the patients with myomatous uterus or for patients with multiple fibroids as the myomectomy will not be effective for these patients [30].

CONCLUSIONS

UAE is a new procedure that needs no general anesthesia, no surgical incision, and no blood loss or transfusion. It provides a good symptom relief for most women, the recovery and time to return to normal activities are shorter than hysterectomy and open myomectomy. However, when considering alternative approaches- hysterectomy or myomectomy, there are differences in terms of short-term outcomes, cost, recovery time, and durability of symptom control.

As the fibroids are one of the reasons for repeated abortion and infertility, UAE could be a solution for women who want to be pregnant. Moreover, UAE for fibroids is an effective and safe therapeutic modality for symptomatic fibroids in women who are done with childbearing, and should be the first consideration when surgery is refused.

Conflict of interest

The authors declare no interest conflict.

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REVIEW

THE VITAMIN D STATUS IN MENOPAUSAL WOMEN

Simona Elena Albu[1,2], Andreea Geleriu[3], Mara Cârsote[1,3], Alexandra Mihai[3], Cristina Vasiliu[1,2], Cătălina Poiană[1,3]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[2]*University Emergency Hospital, Bucharest, Romania*
[3]*C.I.Parhon National Institute of Endocrinology, Bucharest, Romania*

Summary

The vitamin D domain is dynamic during the last decades. The menopause associates a high prevalence of vitamin D deficiency. This is connected to areas that are still a matter of debate: cardiovascular risk, cancers, immunity and muscle-skeletal diseases. In this review we summarize the literature data related to these topics.
Key words: vitamin D, menopause, bone

Résumé

Le condition de la vitamine D chez les femmes ménopausées

Le domaine de la vitamine D est dynamique au cours des dernières décennies. La ménopause associe une forte prévalence de la carence en vitamine D . Cela est lié à des zones qui sont encore un sujet de débat: le risque cardiovasculaire, les cancers, l'immunité et des maladies musculo- squelettiques. Dans cette revue, nous résumons les données de la littérature relatives à ces sujets.
Mots clefs: vitamine D, ménopause, os

Introduction

For the last decades the vitamin D status became a dynamic topic since its correlations not only to the bone and muscle diseases but also to cancer, immunity, autoimmunity, inflammation. The menopausal years are largely approached in clinical studies related to all these areas while the hope of life and thus the period of time in menopause is longer. Our aim is to review the literature data regading the vitamin D levels focusing on menopause.

General context

Epidemiologic data

Vitamin D deficiency and its consequences have been studied intensively during the last decades, due to a relatively high prevalence in the general population, as it affects up to 30-50% of the adults in the U.S.A, and its connection with osteoporosis and other musculoskeletal and metabolic disorders. (1) The best tool to assess the vitamin D status is 25-hydroxyvitamin D or 25(OH)D which is detected by a simple blood test. Definition of 25(OH)D deficiency is not well established, with a threshold that oscillates depending on the study cited, making it hard to compare trial results. In postmenopausal women the prevalence of 25(OH)D inadequacy (meaning <20 ng/mL) varies largely between 1.6 up to 86%, with the highest percentage among institutionalized women. (2,3,4) If considering the postmenopausal osteoporotic females, the prevalence of serum 25(OH)D under 12 ng/mL is 12.5 up to 76%, and with a prevalent osteoporotic fracture the prevalence reaches 50 to 70% for a cut-off of 15 ng/mL. (2,5,6) Vitamin D deficiency varies by region with a lower prevalence in the U.S.A (8%), due to a greater availability of fortified supplements, and higher prevalence in Latin America (39.7%) and Southern Europe (39.3%). (2,3,6) An European study performed on 8532 postmenopausal women with osteopenia or osteoporosis revealed a general prevalence of 25(OH)D inadequacy of 79.6% when considering the 80 nmol/L cut-off and 32.1% for the 50 nmol/L cut-off, respectively. A higher percentage of 25(OH)D inadequacy was found

Correspondence address: *Mara Cârsote, MD*
Aviatorilor Ave 34-36, sector 1, 011863, Bucharest *e-mail: carsote_m@hotmail.com*

among those under 65 years. The 25(OH)D level was significantly different across the nine countries included in the study ($p<0.0001$), with a mean of 61 nmol/L. (7) An international epidemiological investigation conducted in Latin America among postmenopausal women with osteoporosis found a higher prevalence of vitamin D insufficiency in Mexico (67%) compared to Chile (50%) and Brazil (42%), for a threshold of <75nmol/L. (8) Hypovitaminosis D is widely spread in India as well, with a peak prevalence of vitamin D deficiency (defined by a threshold of <20 ng/mL) among postmenopausal osteoporotic women of more than two-thirds (64.3%), with values that reach up to 78% in a study conducted by Arya et al. (9) A strong correlation was established between vitamin D values and the initial lumbar spine Bone Mineral Density (BMD) ($p<0.05$). (10) There are several other risk factors for vitamin D inadequacy, including: race (dark skin), old age (>70 years), low nutritional intake, inappropriate sun exposure, wintertime, chronic renal disease, liver disease, overweight and obesity. (2,11,12) A cross-sectional study performed in Spain on 1250 postmenopausal women found that poverty strongly correlates with vitamin D insufficiency, low lumbar spine BMD and osteoporotic fractures. A low socio-economic status was also associated with a higher Body Mass Index (BMI) and a higher prevalence of metabolic syndrome, but a connection with vitamin D deficiency could not be established. (13) The importance of vitamin D for dietary calcium absorption and skeletal health is well-known. In vitamin D deficiency calcium absorption is severely impaired, falling from 30-80% in replete state to under 15%, leading to rickets or / and osteomalacia, muscle weakness and increased risk of falls. (10,14,15) Supplemental vitamin D has proved beneficial in fracture prevention by increasing bone density and muscle strength, therefore reducing the risk of falling in the elderly population (> 65 years) by up to 13%, an effect which is dose-dependent. (16) Serum levels of 30-40 ng/mL 25(OH)D or supplemental vitamin D in daily doses of more than 400 IU act to reduce non-vertebral fractures by 20% and hip fractures by 18%. (17)

Metabolic complications

Several studies have indicated a link between obesity and vitamin D deficiency. (11,12) Low availability of vitamin D due to sequestration in the adipose tissue was one of the hypotheses advanced to explain this finding. (18) A cross-sectional study on 250 overweight and obese adults found modest inverse correlation between vitamin D level and weight ($r=-0.21$, $p=0.0009$), BMI, waist, and glycated haemoglobin (HbA1c), but no association with body fat or metabolic syndrome per se ($p>0.05$). (12,19) Besides its importance on calcium balance, vitamin D appears to be involved in cellular function as well – particularly in the pancreatic beta-islet cells, playing a role in cell proliferation and differentiation and in the adipose tissue, modulating glucose metabolism and insulin action. (12,20) When referring to postmenopausal women without known diabetes, a study by Need et al. demonstrated an inverse relation between fasting plasma glucose and serum 25(OH)D ($p<0.001$), with a higher increase of plasma glucose particularly when 25(OH)D drops under 40 nmol/L. (11) Recent studies suggest that plasma levels of 25(OH)D under 15 ng/mL may act as an independent risk factor for cardiovascular events through direct effects modulated by the vitamin D receptor but also by influencing other cardiovascular risk factors. (21) Vitamin D receptors are also present in skeletal and cardiac muscle, and inappropriate serum 25(OH)D could impair muscle function as a result of low calcium intestinal absorption. (22) Moreover, recent studies suggest a role for 1,25(OH)2D in reducing renin-angiotensin activation, reducing cardiac hypertrophy and inflammation. (22) In end-stage renal disease patients 25(OH)D deficiency was associated with endothelial dysfunction, atherosclerosis and increased mortality for those on hemodialysis. (23) The effect of vitamin D on arterial hypertension remains a controversial issue. While short-term supplementation of calcium and vitamin D (800 IU per day) lowered systolic blood pressure more than calcium alone in a study by Pfeiffer et al. the WHI study failed to demonstrate a similar effect for doses of 400 IU per day vitamin D. (24,25) A prospective Danish study following 2013 healthy postmenopausal women for 16 years found a prevalence of vitamin D deficiency of 39% for a threshold of 20 ng/mL. The vitamin D deficient group had lower hip-waist ratio and HDL cholesterol and higher BMI, triglycerides and fasting plasma glucose. 15% of the vitamin D deficient group compared with only 10% of the vitamin D replete group experienced an adverse event as follows: heart failure (1.3% vs. 0.7%, $p=0.15$), myocardial infarction (1.7% vs. 1.8%, $p=0.82$), stroke (6% vs. 3.4%,$p=0.008$, and death (8.3% vs. 5.7%, $p=0.036$). (22) Whether vitamin D supplementation can reduce cardiovascular mortality is still a matter of debate.

Autoimmune diseases

Higher prevalence of autoimmune disorders in countries with less sunshine and studies on animal models has led to the hypothesis that vitamin D may play a role in modulating the autoimmune response. (26) Several trials suggest that high-dose vitamin D supplementation may decrease the risk of developing type 1 diabetes or multiple sclerosis. (27,28) Low levels of 25(OH)D have recently been associated with rheumatoid arthritis and systemic lupus erythematosus disease activity. (29) In a prospective cohort study conducted in Iowa high vitamin D intake correlated with a lower risk of developing rheumatoid arthritis ($RR=0.67$, $p=0.05$). (30)

Cancers and vitamin D

Recent data suggest that vitamin D promotes cellular differentiation and apoptosis and reduces tumour proliferation and angiogenesis. As a consequence 25(OH)D levels could be inversely correlated with an increased risk of cancer such as colorectal or breast cancer and with an adverse outcome. (31) In postmenopausal women serum 25(OH)D over 20 ng/mL was associated with a lower risk of breast cancer. (32) Supplementing calcium and vitamin D

(1100 IU/day) in women over 55 years for 4 years increased 25(OH)D from 29 ng/mL to 38 ng/mL and resulted in a risk reduction of 60% for breast cancer. (33) In a cohort of post-menopausal breast cancer survivors on aromatase inhibitor treatment, the prevalence of vitamin D deficiency was 35%, for a threshold of 30 ng/mL. Non white women had a two-fold risk for inadequate vitamin D levels due to high level of melanin in the skin which impairs cholecalciferol synthesis. For this category of patients, vitamin D deficiency is associated not only with an increased risk of falls and hip fractures, but also with a higher rate of breast cancer recurrence and mortality. (1)

Conclusion

Overall a high prevalence of vitamin D is seen in menopause; the potential links are with cardiovascular diseases, autoimmune maladies and some types of cancer.

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REVIEW

HEMOPHILIA TYPE A - FROM PATHOGENESIS TO COMPLICATIONS

Oana Bădulescu[1], T. Cucoș[2], Beatrice Chiru[2], Mădălina Mocanu[3], Manuela Ciocoiu[1], Magda Bădescu[1]

[1]Department of Pathophysiology, University of Medicine and Pharmacy „Grigore T. Popa", Iași, Romania
[2]Student, University of Medicine and Pharmacy „Grigore T.Popa", Iași, Romania
[3]PhD Student, Department of Pathophysiology, University of Medicine and Pharmacy „Grigore T. Popa", Iași, Romania

Summary

The word "hemophilia" comes from the Greek words "haima" which means "blood" and "philia" which means "love" and describes a series of conditions that impair the body's natural capacity to control blood clotting. Type A hemophilia is the most common form, with an incidence of approximately 1 in 10.000 males and it is caused by structural defects involving factor VIII. In severe forms, type A hemophilia is characterized by episodes of sudden bleeding into joints or other tissues, which require prompt haemostatic treatment and factor VIII substitution therapy. Even in the absence of hemorrhagic symptoms, proper and timely factor VIII substitution therapy from the moment of diagnosis until the age of 18 helps prevent the appearance of hemophilia associated complications such as hemophilic arthropathy, hematomas and pseudo tumors. This article reviews the causes and pathophysiology of the illness and also stresses the importance of appropriate treatment by analysing the pathogenesis and pathophysiologic mechanisms of long term complications associated with type A hemophilia.
Key words: hemophilia, arthropathy, hematoma, bleeding

