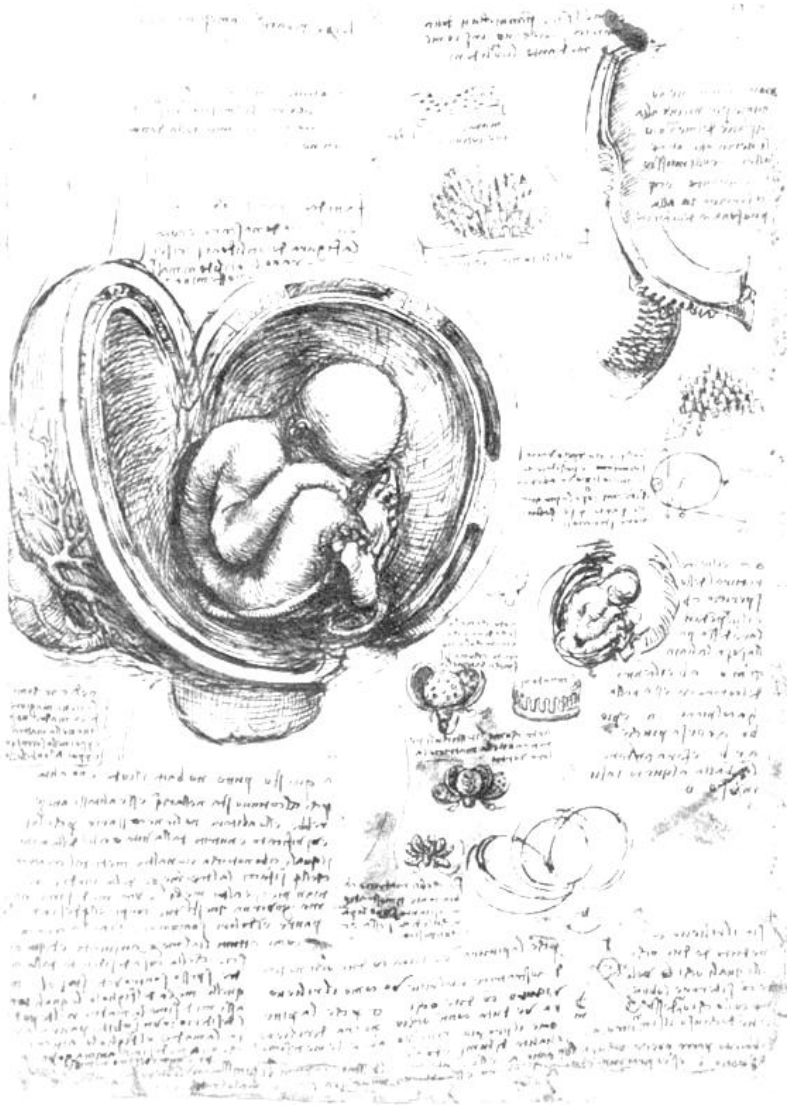
Volume XIX, Nr. 3, 2013, Timişoara, Romania
ISSN 2065-376X

MEDICINE IN EVOLUTION



CENTER OF PROMOTING HEALTH EDUCATION AND MOTIVATION FOR PREVENTION IN DENTISTRY
CENTER FOR CONTINUOUS MEDICAL EDUCATION

medicineinevolution.umft.ro

Journal edited with the support of

ROLF MARUHN
GERMAN CONSUL TO TIMISOARA

&

Printed at: WALDPRESS, Timisoara,
17 Brandusei Street,
Phone/Fax: 0040256422247

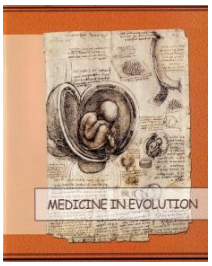
Edited at: EUROSTAMPA, Timisoara
26, Revolutiei 1989 Street,
Phone: 0040256204816

EDITORIAL BOARD

CONTENTS

ARTICLES

THE ENERGETIC COST FOR TRANSTIBIAL ARTERIOPATIC AMPUTEES DURING UPHILL WALKING



AIORDACHIOAE GIGI ADRIAN[1], HARAGUS HORIA[2], VERMESAN DINU[2], STOIA IONUT[3], POP ALEXANDRU[1]

[1]West University "Vasile Goldis" Arad
[2]University of Medicine and Pharmacy "Victor Babes" Timisoara
[3]Polytechnic University Timisoara

ABSTRACT

Because locomotion independence is essential for improving life quality, we have decided to determine the metabolic cost and cardiovascular stress in different arteriopatic patients and other types of amputees.