Résumé

L'hémophilie de type A - depuis la pathoenèse aux complications

Le mot "hémophilie" provient des mots grecs "haima" qui signifie "sang" et "philia" qui signifie "amour" et représente une coagulopathie caractérisée par le déficit du facteur VIII de coagulation. L'hémophilie de type A est la plus répandue parmi les formes d'hémophilie, ayant une incidence, conformément aux données de la littérature, de presque 1 à 10.000 d'hommes. Les formes sévères de ce type d'hémophilie sont caractérisées par des fusées éclairantes de saignement, le plus fréquemment au niveau articulaire et musculaire, mais aussi au niveau d'autres organes et tissus, ce qui impose l'administration immédiate du traitement de substitution avec le facteur VIII de coagulation et des hémostatiques. Même dans l'absence de la symptomatologie de saignement, l'institution d'un traitement prophylactique de substitution correct encore depuis le diagnostic de la maladie et jusqu'à l'âge de 18 ans, évite l'installation des complications chroniques de l'hémophilie, sous la forme des arthropathies hémophiliques et du déficit moteur secondaire de celles-ci. Cet ouvrage se propose de mettre en évidence les causes et les mécanismes physiopathologiques qui interviennent dans l'hémophilie de type A; dans la même mesure, l'ouvrage souligne l'importance d'un traitement prophylactique correctement administré, qui prévient l'installation des complications chroniques sévères qui confèrent le caractère invalidant de la maladie, complications qui présentent une fréquence augmentée chez les patients hémophiliques incorrectement traités.
Mots-clés: hémophilie, arthropathies, hématome, saignement

Correspondence address: *Oana Viola Bădulescu MD, PhD*
Department of Pathophysiology, University of Medicine and Pharmacy "Grigore T. Popa"
Universității street, no.16, 700115, Iași, România e-mail: violabadulescu@yahoo.com

Hemophilia (coming from the Greek haima, meaning blood and philia meaning love) is a disorder characterized by an impaired clotting capability of the body, caused by a deficiency of coagulation factor VIII or factor IX. Based on which factor is involved, hemophilia can be classified in 2 types, type A and type B, the former representing a deficiency in factor VIII, while the latter in factor IX. Clotting factors VIII and IX are both encoded on the long arm of chromosome X, meaning that in males with an X chromosome carrying a defective gene, hemophilia is bound to appear as a severe, moderate or mild hemorrhagic disease. The approximate occurrence of hemophilia is estimated at 1 every 5.000 to 10.000 male births. Both hemophilia type A as well as type B feature a similar clinical pattern, in severe form, characterized by multiple bleeding episodes into tissues which can lead to crippling hemarthropathy and the forming of hematomas, unless treated prophylactically with factor VIII or IX, respectively.

The molecular basis of type A hemophilia consists in a mutation of the gene that encodes coagulation factor VIII, which is located on the long arm of the X-chromosome. As a result, hemophilic patients are almost exclusively males. The factor VIII gene is a very large and complex gene, approximately 186 kb, consisting of 26 exons and 25 introns. Hemophilia A can result from multiple factor VIII gene alterations, such as gene rearrangements, missense mutations, nonsense mutations, deletions of all or portions of the gene or insertions of genetic elements. (1) Interestingly enough, reduced levels of factor VIII can also be caused by a genetic alteration outside the factor VIII gene locus. In patients who have a combined deficit of both factor V and VIII, the gene responsible for the defect lies on the long arm of chromosome 18, whereas the genes for factors V and VIII are located on chromosome 1 and X.

Depending on the site and nature of the mutation, clinical symptoms of hemophilia may vary, ranging from mild, moderate to severe.

The estimated incidence of hemophilia A is only one in every 5000 to 7000 live male births. It has been found to occur in all ethnic groups in all parts of the world (2) It has however been shown that there are significant variations in reported hemophilia A prevalence around the world. Studies have shown that prevalence (per 100.000 males) in high income countries is higher. (3) The main reasons for underreporting cases of type A hemophilia are : lack of diagnostic capability, no access to care, no economic means and no available factor VIII substitution therapy. Lack of treatment and surveillance in those with severe forms of hemophilia often lead to death in childhood or early adult life, thus resulting in a decreased prevalence figure. (4)

Factor VIII production, processing and structure

Factor VIII is a glycoprotein procofactor, which in conjunction with other factors plays a crucial role in the coagulation cascade. Although the primary site of release in humans is ambiguous, it is synthesized and released into the bloodstream by the vascular, glomerular, and tubular endothelium, and the sinusoidal cells of the liver. (5) Coagulation factor VIII is comprised of 6 protein domains, as follows : A1-A2-B-A3-C1-C2, out of which it seems that the B domain does not have a significant role in stabilization or activation. Following synthesis, factor VIII is secreted into the blood stream in a partially cleaved form, the cleavage taking place at different points of the B domain. In the blood stream von Willebrand factor (vWF) acts as a carrier protein for factor VIII and helps stabilize it. Factor VIII has a half time of 8 to 12 hours, a half time which is markedly decreased in vWF deficiency, which accounts for the reduced factor VIII levels in many patients with vWF deficiency.

Factor VIII role in the coagulation cascade

Normal hemostasis is defined as the termination of bleeding by mechanical or chemical means or by the complex coagulation process of the body, which consists of vasoconstriction, platelet aggregation, and thrombin and fibrin synthesis. (6) In hemophilia, the body's normal blood clotting capabilities are disrupted, leading to a permanent tendency to hemorrhages, spontaneous or traumatic, due to deficient clotting factor activity. The coagulation cascade consists of a largely sequence of enzymatic conversions, in which, each step forward in the cascade consists of the conversion of a inactive proenzyme into an activated enzyme form, with thrombin as the final product. Factor VIII plays a crucial role in the formation of the factor X activation complex, which is a common point to which both the intrinsic, as well as the extrinsic eventually lead. (7) This complex consists of IXa, VIIIa, platelet phospholipids and Ca+. In order to enhance the proteolytic capability of factor IXa, the proteolytic cleavage of factor VIII, with subsequent activation, is required. In this manner, factor VIIIa exerts its role as a cofactor in the factor X activating complex. Factor VIIIa and factor IXa both attach to membrane phospholipids released by platelets or to the platelets themselves forming the factor X activating complex. Down regulation of the formed factor X activating complex, upon successful hemostasis, involves inactivation or inhibition of the proteolytic factor IXa or of the cofactor, factor VIIIa. Inactivation of factor VIIIa occurs either through proteolytic degradation or through spontaneous dissociation. (8)

Type A hemophilia complications

From a clinical standpoint, type A hemophilia is characterized by excessive bleeding in various parts of the body. The most characteristic signs of the disease are soft tissue hematomas and hemarthroses.Type A hemophilia can be classified in either mild, moderate or severe, based on the level of factor VIII activity in the blood stream. Patients who are severely affected are prone to frequent spontaneous hemorrhage, without known trauma, except for the usual daily activities. Moderately affected patients present with hematomas and hemarthroses usually only following trauma, and mildly affected patients have infrequent bleeding episodes and can go undiagnosed, being discovered only as a result of excessive postoperative

hemorrhage. It should also be noted that as much as 10% of so called "asymptomatic" female carriers have factor VIII activity levels below 30%, exhibiting mild forms of hemophilia. (4,7)

Hemarthoses

Hemarthoses are one of the most frequent and serious complications that a type A hemophilia patient can develop. Bleeding episodes are a result of damage of the vascular bed of the synovial membrane, which has a high frequency of capillaries, with a peak density just below the lining layer between 6 and 11 μm deep. (9) Hemophilic hemarthropathy follows as a consequence of repeated bleeding inside the joint cavity leading, in time, to pain, deformity and disability. Patients with hemarthroses present themselves with joints that are swollen and warm to the touch, with a limited degree of motion. The joints most frequently involved are hinge joints, such as knee and elbow joints, rather than socket joints such as hip and shoulder joints. The key feature to the physiopathologic mechanism of hemophilic arthopathy is blood induced joint disease (BIJD). Changes that occur in hemophilic arthopathy involve all three components of the joint: the synovia, the cartilage and the bone. Intraarticular bleeding may first take its toll on the joint cartilage, as iron-catalyzed reactive oxygen species induce chondrocyte apoptosis. (10) Studies have shown that when cartilage is introduced to whole blood, the synthesis of proteoglycan is also inhibited.(11) Recurrent hemarthroses lead to the formation of synovial iron deposits in the form of hemosiderin, which increase synovial fibroblast DNA synthesis, which in term leads to cell proliferation, synovial hypertrophy and chronic inflammation. (12) Also, angiogenesis induced by growth factors such as vascular endothelial growth factor (VEGF), is essential for the development of synovitis, providing an appropriate vascular bed for subsequent synovial hyperthrophy and progression of BIJD. (13) As a result of synovial proliferation and inflammatory cell infiltration, the joint cavity becomes a hypoxic, hypercapnic and acidic environment, which, in conjunction with the cascade of cytokines, reactive oxygen species and other inflammatory mediators starts to adversely affect the cartilage and the underlying bone tissue. (14)

Hematomas

Hematomas are collections of blood which are found outside the blood vessels and one of the common signs of most blood clotting disorders. Hemorrhage into connective tissues or into muscle may ensue following trauma or spontaneously. In normal individual, hematomas usually follow a benign course, slowly resorbing without treatment. However, in hemophilia, patients, hematomas present themselves with a tendency for enlargement and dissection further into deeper anatomical planes. A series of complications can follow, depending on the site of hematoma formation. Particularly dangerous are hematomas located at the level of the upper airways, which although initially presenting as a "sore throat", can lead to potentially life threatening situations, with airway obstruction. Hematomas into muscle tissue are more common, affecting mostly the calf, thigh, buttocks and forearm and can lead to muscle contracture, nerve palsies and muscle atrophy as a result of a rise in intracompartmental pressure. Hematomas can occur in various locations in the body and are often not visible during clinical examination. Therefore, in such situations, computed tomography and magnetic resonance imaging are advised in order to pinpoint the location.

Pseudotumors

Pseudotumors are a rare, but potentially dangerous finding in hemophilia patients, consisting in blood cysts that occur in soft tissue or bone, as a result of unresolved hematomas which get surrounded by a thick, fibrous capsule, as a result of myofybroblast proliferation and collagen synthesis.

Pseudotumors are divided into three types, depending on the level of tissue involvement. Type 1 is a simple cyst confined within the muscles fascial envelope; type 2 represents a cyst which develops in soft tissue such as muscle or tendon, but affects the vascular supply of the adjacent bone and periosteum, resulting in bone damage; type 3 is a cyst which is located between the bone and the periosteum as a result of subperiostal bleeding, leading to separation of the two tissues and subsequent damage. (15, 16) Pseudotumors are tipically seen in adult hemophiliacs, occurring mostly in long bones such as the femur or tibia and present themselves with a slow progressive growth with subsequent underlying bone erosion. Such pseudotumors present as a painless, firm, expanding mass, which is non-tender and adherent to deeper tissue, frequently remaining painless and asymptomatic, until the patient develops a pathological fracture.

Neurologic complications

Intracranial bleeding is considered the most dangerous hemorrhagic event in hemophilic patients. (16) Central nervous system hemorrhage usually follows trauma and it can be a cause of death unless treated urgently. Therefore, intracranial hemorrhage should be suspected in hemophilic patients presenting with unusual headaches. Another neurologic finding, which is far more frequent is peripheral nerve compression, as a result of muscle hematomas. Long term compression of sensory and motor nerves can result in sensory loss, muscle weakness and even atrophy and loss of reflexes.

Therapy

Hemorrhagic episodes in patients with type A hemophilia can be managed by replacing factor VIII. Patients can be treated with prophylactic or with intermittent, on demand factor VIII substitution therapy whenever bleeding episodes occur. However, a prophylactic approach early in childhood helps reduce the incidence of hemophilia associated complications, such as hemarthroses and hematomas thus, improving the quality of life for the patients.

Conclusion

Type A hemophilia is a X-linked hereditary disease involving deficient synthesis of factor VIII, which impairs the body's natural clotting capability. This disease is associated with a series of complications which pose a serious threat to the patient's life and also reduce quality of life to a considerable extent, unless treated accordingly. Prophylactic approaches to the treatment of hemophilia have proved successful in assuring that patients lead a relatively normal way of life, with a considerable decrease regarding the onset and evolution of hemophilia associated complications.

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HISTORY OF MEDICINE

OVERLOOKED BYZANTINE PHYSICIANS' WORK ON PEDIATRICS

G. Tsoucalas[1], I. Tsoucalas[2], Marianna Karamanou[1], K. Laios[1], G. Androutsos[1]

[1]*History of Medicine Department, Medical School, University of Athens, Greece*
[2]*Private physician, Chania, Greece*

Summary

Byzantine medical writings lack significant references on pediatrics compared to other medical subjects. However, some Byzantine physicians developed important pediatric skills. In our article, we present three characteristic examples of Byzantine physicians which dealt effectively with pediatric disorders. Symeon Seth (c. 11th century) was among the first to introduce natural substances and medications in pediatric therapeutics. Damnastes (c. 11th century), developed a mathematical calendar with the events of gestation while Ioannis the Episcope of Prisdrianon (c. 12th century) studied juvenile diabetes mellitus.
Key words: Byzantine medicine, pediatrics, Symeon Seth, Damnastes, Ioannis the Episcope of Prisdrianon

Résumé

L'œuvre oubliéé de médecins byzantins en Pédiatrie

Les écrits médicaux byzantins manquent de références significatives sur la pédiatrie par rapport aux autres sujets médicaux. Cependant, certains médecins byzantins ont développé des compétences pédiatriques importantes. Dans notre article, nous présentons trois exemples caractéristiques des médecins byzantins qui traitent efficacement les troubles pédiatriques. Siméon Seth (c. 11ème siècle) a été parmi les premiers à introduire les substances naturelles et les médicaments en thérapeutique pédiatrique. Damnastes (c. 11ème siècle), a développé un calendrier de grossesse basé sur mathématique et Ioannis l'épiscope de Prisdrianon (c. 12ème siècle) a étudié le diabète juvénile.
Mots-clés: médecine byzantine, pédiatrie, Siméon Seth, Damnastes, Ioannis l'épiscope de Prisdrianon

Introduction

Byzantine medical writings lack of significant references on pediatrics. It seems that physicians of that time had not acquired extensive knowledge on pediatrics and were often administrating a variety of ineffective mixtures of herbs and charms. [1] However, folk magical tradition, difficulty in access to information due to the empire's vast land and traditional medical thinking, did not impede a few Byzantine physicians to develop important pediatric skills. [2] We present three characteristic examples of Byzantine physicians which dealt effectively with pediatric issues.

Symeon Seth (c. 11th century)

Symeon Seth (or Symeon Magister of Antioch, son of Seth), lived in the 11th century AD and was a political lord in Antioch. He was known as physician and philosopher. He was employed as a medical officer in Constantinople, at the court of Emperor Michael VII Doukas (c.1050 – c.1090). His most important works are "An explanatory dictionary on herbs", "A report of food properties in alphabetical order", "Philosophy and medicine", "On natural things" and "Synopsis on urine".[1,3] Symeon's work, was mainly influenced by Aristotle (384-322 BC) and Arabic sources. He was fluent in Arabic and Greek languages and became fascinated with medical books of both therapeutic traditions. In an attempt to highlight the oriental element in medical practice of his time, he studied the known herbs from Greek and Asian territories and introduced new pharmaceutical substances originating from Persia, India and the Arabian Peninsula. [4]

Correspondence address: *Marianna Karamanou, MD, Ph.D*
4 str Themidos, 14564, Kifissia, Athens, Greece *e-mail: mariannakaramanou@yahoo.com*

In Symeon's writings there is a notable high frequency of references to childhood diseases. Regarding infectious diseases in children and the treatment of parotitis, he recommended peas in compresses. For rabies he recommended the rubbing of the affected area with wild menthe mixed with salt. For pediculosis he was prescribing caustic topical agents to prevent the reproduction of lice. [5-7]

Moreover, he introduced the use of peppermint for children suffering from severe anorexia, while he recommended various ointments for generalized rashes. For earache he believed that malva extract could ease the pain and for childhood epilepsy he recommended a beverage of viola odarata which could cure from seizures. [5-7]

In paediatric therapeutics Symeon Setha introduced a great number of natural substances and medications known in the oriental world.

Damnastes (c. 11th century)

Damnastes lived probably during the 11th century AD, but according to other sources he could lived during the 1st-2nd century AD [8-10]. It was supposed that Damnastes and the medical author Damastes (a contemporary of Soranus of Ephesus) is one and the same historical person [9]. Damnastes was expert in pediatrics, midwifery, gynecology and obstetrics [8]. In his work, "On the Care of Pregnant Women and Infants", he provided a calendar with the events of gestation given duration of days depending on how long after conception the baby is born [11]. This contradicts with the ancient belief that eight- month pregnancies were doomed [9]. Unlike several ancient medical writers, Damnastes made no distinction between the sexes and how fast they developed inside their mothers' uterus and he wrote that male and female children follow the same developmental schedule. [8,11] Interestingly Damnastes held to the belief, common among the ancient Greek medical writers, that the development of a baby followed patterns reflected in musical harmony and universe. [9]

Ioannis the Episcope of Prisdrianon (c. 12th century)

Ioannis, the Episcope of Prisdrianon lived during the 12th century AD. He mainly studied juvenile diabetes mellitus, the concept of hypoglycemia, diseases of the bowel and kidneys. He preceded his studies extracting diagnostic conclusions from testing urine, and wrote a work "On Urine". He specifically mentioned a diagnostic method for cancer from testing the urine. [1,12] Ioannis mentioned that in cases of juvenile diabetes, upsetting signs include clear and white urine with no sediment as well as emerging symptoms like polyuria and polydipsia. Watery urine was also considered an ominous prognostic sign [13]. Moreover, he described the characteristic symptoms of kidneys' ulcers, such as pyuria, haematuria, residue-like flakes and a strong smell. [13]

Conclusion

Several times in the course of history, physician's reputation relied not only on his specific abilities but also on the readiness of the community to apply his methods. The ignorance of many residents of the Byzantine Empire on proper medical practice, the vastness of the Empire, the inability of some to distribute cohesive written scientific essays, played their part in making a physician's work popular. The reputation of Symeon Seth, Damnastes and bishop Ioannis of Prisdrianon in pediatrics is only as visible as the overdue recording of their names in medical history. Their contribution, though, is remarkable.

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CASE REPORT

LARYNGEAL PAPILLOMATOSIS IN CHILDREN

**Roxana Ionescu[1], Raluca Grigore[1,3], A. Nicolaescu[1], Silvia Ghilinschi[1], Oana Păun[1]
B. Popescu[1,3], C.R. Popescu[1,3], Diana Ionescu[2], Olimpia Cojoc[2], Ș. V.G. Bertești teanu[1,3]**

[1]ENT Head & Neck Surgery Clinic - „Colțea" Clinical Hospital Bucharest
[2]Pediatric ENT Clinic, "Gomoiu" Clinical Hospital Bucharest
[3]„Dr. Carol Davila" University of Medicine and Pharmacy Bucharest - E.N.T. Department

Summary

Background: Recurrent respiratory papillomatosis (RRP) is a disease caused by the human papillomavirus (HPV). Warty growths in the upper airway may cause significant airway obstruction or voice change. RRP has a bimodal age distribution and manifests most commonly in children younger than 5 years (juvenile-onset RRP [JORRP]) or in persons in the fourth decade of life (adult-onset RRP [AORRP]). JORRP is more common and more severe than AORRP. JORRP is caused by exposure to HPV during the peripartum period. The mode of infection in adults is still not known, but sexual transmission is likely.
Materials and Methods: A 3 year-old boy presented in V. Gomoiu Clinic, Department of Pediatrics, for high fever (40.3 degrees Celsius), chills, cough, vomiting and important nasal obstruction. ENT interdisciplinary examination reveals the existence of a tumor in the upper pole of the left palatine tonsil. The treatment was surgical, total removal of the tumor.
Results and Discussion: During anesthesia (difficult intubation because of the impossibility of viewing glottic region), the surprise was the discovery of tumor extension to the entire supraglottic floor. After complete ablation of tumors under direct laryngoscopy, we found evidence of small, cauliflower-like tumors in the first tracheal rings. Histological examination of the resection specimen confirms the diagnosis of papillomatosis. The discussion is that is known that the glottis is often affected, and in this case is not; because of this patient showed no symptoms as dysphonia and dyspnea. The treatment was complete resection of the tumors without tracheotomy.
Conclusion: The anesthesiologist's and surgeon's skill and experience were essential to complete the surgery without complications during and after.
Key words: papillomatosis, laryngeal benign tumors, HPV

Résumé

La papillomatose laryngée chez les emfants

Introduction: La papillomatose laryngiée récurrente (RRP) est une maladie chronique déterminé par l'infection avec le virus HPV. Excroissances caractéristiques en le pôle supérieur aérodigestif peuvent déterminer dysphonie ou obstruction significative. La RRP affecte en principal les enfants (moins de 5 ans - la papillomatose juvénile - JORRP) et les adultes (plus de 40 ans - la papillomatose adulte - AORRP). La JORRP est plus fréquente et aussi plus sévère. L'infection en la période postpartum avec HPV est responsable.
Méthodes: Un enfant de 3 ans s'est présenté à la Clinique V. Gomoiu section de pédiatrie pour fièvre (40.3), frissons, toux, vomissements et obstruction nasale. Le consultation interdisciplinaire d'otorhinolaryngologie a démontré une tumeur dans le pôle supérieur de l'amygdale gauche. On décida à faire une résection totale de la tumeur.
Résultats et Discussion: Pendant l'anesthésie (ou il y avait une intubation difficile) la surprise a été qu'on découvrait des tumeurs multiples qui occupent en totalité l'étage supraglottique. Après l'excision de ces tumeurs par laryngoscopie directe nous avons aussi découvert des petites tumeurs sur les prémiers anneaux trachéaux. Le résultat pathologique a été papillome. La particularité de ce cas est que les cordes vocales n'ontpas été affectées. Le traitement a été représenté par l'excision totale des tumeurs sans trachéotomie.
Notre conclusion est que la préparation et l'expérience du chirurgien et aussi l'anesthésiste ont fait possible cette intervention chirurgicale sans complications.
Mots clefs: papillomatose, tumeurs bénignes laryngées, VHP

Correspondence address: *Raluca Grigore M.D.*
Colțea Clinical Hospital - E.N.T. Head & Neck Surgery Clinic
I.C. Brătianu Boulevard, number 1-3 Sector 3, Bucharest, Romania
e-mail: roxanaelena.ionescu@gmail.com

INTRODUCTION

Laryngeal papillomatosis is a benign papillary tumor derived from squamous epithelial cells, generally observed in children. It arises at the expense of the laryngeal mucosa with possible extension to the trachea and bronchi. Although its clinical features are well known, its pathogenesis is still poorly elucidated, apart from the role of viral infection that has now been proven. More than 70 viral subtypes have been identified, but serotypes HPV6 and HPV11 are involved in the majority of cases (1-2). Recurrent respiratory papillomatosis (RRP) can be a devastating disease for a child, occasionally necessitating up to 150 surgeries over the child's lifetime. The disease can progress to involve the lungs and transform into squamous cell carcinoma of the airway. Recurrent respiratory papillomatosis (RRP) is one of the most common causes of hoarseness and airway obstruction in children. Papillomas may develop anywhere in the respiratory tract, from the nose to the lung; however, >95% of cases involve the larynx. The sites of respiratory system involvement have been described more completely for JORRP; 52% of children have only laryngeal involvement. The trachea is the next most commonly involved site. However, 31.8% of children had papillomas in areas outside of the trachea and larynx (eg, oropharynx, nasopharynx, mouth, bronchi, lung parenchyma). (2).

Epidemiology and frequency

Based on a 1996 survey, it was estimated that there would be 80-1500 new cases of RRP in children younger than 18 years in the United States in 1999 (3). An earlier survey estimated the incidence in children aged 14 years or younger as 4.3 cases per 100,000 population. In those older than 15 years, the estimated incidence is 1.8 cases per 100,000 population.(4). Researchers in Denmark have studied the incidence of JORRP and concluded that the incidence in Denmark is the same as that in the United States. JORRP affects males and females in equal numbers, whereas AORRP is more common in males. The mean age at diagnosis of JORRP is 3.8 years. The adult form usually manifests in the third or fourth decade of life but may rarely manifest in patients older than 60 years.

Mortality/Morbidity

Because the disease is uncommon and requires direct laryngoscopy for diagnosis, children usually have symptoms for a year before a physician makes the diagnosis. The morbidity of this disease has been studied more completely for JORRP, in which the average number of surgical procedures required is 4.4 per child per year and the average number of procedures per child's lifetime is more than 20.This exacts a tremendous financial cost and severely affects quality of life, including the ability to attend school and work. Ten to 15% of children with JORRP ultimately require tracheostomy, usually when younger than 2 years. Many eventually tolerate decannulation. The need for tracheostomy in adults appears to be less common than in children, but repeated surgical procedures are the rule, and procedures may be required as often as every few weeks. Malignant degeneration of papillomatous lesions to squamous cell carcinoma occurs in 3-5% of patients with RRP.

History

RRP is a rare disease, and adult patients may have symptoms for months or longer before the disease is recognized. Because the larynx is the most frequently affected site for both JORRP and AORRP, symptoms of upper airway obstruction predominate. Upper airway obstruction may be life threatening and may be the presenting symptom. Hoarseness is the most common presenting symptom. Other symptoms include the following: voice change; choking episodes, foreign body sensation in the throat, cough, dyspnea, inspiratory wheeze, stridor.

Physical findings often are nonspecific. Voice change may be noted. Inspiratory wheezing, stridor, or both may develop over the trachea or the upper thorax.

Patients with JORRP commonly present with a weak cry, episodes of choking, hoarseness, or failure to thrive. Patients with AORRP present with hoarseness, choking spells, voice change, dyspnea, or a foreign body sensation in the throat.

Causes

HPV causes RRP. HPV-6 and HPV-11 are the most common types associated with RRP, but, rarely, affected tissues contain HPV-16 and HPV-18. HPV is the most common sexually transmitted disease in the United States; as many as 75% of women have genital HPV at some time in their lives. Thirty to 60% of mothers of children affected with JORRP have genital HPV, compared with 5% of mothers of unaffected children. A study using questionnaires of affected children or their parents (identified through the RRP Foundation) verified that the 3 risk factors for JORRP are (1) firstborn child, (2) vaginal delivery, and (3) mother younger than 20 years. The risk factors for JORRP do not apply to adult-onset cases. This suggests that adult disease does not represent reactivation of latent disease. The mode of transmission of HPV in AORRP is not known. Child-to-parent transmission by cough has never been documented. Sexual transmission is likely.

Differential Diagnoses

- Benign laryngeal or tracheal tumors
- Benign Lung Tumors
- Foreign Body Aspiration
- Gastroesophageal Reflux Disease
- Laryngeal infection
- Malignant laryngeal or tracheal tumors
- Malingering
- Polychondritis
- Reflux
- Relapsing polychondritis
- Secondary Lung Tumors
- Squamous cell lung cancer
- Subglottic stenosis
- Tracheomalacia

- Vocal cord dysfunction
- Vocal cord paralysis

Histologic findings

Under low power, the lesion has a papillary appearance. This results from the exophytic growth of keratinized squamous epithelium overlying a fibrovascular core. Koilocytes, vacuolated cells with clear cytoplasmic inclusions, are noted and are indicative of viral infection. Metaplasia and dysplasia occur in varying degrees.

Treatment

The goals of therapy are to relieve airway obstruction, improve voice quality, and facilitate remission. The primary treatment involves repeated surgical debulking, usually by means of microdebridement, angiolytic laser, cryotherapy, or carbon dioxide laser. This may be followed by an injection of cidofovir into the resection site in patients with moderate-to-severe disease. Tracheostomy may be needed if significant airway obstruction occurs. A quadrivalent vaccine for prevention of genital HPV infection was approved in 2006. This vaccine protects against HPV types 6, 11, 16, and 18 and therefore has promise for decreasing the incidence of RRP. Vaccine therapy for those already affected with HPV is under study. A bivalent vaccine for HPV is also available, but will not affect RRP incidence as it is protective against only HPV types 16 and 18.

Indications

Indications for surgery in recurrent respiratory papillomatosis (RRP) are based on the presence or absence of a lesion that causes symptoms. Laryngeal lesions, if present, usually cause symptoms and must be removed or treated. In a patient undergoing multiple surgeries a year, a lesion may only need to be removed because it is symptomatic and not necessarily every lesion needs to be removed in every surgical procedure. Surgical excision is the current standard of care in the treatment of recurrent respiratory papillomatosis (RRP). Adjuvant medical therapy has been investigated over the past 2 decades and continues to this day. If the child or adult has only hoarseness, surgery can be scheduled as an elective procedure. If the child or adult has airway obstruction, immediately treat it as an emergency procedure.

Contraindications

No contraindications to surgical removal of recurrent respiratory papillomatosis (RRP) exist.

CASE REPORT

We present the case of a 3 year old boy, who presented to the Pediatric Clinic of "Gomoiu" Hospital, for high fever (40.3 degrees Celsius), chills, cough, vomiting food, important nasal obstruction for 48 hours. After the ENT examination, we diagnosed him with tumor in the upper pole of the left palatine tonsil and chronic adenoids. The patient is transferred in the ENT Department of the same hospital. The specific clinical and laboratory investigations were within normal limits (complete blood count, urinalysis, specific tests for tuberculosis, syphilis, AIDS, lung radiography).

Considering the characteristics of the case we decided for the surgical treatment in order to have an accurate diagnosis, based on pathology exam. The interesting fact was that during the anesthesia (with difficult intubation because of the impossibility of viewing hole glottis), we discovered tumor extension to the entire supraglottic floor (fig. 1 and 2), without any specific symptoms before surgery. After complete ablation of tumors under direct laryngoscopy, it finds evidence of small, cauliflower-like tumors in the first tracheal rings. We complete the surgery without tracheostomy (fig. 3). Histological examination of the resection specimen confirms the diagnosis of laryngeal papillomatosis, but the serotypes

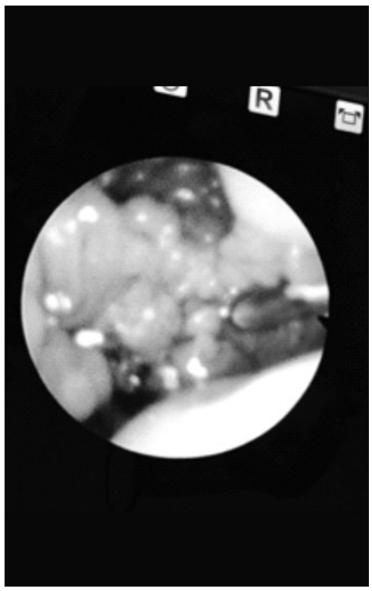

Figure 1

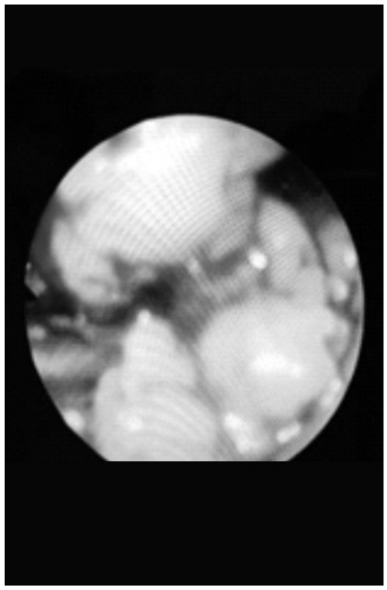

Figure 2

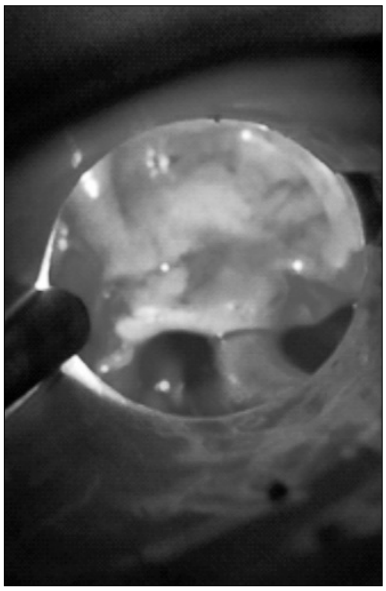

Figure 3

of HPV are still in work. The evolution after surgery was favorable with adjuvant treatment (antibiotics and steroids), and the patient was discharged with the recommendation to come back after 3 weeks.

Results and Conclusions

Recurrent respiratory papillomatosis (RRP) is most commonly observed in children, but it can occur in adults. Although lesions histologically and pathologically seem similar in children and in adults, clinically they behave much differently. Children often require multiple surgical procedures, and their disease often becomes quiescent in adolescence. Adults with recurrent respiratory papillomatosis (RRP) usually require only a few surgical excisions for cure. Recurrent respiratory papillomatosis (RRP) can be a devastating disease for a child, occasionally necessitating up to 150 surgeries over the child's lifetime. The disease can progress to involve the lungs and transform into squamous cell carcinoma of the airway. Recurrent respiratory papillomatosis (RRP) is one of the most common causes of hoarseness and airway obstruction in children. Indications for surgery in recurrent respiratory papillomatosis (RRP) are based on the presence or absence of a lesion that causes symptoms. Laryngeal lesions, if present, usually cause symptoms and must be removed or treated. Surgical excision is the current standard of care in the treatment of recurrent respiratory papillomatosis (RRP). Adjuvant medical therapy has been investigated over the past 2 decades and continues to this day.

Conclusion

We presented this case for didactic reasons bringing into discussion aspects like poor symtoms, the large extensions of this tumors and the extensive surgery we can practice (child quality of life). Despite all the diagnostic tools the surgeon can be faced with challenging cases from the surgical point of possible intraoperative or postoperative complications.

RRP usually is a pediatric disease. The main problem is recurrent airway obstruction, so that we should teach parents to recognize potential warning signs, including a weak cry, hoarseness, stridor, wheezing, cyanosis, and decreased exercise tolerance. Airway obstruction may recur as soon as 2-4 weeks after laser procedures, and recognizing its development before critical, life-threatening obstruction develops is important.

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CASE REPORT

MALIGNANT SCHNEIDERIAN INVERTED PAPILLOMA

Ş.V.G. Berteşteanu[1,2], A. Nicolaescu[1], A. Toma[1,2], B. Popescu[1,2], C.R. Popescu[1,2], R. Ionescu[1], O. Păun[1], D. Mirea[3], D. Cristian[2,4], R. Grigore[1,2]

[1]*"Colţea" Clinical Hospital Bucharest - E.N.T. Head and Neck Surgery Clinic*
[2]*"Carol Davila" University of Medicine and Pharmacy Bucharest - E.N.T. Department*
[3]*"Elias" Emergency Hospital Bucharest - E.N.T. Clinic*
[4]*"Colţea" Clinical Hospital Bucharest - General Surgery Clinic*

Summary

Background: Malignant sinus neoplasms represent a rare, low-frequency pathology of the paranasal sinuses, accounting for about less than 1% of the total malignancies number and just about 3% of those arising in the head and neck region. Because of anatomical considerations they are frequently diagnosed in late stages. Current optimal treatment requires a multidisciplinary approach, but surgical removal is key to a successful outcome.
Methods: We present a case of a 60 y.o. male diagnosed already with maxillary sinus neoplasm (SCC) and operated on twice in the last year, who underwent chemo and radiotherapy in our clinic, and who presented with tumoral recurrence.
Results: This case was a desperate one, and for this type of patient a radical surgical procedure was required (the so-called "salvage surgery"). En-bloc resection of the left meso and suprastructure with left orbital exenteration was performed, followed by reconstruction of the orbital defect with a small local fascio-cutaneous facial flap.
Conclusion: Even with modern combined therapies, management of paranasal sinus malignant neoplasms is always shadowed by a consistent recurrence rate. Desperate salvage surgery procedures are the last hope for these patients, and the outcome is poor even after these radical interventions. The authors consider that the key to obtaining the best possible outcome when treating sinus malignancies is "per-primam" radical resection of the tumor.
Key words: Schneider inverted papilloma, sinus neoplasm, salvage surgery

Résumé

Papillome inverti schneidérien malignisé

Introduction: Les tumeurs cancéreuses des sinus paranasaux representent une pathologie rare, jusqu'à 1% du nombre total des cancers et 3% des cancers de la tête et du cou. À cause de leurs rapports anatomiques ces cancers sont diagnostiqués fréquemment trop tard. Le traîtement actuel optimal fait nécessaire un abord multidisciplinaire, mais la chirurgie est la clé pour obtenir de bons résultats.
Méthodes: Nous présentons un cas d'un homme de 60 ans qui a été diagnostiqué avec du cancer du sinus maxillaire (carcinome) et qui a été operé deux fois l'année dernière et a fait de la chimio et radiothérapie dans notre clinique
Résultats: Ce cas a été un cas très difficile et pour ça un certain type d'intervention chirurgicale radicale a été nécessaire (qui s´appelle chirurgie salvatrice). On a performé une résection en-bloc du méso et suprastructure avec les contenus de l'orbite gauche et après ça on reconstruit le défaut facial avec un petit lambeau fascio-cutané facial.
Conclusions: Avec des méthodes modernes de traîtement le management des cancers des sinus paranasaux est grevé en permanence d'une rate de récurrence importante. Pour certains de ces malades la chirurgie radicale est la dernière solution mais ça ne garantie pas la cure de la maladie. Les auteurs pensent que la clé pour obtenir des résultats favorables dans ce type de cancer est la chirurgie radicale de première intention.
Mots clé: papillome inverti de Schneider, cancer du sinus, chirurgie radicale

Correspondence address: *Alexandru Nicolaescu M.D.*
Colţea Clinical Hospital, bd.I.C. Brătianu no. 1-3, sector 3, Bucharest, Romania
e-mail: alexandrunicolaescu@ymail.com

BACKGROUND

Malignant neoplasms of the paranasal sinuses represent less than 1% of the total number of cancers and about 3% of the total number of cases in the head and neck region. (1) There has been demonstrated a greater risk in males than in females (2:1) and known risk factors include heavy-smoking, infection with HPV type 16 and 18, industrial exposure to wood dust, nickel, leather, textile dust, chromium, formaldehide and asbestos. (1)

Sino-nasal malignancies are a farely heterogenous group considering the multitude of histological types, but the majority are represented by squamous cell carcinomas (SCC) - about 60-70% and adenocarcinomas (10-20%). The most frequent site of involvement is the maxillary sinus (almost 70% of cases), followed by the nasal cavity (20-30%), the ethmoid sinuses (10-15%) and less than 5% develop in the frontal and sphenoid sinuses. (1)

Very important and sometimes hard to distinguish are the so-called Schneiderian papillomas, which by definition are benign tumors that arise from the ectodermally-derived respiratory epithelium lining the nose and paranasal sinuses (Schneider's membrane) and are clasically divided into 3 forms: inverted, fungiform and oncocytic. (2) The particularity of these types of tumors is the local agressiveness with which they invade and obliterate adjacent structures and probably the most important is their capacity to evolve toward malignancy.

Signs and symptoms depend on the location and extension of the tumor. In case of large tumors (T3 and T4), tumoral spread to adjacent structures can manifest itself with visual disturbances, epiphora, CSF leak, external swelling of the cheek and forehead or irritation of the first and second branch of the trigeminal nerve (causing hyperesthesia and pain). (1)

Positive diagnosis is always made by histo-pathological analysis of samples harvested from the primary tumor, and the complete clinical examination should always be augmented by panendoscopy and imaging studies (preferably both CT and MRI). (1) Other investigations such as arteriography (for determining the resecability of the internal carotid artery - if involved in the tumoral process) can be necessary.

Current standard treatment protocol is a case-by-case approach discussed in a tumor board meeting which takes into consideration all the individual aspects (for example feasibility of complete resection, functional outcome, histology, tumor stage, surgeon's experience and technical expertise and patient's personal preferences) of the case in hand. The preferred treatment option is surgery followed by radiation therapy (3) and chemotherapy. (1)

CASE REPORT

Patient N.G. aged 60 presented in our clinic in March 2015 with recurrent epistaxis, nasal obstruction and anosmia, left lacrimal purulent discharge and reduction of visual acuity of the left eye. From the patient's medical history we recorded that the patient was diagnosed with left maxillary sinus tumor (HP result: Scheinderian inverted papilloma) in March 2014 and operated in our clinic where we performed left partial meso and supra-structure resection, as well as functional left neck dissection and left external carotid artery ligation. After the histological result other therapies were deemed not necessary, and the patient was followed-up clinically and imagistically every month. After a 2 months hiatus in which the patient didn't present to his follow-up visit he presented in October 2014 with tumoral recurrence and a second surgical procedure was performed: radical left maxillary antrostomy (adapted after Caldwell-Luc procedure) with complete macroscopic resection of tumoral tissue and right functional neck dissection and right external carotid artery ligation. The histological result confirmed the initial diagnosis of Schneiderian inverted papilloma but found large areas of high-grade dysplasia and small areas of carcinoma. The patient began radiation therapy and was administered between January and February 2015 a maximal dose of 60 Gy on the target area, which was well tolerated.

Other pathological conditions worth mentioning: acute myocardial infarction (2010) - with PTCA LAD stenting, stage III hypertension, mixt dislipidemy, heavy tobacco smoker.

Clinical findings were: facial assimetry with a left induration of the paranasal and suborbital region, left ocular globe hypomobility, lacrimal purulent discharge of the left eye, left optical field reduction, painful sinus points. (fig. 1 & 2) Nasal endoscopy showed a ulcerated tumoral mass with sub total destruction of the nasal septum with multiple bleeding points on the surface. (fig. 3)

CT scan performed showed (fig. 4): irregular solid heterogenous tumoral mass localised in the left maxillary sinus with associated osteolysis of the sinusal walls as well as the wing of the sphenoid, ethmoidal cells and insertion of the zigomatic arch. The tumor extends to the frontal and sphenoid sinus on the left side, nasal septum as well as marginally to the left orbit where it displaces the contents and is adherent to the vasculo-nervous optical pedicle.

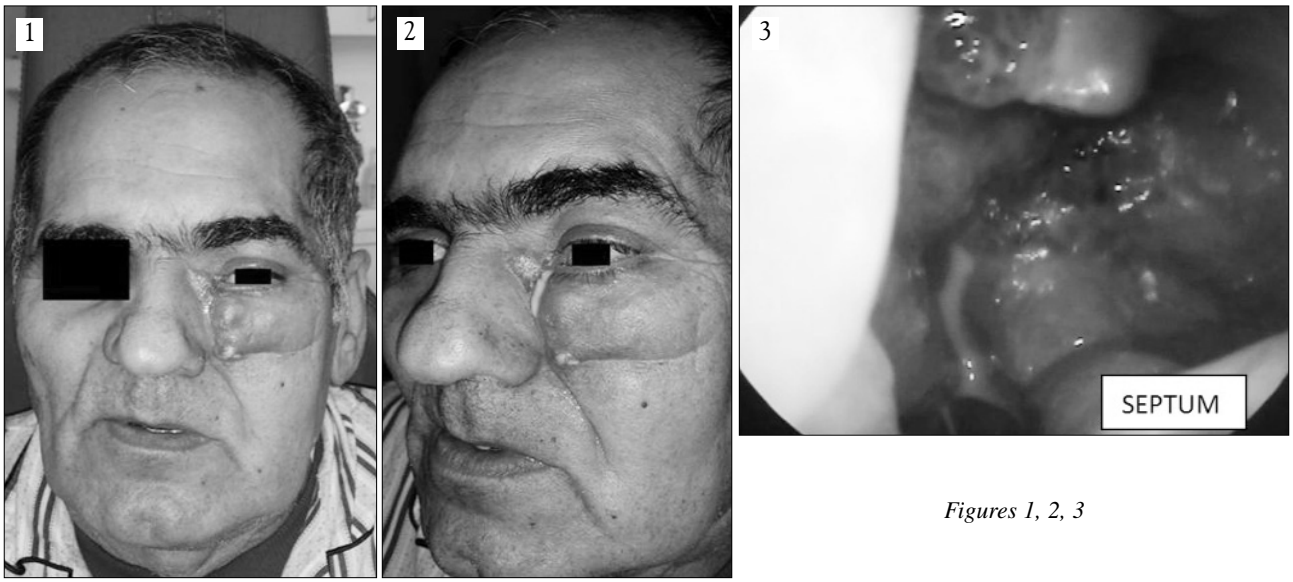
Other paraclinical investigations were without clinical significance.

Surgical treatment and results

We performed a left paralateral nasal incision elongated along the zigomatic and frontal arch to circumscribe the orbit, followed by careful dissection of the tumor from the bony orbit and an en-bloc resection of the left suprastructure tumor along with the left orbital contents. (fig. 5,6,7)

The resulting facial defect (fig. 8) of considerable size, after carefully controlling the hemostasis, was packed with a haemostatic sponge and mesh and a naso-gastric intubation tube was placed. To obtain a functional outcome, plastic reconstruction with a local fascial and skin flap from the cheek was performed. (fig. 9)

Postoperative wide spectre antibiotic treatment was prescribed along with non-steroid antiinflammatory drugs and fractionated heparin. Clinical evolution was adequate, and the patient was discharged 10 days after surgery. Follow-up



Figures 1, 2, 3

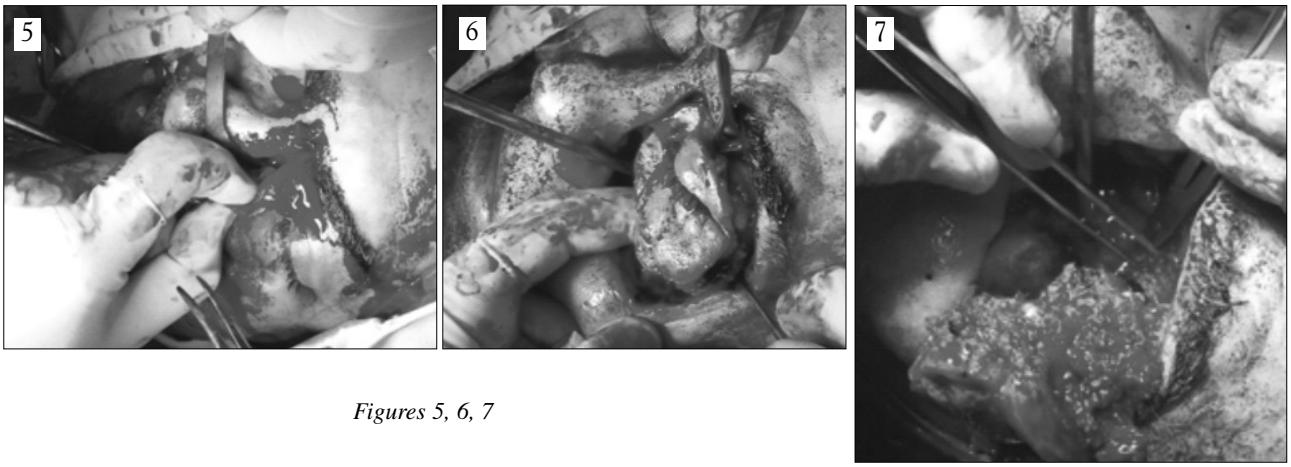
visits were programmed for the first week postoperatively (fig. 10), then every 2 weeks for the first two months then monthly for the first year.

Conclusions and case particularities

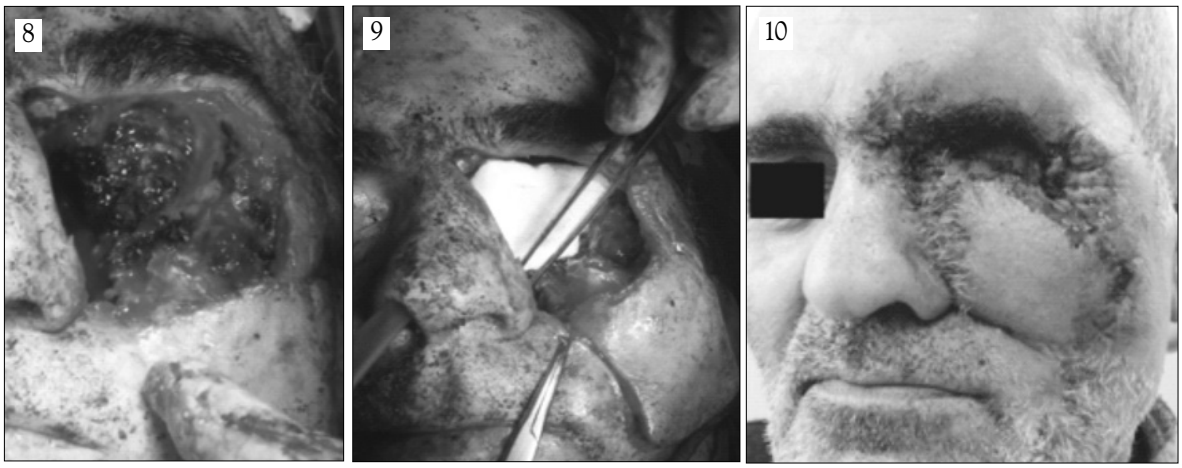
The particularity of this case is the histological type of tumor, and the evolution towards malignancy of this tumor. Schneiderian inverted papillomas are not frequent tumors (0.4 - 4.7% of all sinonasal tumors (2)) and according to some authors only 12.5% of cases progress toward malignisation. (4) In concern to this particular case, we find hard to believe that the initial tumor wasn't already malignant because of the rapid recurrence after the first surgical procedure, but without the histological as well as imagistic proof, radical resections cannot be justified. The local agressiveness as well as the rapid recurrence and evolution were decisive factors in favor of a radical surgical procedure meant to resect the whole neoplastic tissue.

Outcome in case of carcinomas of the nose and paranasal sinuses depends of course on the stage of the disease as well as on the treatment applied. In this case the tumor was classified as a T4a and according to some

Figure 4



Figures 5, 6, 7



Figures 8, 9, 10

authors recurrence is to be expected in 48% of cases and 5-year survival is about 50%. (5) Because the patient already had maximal radiation therapy at the beginning of the year, consolidation of the surgical treatment will be reduced just to chemotherapy.

The key for obtaining the best possible outcome when it comes to sino-nasal tumors is, in our opinion, the correct and immediate diagnosis and staging of the tumor. Correct staging permits applying the best surgical procedure (even if its radicality is sometimes hard to accept by the patient) and ultimately offers the patient the best chance of survival.

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CASE REPORT

THE ANABOLIC OPTION IN SEVERE MENOPAUSAL OSTEOPOROSIS: IS THERE A DARK SIDE?

Simona Elena Albu[1,2], Mara Cârsote[1,3], Anda Dumitrașcu[3], A. Goldstein[3], Adriana Gruia[4], Cristina Vasiliu[1,2], Cătălina Poiană[1,3]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[2]*Universitary Emergency Hospital, Bucharest, Romania*
[3]*C.I.Parhon National Institute of Endocrinology, Bucharest, Romania*
[4]*Medlife Medical Centre, Bucharest, Romania*

Summary

Severe menopausal osteoporosis needs supplementary investigations if new fractures are registered under therapy or a consumptive syndrome is associated. 84-year old female has a 7-year history of osteoporosis treated with alendronate. She presents back pain and recent weight loss. The central Dual Energy X-ray Absortiometry points low T-score of -4.1 at total hip. The calcium metabolism tests are normal. Technetium whole body bone scintigrame shows old vertebral fractures and a new one at T11 and at ninth lateral rib but the differentiation between primary osteoporosis and a bone metastasis cannot be done therefore computed tomography is performed. T11 cuneiform vertebral and a general lumbar bone density loss is registered but no neoplasia. Finally anaemia was considered to be in an ulcer context and anabolic therapy with daily subcutaneous teriparatide is started with a good evolution for the following months. The case finding strategy to start anabolics for severe osteoporosis is associated with a high index of suspicion if new fractures associate weight loss, anaemia or advanced age.
Key words: osteoporosis, menopause, teriparatide

Résumé

L'option anabolisante dans l'ostéoporose sévère à la ménopause: y-a-t-il une côté obscure là dedans?

L'ostéoporose sévère à la menopause nécessite des investigations supplémentaires si des fractures nouvelles surviennent pendant la thérapie ou un syndrome consomptif est associé. Une patiente âgée de 84 ans avec ostéoporose depuis 7 ans a été traitée avec alendronate. Elle présente une douleur spinale et une perte récente de poids. L'absortiométrie duale d'Enérgie par rayons-X DEXA indique un score T de -4.1 total à la hanche. Les testes du métabolisme du calcium sont normaux. Le scintigramme osseux montre des fractures vértébrales anciennes et une nouvelle fracture à T11 et au niveau de la 9ème côte. La différenciation entre l'ostéoporose primaire et une métastase osseuse ne peut pas être faite, donc on effectue la tomographie computérisée. Un aspect cunéiforme de la vertébre T11 et une déminéralisation spinale générale sont trouvés, mais pas de néoplasie. Finalement, l'anémie a été considèrée comme provoquée par un ulcère et on a commencé une thérapie anabolisante avec tériparatide sous-cutanée, avec une bonne évolution pour les mois suivants. La stratégie de trouver les cas nécessitant des anabolisants en cas d'ostéoporose sévère est associée à un indice élevé de suspicion si les nouvelles fractures associent de la perte de poids, de l'anémie, d'âge avancé.
Mots clés: ostéoporose, ménopause, tériparatide

Background

Menopausal osteoporosis is a complex disease targeting an increasing number of women. The pathogenic pathways are numerous and yearly data are brought proving that new factors are actually involved in the bone loss. The golden standard for osteoporosis diagnosis is central (spine, hip, non-dominant forearm) is Dual Energy X-ray Absortiometry or DXA (DEXA). (1) DXA provides the bone mineral density derived T-score

Correspondence address: *Mara Cârsote, MD*
Aviatorilor Ave 34-36, sector 1, 011863 postal code e-mail: carsote_m@hotmail.com

in order to diagnose normal DXA, osteopenia, osteoporosis. (1) Even DXA represents the best tool we have for osteoporosis up to this moment the severe osteoporosis is diagnosed based on clinical pattern meaning the prevalent or incident fragility fractures, regardless the T-score. (2) Once the diagnosis of severe osteoporosis is established, the therapy options are changed. Changing the current anti-resorptive medication with another one but also with an anabolic drug as teriparatide is the logical approach once an osteoporotic fracture is registered. (3) The use of teriparatide is encouraging for enhancing the benefits not only on bone mass but also on muscle state, fracture healing, and the general well of being since it represents an anabolic. (4) On the other hand, this type of drug should virtually have a dark side acting as a growth factor on different kind of neoplasia (known or unknown on a certain patient with severe osteoporosis). Even the exact algorithm to exclude the virtual cancers behind severe osteoporosis is not established yet a high index of suspicion is indicated in selected population. The only certain oncologic connection is to osteosarcoma in rats and the contraindication in humans with primary or secondary bone cancers. (5) Currently, teriparatide injections are approved in many countries, including Romania. The daily dose is necessary for 24 months. Good results are seen in spine and spine bone mineral density and vertebral and non-vertebral fractures, nevertheless in older women suffering from severe osteoporosis. (6,7)

Our aim is to present an interesting case of severe osteoporosis with challenging in the confirmation if the vertebral fractures as being related to primary osteoporosis and not to bone metastases in order to benefit from the anabolic medication.

Case report

This is a case report where multiple disciplinary data are presented from endocrine, gynaecological, imagery scans. The medical history, anamnesis, clinical and para-clinical data are displayed. The blood biochemistry tests were performed as well as bone turnover biomarkers and calcium phosphate metabolism. The central DXA data are available. Also computed tomography and whole body bone scintigram are presented. The informed written consent of the patient was obtained.

84-year old female who is non-smoker has a long time history of osteoporosis is admitted for asthenia, persistent lumbar pain, and bone mass loss as showed by central DXA exam and weight loss (3 kilograms within last 6 months with normal appetite). She was treated for seven years with weekly alendronate and calcium/vitamin D supplements in different formulas. She associates glaucoma and arterial hypertension controlled under adequate medication. Three decades ago she suffered a partial thyroidectomy for multi nodular goitre and she is under levothyroxine substitution since then.

The clinical (endocrine and gynaecological) exam pointed kyphosis and a body mass index of 18 kg/m^2. The glucose (and A1c glycated haemoglobin), liver enzymes, and renal function profile are normal. Mild anaemia of 10 g/dl haemoglobin level is detected (normal red blood cells parameters). The endocrine tests pointed correct thyroid substitution under daily 75 micrograms of levothyroxine. (table 1) Because of the weight loss and asthenia the 24-hour cosyntropin test is performed. The basal ACTH is normal and plasma cortisol of 13 μg/dL. The cortisol value 24 hours after the test (of 62.3 μg/dL) points adequate stimulation, thus intact pituitary adrenal axes. (table 1) The neuronendocrine screening tests are available. Serum chromogranin A, serotonin, neuron specific enolase, calcitonin are normal. (table 1) The bone metabolism is assessed. The total and ionic calcium as well as blood phosphorus is normal. (table 2) The bone biomarkers are: serum alkaline phophatase of 87 U/L which is within the normal limits; the serum CrossLaps as a bone resorption marker is 0.25 ng/mL (normal); serum osteocalcin as bone formation marker is 10.37 ng/mL, mildly suppressed probably in correlation to previous long term alendronate therapy. (table 2) 25-hydroxy vitamin D is normal of 56 ng/mL. The intact blood parathormone (PTH) level is also normal. (table 2) Gynaecologic (breast and uterine) control is normal. The central DXA assessment reveals non-usable data at lumbar spine because of vertebral fractures; total hip bone mineral density of 0.494 g/cm^2, T-score of -4.1, Z-score of -1.3; femoral neck bone mineral density of 0.508 g/cm^2, T-score of -3.8, Z-score of -1; third distal non-dominant forearm bone mineral density of 0.262 g/cm^2, T-score of 6.3, Z-score of -3.3. Because of the lumbar aspect at DXA the whole body bone scintigram (Tc99m, 20 mCi) is performed. Old vertebral fractures at the thoracic vertebra T9 and T10 and a possible recent one at T11 are found and also at the ninth rib fracture. (fig. 1) Based on these it is not possible to differentiate a recent

Table 1 - The endocrine and neuroendocrine parameters of the 84-year old female with severe osteoporosis

Parameters	Present value	Normal ranges	Observations
TSH (μUi/mL)	4.32	0.5 – 4.5	under L-thyroxine
ACTH (pg/mL)	15.65	3 - 66	
Plasma cortisol (μg/dL)	13	6.7 – 22.6	between 7-10 a.m.
Chromogranin A (ng/mL)	89.7	20 - 125	
Serotonin (ng/mL)	163.7	80 - 450	
Neuron Specific Enolase (ng/mL)	8	0 - 12	
Calcitonin (pg/mL)	0.5	5.17 – 9.82	

Table 2 - The calcium metabolism parameters of the 84-year old female with severe osteoporosis

Parameters	Present value	Normal ranges	Units
Total calcium	9.1	8.5 – 10.2	mg/dL
Serum Phosphorus	4.3	2.5 – 4.5	mg/dL
Alkaline Phosphatse	87	38 - 105	U/L
CrossLaps	0.25	0.226 – 1.008	ng/mL
Osteocalcin	10.37	15-46	ng/mL
25-hydroxy vitamin D	56.13	30 - 100	ng/mL
PTH (parathormone)	54.26	15 - 65	pg/mL

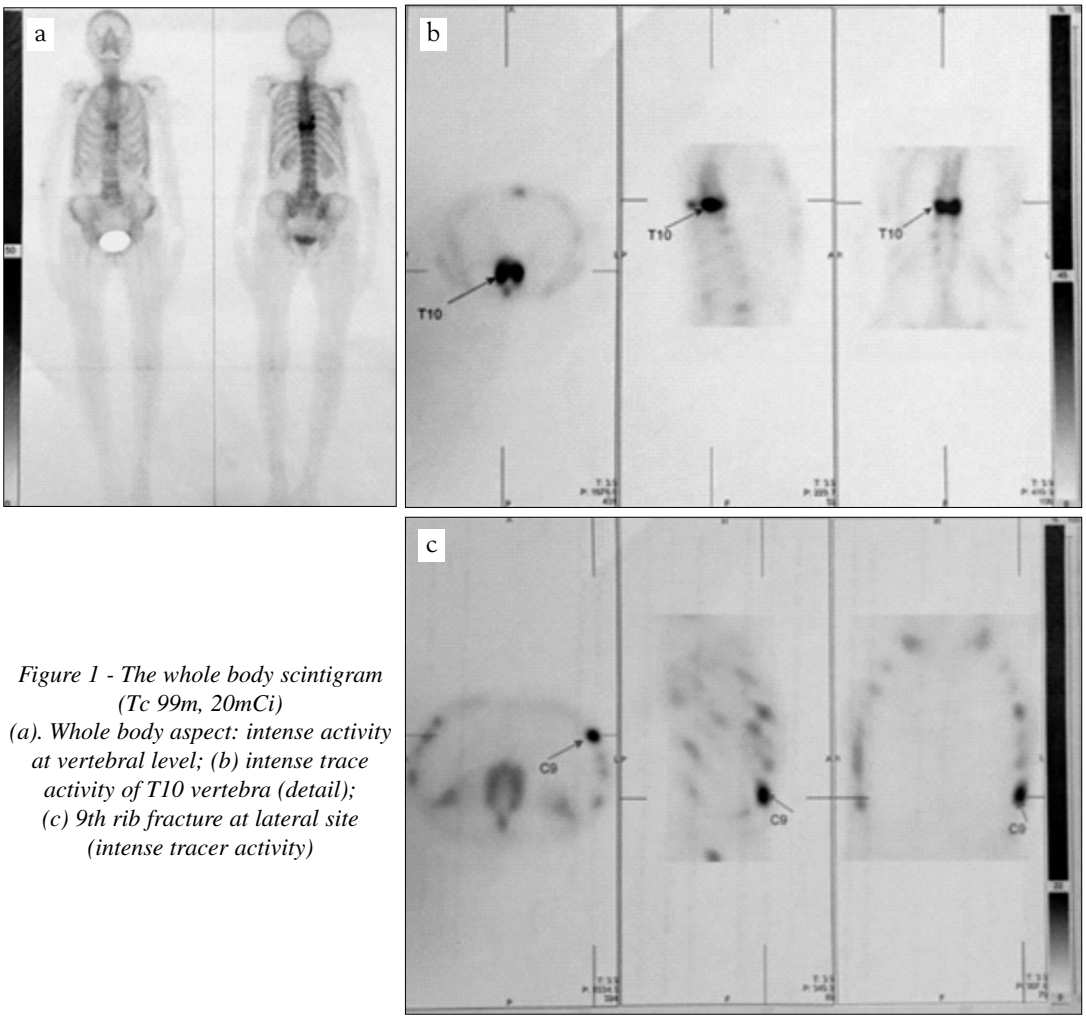

Figure 1 - The whole body scintigram (Tc 99m, 20mCi) (a). Whole body aspect: intense activity at vertebral level; (b) intense trace activity of T10 vertebra (detail); (c) 9th rib fracture at lateral site (intense tracer activity)

osteoporotic fracture to a bone metastasis thus thoracic and abdominal computed tomography is performed. The cuneiform aspect of T10 vertebra is confirmed as well as multiple vertebral fractures. (fig. 2) No neoplasia is detected. The gastroenterological consult confirmed a gastric ulcer and no cancer are found. Based on all the parameters and investigations, severe osteoporosis with recent fractures is confirmed and anabolic therapy with daily 20 µg subcutaneous injections is started. The patient is followed up for 4 months and she feels well with less lumbar pain and no new fracture registered.

DISCUSSIONS

This is a captivating case where the multiple disciplinary approaches were essential to complete the patient evaluation. During the last decades the osteoporosis became a worldwide public health problem thanks to the improvement in the detection methods and devices but also because of the interest in enhancing the quality of life in a population that has a longer hope of life. (8) Primary osteoporosis has an age related pattern and severe cases like the one we presented might be seen in older women. The challenging of the case is the fact that exactly severe senile osteoporosis

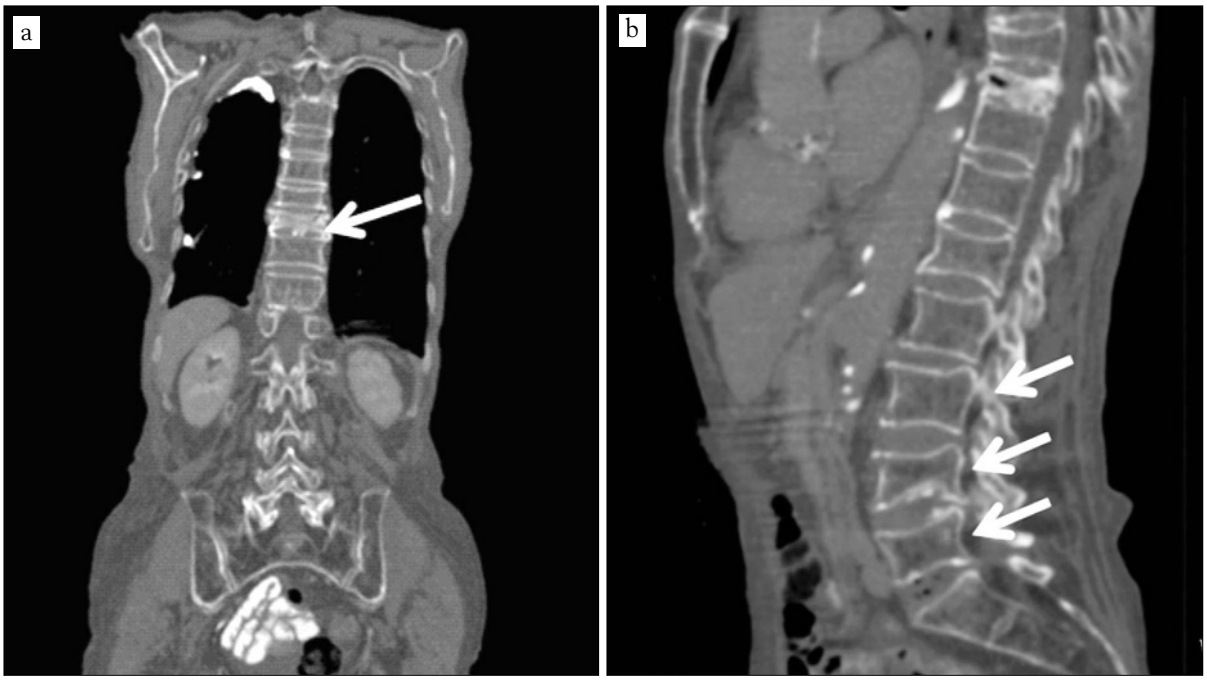

Figure 2 - Computed tomography with contrast substance. (a) Cuneiform vertebra at T10 (arrow). Reduced bone mineral density (computer tomography aspect); (b) Kyphosis, multiple vertebral fractures (arrows), degenerative aspects of the spine

with poor response to previous therapy that benefits most of anabolic therapy as paratide injections. It is essential that newly developed vertebral and possible rib fractures not to associate a secondary cause as bone metastases from unknown primary source where the anabolics are formally contra indicated. (9) That is why we performed supplementary tests as technetium whole body scintigram and thoracic and abdominal computed tomography. The specific blood assays for osteoporosis where normal including the vitamin D status which pointed a correct supplementation up to the admission. The secondary causes of osteoporosis as poliarthritis, hyperthyroidism, etc were excluded based on clinical, biochemistry and endocrine parameters. The specific algorithm in order to check for potential cancer in a case of a patient with bone mass loss associated with anemia, and weight loss is not definite. Severe osteoporosis has a very good response to teriparatide but an anabolic drug might act as a proproliferative factor thus the potential oncologic profile of the patient is important. (10)

Conclusion

Based on our observation, the case finding strategy in order to initiate anabolic medication for severe osteoporosis is associated with a high index of suspicion in cases associating not only new fractures despite previous anti-resorptive therapy but also weigh loss, anaemia or advanced age.

Conflict of interest

None

Acknowledgements

We thank to all the medical teams involved in this case. Special thanks to dr. Lavinia Vija M.D., Ph.D.

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CASE REPORT

SACRAL CHORDOMA IN 78-YEAR OLD FEMALE WITH MORE THAN 15-YEAR HISTORY OF SEVERE OSTEOPOROSIS

Simona Elena Albu[1,2], Mara Cârșote[2,3], Anda Dumitrașcu[3], Cristina Căpățînă[2,3], Diana Păun[2,3], Cătălina Poiană[2,3]

[1]*University Emergency Hospital, Bucharest, Romania*
[2]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[3]*C.I.Parhon National Institute of Endocrinology, Bucharest, Romania*
[4]*Anima Medical Centre, Bucharest, Romania*

Summary

This is a case presentation of a 78-year old female known with a long history of severe osteoporosis who continued to have fractures despite specific anti-osteoporotic therapy that in addition to her lumbar and pelvic pain was discovered with a sacral tumour of 5.9 cm. The CT and the PET CT scans pointed benign chordoma features but no radical intervention was possible. This type of tumour represents a challenging differential diagnosis of lumbar pain in elderly osteoporotic women especially if multiple vertebral fractures are already present.
Key words: sacral chordoma, osteoporosis, back pain

Résumé

Chordome sacral chez une femme âgée de 78 ans avec une histoire de plus de 15 années d'une ostéoporose sévère

Il s'agit de la présentation d'un cas d'une femme âgée de 78 ans avec une longue histoire d'ostéoporose sévère, ayant continué à avoir des fractures malgré la thérapie anti-ostéoporotique spécifique; à part sa douleur lombaire et pelvienne, on lui a découvert une tumeur sacrale de 5,9 cm. La TC et la TEP TC ont montré les caractéristiques d'un chordome bénin, mais aucune intervention radicale n'a été possible. Ce type de tumeur représente un diagnostic différentiel provocateur de la douleur lombaire chez les femmes ostéoporotiques âgées, si de multiples fractures vertébrales sont déjà présentes.
Mots clés: chordome sacral, ostéoporose, douleur dorsale

Introduction

Sacral chordoma is a usually benign slow-growing tumour causing long term low profile symptoms, thus the accurate diagnosis is usually delayed up to severe pain or mechanical complications depending on site and tumours' dimensions. The surgery is one option therapy if possible and if the diagnosis is not too late. (1) Total en bloc or partial sacrectomy represents an alternative in sacral tumour but the severe prognosis and poor outcomes stills. (2) Total sacrectomy is a dramatic procedure and serial skin and soft tissue reconstruction is necessary. (3) Molecular studies tried to find the potential genetic link in tumour recurrences and some authors suggested a consistent mitogen-activated protein kinase (Raf-1) signalling pathway correlation. (4) The presence of a sacrum tumour might be correlated to different medical history especially in elderly population the focus is osteoporosis. If any potential pathogenic correlations exist between these two maladies it is difficult to say, a co-incidental relationship might be in fact seen. On the other hand, the presence of a tumour of sacrococcygeal region originating from cellular remnants of the notochord is a potential confounder of secondary osteoporosis or non-responder osteoporosis or persistent back pain despite anti-osteoporotic therapy. Many assessments procedures are used to evaluate the skeleton status but there are still inconclusive aspects as the relationship between a sacrum tumour and the severe osteoporosis evolution. (5)

Correspondence address: *Mara Cârșote, MD*
Aviatorilor Ave 34-36, sector 1, Bucharest, Romania, 011863 postal code
e-maill: carsote_m@hotmail.com

Aim

We present the case report with a long history of severe osteoporosis accusing a part from her persistent long term back pain also progressive pelvic pain. The investigations lead to the discovery of a large sacral chordoma.

Case presentation

78-year old female has a medical history of both osteoporosis and cardiovascular diseases. She associates high blood pressure under adequate therapy for the last 2 decades, and chronic ischemic heart disease. For the last almost 2 decades she is known with severe osteoporosis, complicated with multiple serial vertebral fractures, double left forearm fractures, a right humerous fracture and a most recent left ulna fracture that was 3 years ago. All these were despite the fact that she was treated with weekly alendronate for almost 10 years, then a year with strontium ranelate, and consecutively for the last 3 years with ibandronate an injection every 3 months. The vitamin D and calcium supplements were continued during this time. In 2014 the Dual-Energy X-Ray Absortiometry (DXA, GE Lunar Prodigy device) showed a femoral neck Bone Mineral Density (BMD) of 0.598 g/cm², T-score of -3.2, Z-score of -0.8. (table 1) The lumbar DXA scan data are not usable because of the multiple vertebral fractures. The femoral neck and total hip BMD analysis during the period of time she was treated improved but this is not correlated to the aggravating fragility (osteoporotic) fracture history. The bone metabolism parameters were normal except for a vitamin D deficiency expressed by a level of 25-hydroxyvitamin D of 18.9 ng/mL (normal levels are between 30 and 100 ng/mL).

During the last years an intermittent back pain with different intensity persisted but for the last months she accused low back and atypical pelvic persistent pain. She was referred for a gynaecological consult that was according to her age but an external palpable mass was found at notochord region. Computed tomography (CT) pointed a sacral tumour that was confirmed by Positronic Emission Tomography PET CT (18F FDG, 203.6MBq) with osteolytic aspects of 4.8 by 2.7 by 5.9 cm without metabolic activity, suggesting a sacral chordoma. The tumour is found at the level of vertebral arches from lumbar L5 vertebral to sacral S2. The lesion is protrusive into the bone compact zone and into the spinal canal. (fig. 1) No other tumour was found, neither pathological lymph nodes aspects at PET CT. The whole body bone scintigram (99MTc-MDP) identified area with intense activity suggesting vertebral osteoporotic fractures at thoracic T9, T11, and lumbar L1, L2, L3, L4 and no activity at the level of the sacrum. The surgical approach was not considered an option by a multi-disciplinary team. Palliative pain medication associated with injectable bisphosphonates and vitamin D supplements were added.

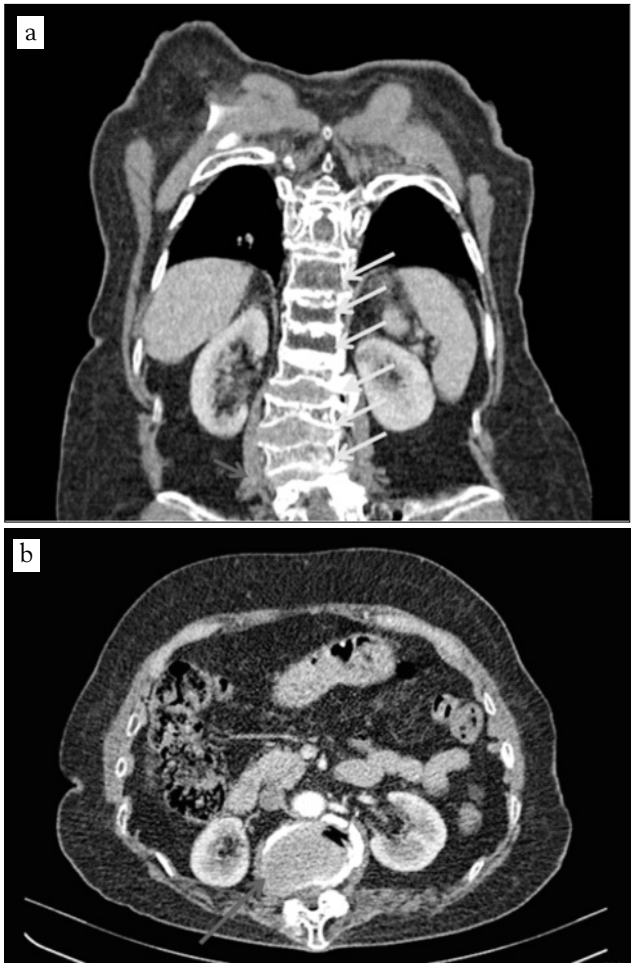

Figure 1 - Computed tomography (CT) aspects (a) Multiple vertebral fractures (right arrows) and a sacral tumour (red arrow) in CT image (coronal plane). (b) Sacral tumour (left arrow) in CT image (transverse plane)

Discussion

This is a woman case with a long history of osteo-

Table 1 - The central DXA assessment (GE Lunar Prodigy device) during follow-up and treatment of severe osteoporosis

Date	Total hip			Femoral neck		
	BMD (g/cm²)	T-score	Z-score	BMD (g/cm²)	T-score	Z-score
2001	0.617	-3	-1.2	not available data		
2010	0.637	-2.9	-0.9	not available data		
2011	0.730	-2.2	-0.2	0.585	-3.3	-1.1
2012	0.719	-2.3	-0.2	0.607	-3.1	-0.2
2013	0.638	-2.1	0	0.606	-3.1	-0.8
2014	0.754	-2	0.2	0.598	-3.2	-0.8

porosis that has been treated for 15 years. Despite the bone mineral density improvement she continued to have fragility fractures and a progressive kyphosis. This case report introduces two medical problems: one is the prolonged history of severe elderly bone loss and the other is the sacrum tumour as a finding in a patient already known with bone pathology. Our patient experienced multiple sites fracture but not hip fracture which is a particular type associated with advanced age. (6) The bisposphonates as used by our patient are known to reduce the fracture incidence regardless the age and the years since menopause. (7) Especially in older adults the failure of therapy is registered and it is not uncommon. (8) When registering the response to therapy the DXA T-score might not be enough since, as seen in this case, the patient continued to have fractures while the bone mineral density improved at hip level. The vertebral fracture assessment and the anatomical changes of the vertebras might count in this specific matter. (9) In addition to the anti-osteoporotic medication the vitamin D and calcium supplements, the lifestyle changes help a better response. (10) In this case there was no evident cause to indicate why there was only a partial response to osteoporosis treatment and that is why the recently diagnosed tumour might raise the question of a secondary type of osteoporosis. No specific data are in literature regarding the two topics. We could not use the DXA measurement during time to see if they are influenced by the chordoma at lumbar level since the patient was previously known with vertebral fractures. There is still a matter of debate to point out the relationship between a lumbar-sacrum tumour and supplementary fracture risk.

CONCLUSION

Sacral chordoma is a challenging differential diagnosis of lumbar pain that is currently seen in elderly women with very long time history of severe osteoporosis especially if multiple vertebral fractures are already present.

Conflict of interest

None

Acknowledgements

We thank to all the medical teams involved in this case.

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TECHNIQUE AND IMAGES

THE ROLE OF MODERN ENDOSCOPIC TECHNIQUES IN EARLY DIAGNOSIS OF UPPER AERODIGESTIVE TRACT MUCOSAL LESIONS

M. Tușaliu[1,2], Ana Alexandra Dragu[2], Maria Nițescu[1], V. Zainea[1,2]

[1]*University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania*
[2]*Institute of Phonoaudiology and Functional ENT Surgery "Prof. Dr. D. Hociotă", Bucharest, Romania*

Summary

The pathology seen in the superior aero-digestive tract is vast, both in terms of the nature of the diseases (especially inflammatory and tumoral) and in the diverse locations of these lesions, which can lead to multiple functional and aesthetic deficits. Therefore, early detection of such changes of the mucosa, sometimes minimal, is one of the most important factors of a successful treatment. Narrow band imaging is a modern examination method intended to increase diagnostic accuracy by using appropriate filters for color wavelengths blue / green / red.
Key words: narrow band imaging, early endoscopic diagnosis

Résumé

Le rôle des techniques endoscopiques modernes dans le diagnostic précoce des lésions de la muqueuse du tract aéro-digestif supérieur

La pathologie vue dans le tractus aéro-digestif supérieur est vaste, tant en termes de la nature des maladies (en particulier inflammatoires et tumorales) que dans les divers endroits de ces lésions, qui peuvent conduire à des déficits fonctionnels et esthétiques multiples. Donc, la détection précoce de ces changements de la glaire, parfois minimes, est l'un des facteurs les plus importants de la réussite du traitement. Imagerie à bande étroite est une méthode d'examen moderne destinée à augmenter la précision du diagnostic en utilisant des filtres appropriés pour les longueurs d'onde de couleur bleu / vert / rouge.
Mots clefs: imagerie à bande étroite, diagnostic endoscopique précoce

Introduction

The variety of benign and malignant lesions found in the upper aero-digestive tract and the various ways of its debut lead to a variety of clinical situations. Accurate diagnosis of all these injuries, and especially their early diagnosis is not always an easy thing to do. Systematic investigation of all areas of the mucosa is essential in this regard. An ENT clinical examination becomes mandatory with rigid or flexible imaging examination of the sinus region, the nasopharynx, oropharynx, larynx or tongue base, with the taking of multiple biopsies of suspicious areas [1-3].

The lesions of the upper aero-digestive tract may cause a range of aesthetic or functional disturbances, such as difficulty of chewing, swallowing, breathing or changes in voice, some with serious impairment in the quality of life. Therefore, early detection of these lesions is one of the most important factors of a successful treatment.

Efforts undertaken at an early stage and accurate diagnosis of these conditions led to the development of new endoscopic examination methods and new technologies designed to get patients with upper aero-digestive tract pathology to the ambulatory. Very small lesions, a few millimeters in diameter, are often very difficult to visualize using classical techniques of endoscopic diagnosis. This led to the introduction of endoscopic methods that allow the detection of these millimetrical lesions. Among other

Correspondence address: *Mihail Tușaliu, MD, PhD*
Institute of Phonoaudiology and Functional ENT Surgery "Prof. Dr. D. Hociotă"
21 Mihail Cioranu street, 5th District, Bucharest, Romania *e-mail: mtusaliu@yahoo.com*

technologies, such as autofluorescence or contact videoendoscopy, used increasingly in recent years, narrow band imaging (NBI) started to be introduced in ENT practice, after it has already proven its effectiveness as a screening method in gastroenterology [4, 5].

NBI is the latest technology that increases the accuracy of diagnosis through the use of filters corresponding with color wavelengths blue / green / red. Magnification endoscopy associated with NBI has two distinct applications: to study the architecture of the surface epithelium and to study the superficial vascularisation.

MATERIAL AND METHODS

In endoscopic examination, identification of lesions is done by studying changes in color and irregularities of the surface of the mucosa. Narrow-band imaging (NBI) is a new endoscopic technique that enhances diagnostic accuracy through the use of filters corresponding to wavelengths of blue / green / red colors. The lighting in narrow band is heavily absorbed by hemoglobin and penetrates only surface tissues, increasing the contrast between the structures. This increases the contrast between the surface epithelium and underlying vascular tissue, resulting in different images at different levels of the mucosa. The depth of the mucous penetration depends on the wavelength used - the surface for the blue color, the depth for the red color and intermediate for the green. Blue filter meets the highest absorption of hemoglobin, emphasizing the capillary vascular drawing on the mucosal surface. By using NBI, capillaries in the mucosal surface appear brown on the screen and veins in the submucosa appear colored in turquoise-blue.

NBI is a non-invasive technique, used under local anesthesia using a flexible videoendoscope inserted through the nose. NBI system additionally contains a special image processor and a special optical filter that allows a light with 415 nm and 540 nm wavelengths. The technology is based on the principle of light penetration depth. The wavelength of 415 nm has a smaller penetration depth, thus increasing image resolution. The wavelength of 540 nm penetrates tissue deeper, thus visualizing the vascular submucosa network better [6-8].

In current practice, this technique allowed us a better characterization of the epithelial changes (metaplasia or dysplasia zones), of the vascular disorganization in upper aero-digestive tract inflammatory diseases and the disorganization of tissue structures in neoplastic lesions in this region. The main utility of this method was thus identifying areas of metaplasia, dysplasia or cancer in ENT for the procurement of targeted biopsies.

DISCUSSIONS

Starting from astronomy to gastroenterology, narrow band imaging technology (NBI) has grown increasingly more in recent years as a viable optical diagnostic method. The principle of visualization in narrow wavelength bands was implemented after telescopes and detection of gastrointestinal cancer to Otorhinolaryngology also, providing greater accuracy in detecting minimal changes to the upper aero-digestive tract mucosa.

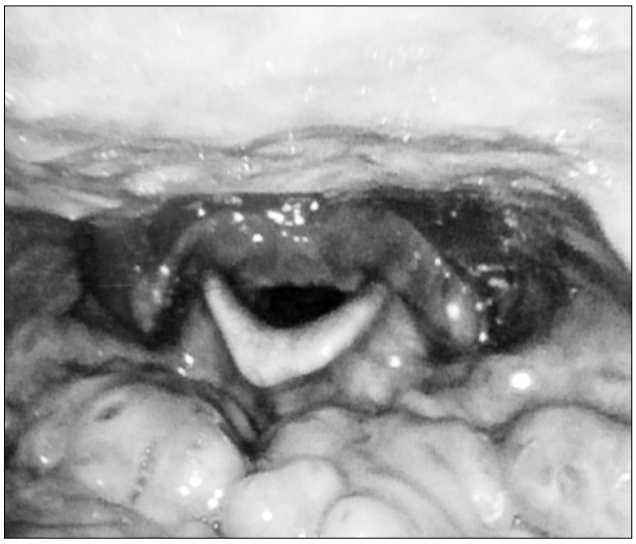

Figure 1 - Endoscopic exam using NBI - Lingual tonsil hypertrophy

Figure 2 – Endoscopic exam using NBI- Recurrent laryngeal cancer

Starting from the observation that the compositional spectrum of reflected light is influenced by tissue structure and blood flow, we arrived to the use of filters corresponding to wavelengths of colors blue / green / red, this view by NBI increasing tissue specific contrast between malignant lesions and mucosa of normal appearance [9-11].

NBI technology is increasingly used in recent years in pharyngolaryngeal pathology diagnosis. The development of endoscopic techniques allowed the introduction of so-called magnification endoscopy with which, combined with HD images, enables in vivo visualisations of vascular tissue microarchitecture. Using HDTV cameras for obtaining high-quality images help differentiate malignant hipervascu-

larised areas from normal mucosa, and enables the visualisation of lesions of only a few mm in diameter. Detailed morphological examination using NBI technology on inaccessible areas allows precise localization in the early stages of the disease process and related photo and video recording of it, with image storage, enabling dynamic tracking and timely evolution of the lesions.

Suspicious lesions observed during endoscopic examination using NBI are well-demarcated areas of brown with brown disseminated dots caused by dilated intraepithelial capillaries in the process of tumor neovascularization. This process of tumor neovascularization can be differentiated from irradiation edema as the latter has no lining divide between brown dots and the mucosa.

NBI can be used intraoperatively, allowing targeted biopsies of suspect areas and the resection with safety margins. It gives the surgeon the opportunity of correct interpretation of changes in the vascular structure inside and around the area of the suspected lesion.

The main advantages of the method consist in the absence of contraindications, of disposable devices, and the ability to use as many times as needed. Special benefits are obtained in the case of a clean mucosa and in the diagnosis of benign nodules, polyps and granulomas. They can be easily viewed by the presence of vessels parallel with the mucosal surface and the lack of brown dots, in contrast with the changes produced by malignant lesions.

The method has its limitations, such as deficient viewing in patients who have undergone radiation therapy and the presence of hyperkeratosis lesions that impede viewing submucosal vascular network. There are also reported false positive results in the case of laryngeal papillomatosis. In this case the use of magnification endoscopy increases the diagnostic accuracy.

Conclusions

NBI is a last generation endoscopic technique, used increasingly more in Otorhinolaryngology for diagnosing of small lesions of the muscosa which are undetectable using classic white light endoscopy, and for getting patients with malignancies of the head and neck to the ambulatory, allowing early detection of tumor recurrences or remainings and also for metachronous tumors. Future studies are mandatory to prove long-term viability of the method in the diagnosis of upper aero-digestive tract mucosal lesions and their therapeutic management.

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These guidelines are in accordance with the "Uniform Requirements for Manuscripts submitted to Biomedical Journals" published in N Engl J Med 1997; 336: 309-315

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