Our study included 18 patients with unilateral transtibial amputation. Gait analysis has been made on an ultrasound space determination apparatus that allows for the creation of a kinematic 3D model manufactured by Zebris, on a platform with adjustable speeds and slopes. The physiologic cost index was calculated to estimate the energetic necessities during gait.

Results show a clear functional and metabolic deficit in vascular amputees. They have a slower confortable pace and a decreased physiologic cost index.

In conclusion, vascular transtibial amputees can use prosthetics to ambulate but the possibilites are restrained because of the weakened metabolic resources.

Key words: *energetic cost, transtibial amputees, peripherial arteriopathy*

Correspondence to:

Horia G Haragus
MD, PhD
Address: I-st Clinic of Orthopedics and Trauma, Emergency Clinical County Hospital, Timisoara, Romania
Phone: +4 0747025064
E-mail address: gigi_aiordachioaie@yahoo.com, horia.haragus@yahoo.com, vermesan@gmail.com
www.ortopedietimisoara.ro

INTRODUCTION

Peripheral arteriopathy is a major health issue in elder patients. They often have associated disease such as diabetes, cardiac, pulmonary and cerebrovascular affections. Their survival after amputation while having atherosclerosis is decreased. A study showed that after 1 year only 72% of the patients are alive, and that after 3 years the percentage decreases at 53%. The contralateral amputation risk is 10% every year. After 1 year, 81% of the remaining living patients were ambulating alone and 73% were living at home. We can clearly notice that a big number of vascular patients can re-gain ambulation and independency after amputation [Dawson].

Elder patients have more health problems and thus, lower gait scores. Not all associated disease influence ambulation, but the presence of chronic obstructive pulmonary disease and arterial peripheric disease influences the functional scores from before amputation. Cardiopathy and diabetes decrease functional scores after amputation. Usually, elder patients with multiple comorbidities have lower functional scores after amputation, but the ethiogeny of the amputation does not affect ambulation directly [Johnson].

The ability to use the prosthesis is of great importance for ambulatory independence. Preoperatory predictive factors regarding bad toleration towards the usage of the prosthetic leg are a proximal above-the-knee anatomic level, an age over 60 yo, a casual household lifestyle, dementia, renal insufficience and and ischemic cardiopathy. Patients with limited ambulation preoperatively, dementia, renal insufficience, coronaric disease and an age higher than 70 yo will have very little benefits from the prosthesis and will most likely not become independent after the transtibial amputation. A strong suggestion is towards treating these patients the same way you treat non ambulating patients and realizing a prophilactic transfemoral amputation. At the opposite pole there is the young, active patient with a below-the-knee amputation which will reach an ambulation level comparable with the revascularized patients [Taylor].

Because the ambulatory independence is essential for improving life quality, we wanted to determine the metabolic cost and cardiovasculary stress compared between arteriopathic patients and amputations of other etiologies.

MATERIAL AND METHOD

Our study included patients operated in many hospitals in Arad and Timisoara. Totally we evaluated 18 cases of unilateral transtibial amputation. Gait analysis determinations were made with a spatial determination 3D kinematic profile apparatus, built by Zebris, on a platform with adjustable speed and slope. Cardiac frequency was determined while standing, at a confortable walking speed (1,6m/s) and at a maximum walking speed on a 15% slope (fig. 1 and 2).

Ten (10) patients had a peripheric arteriopathy etiology, while eight (8) were posttraumatic amputations. The arteriopathic patients have had the following therapeutical indications: acute ischemia (4), gangrene (3), distal amputation re-intervention and critical ischemia (3). Posttraumatic amputees have had a radical treatment evaluated as a first intention therapy in 5 cases, and other 3 patients following a failed reconstructive treatment. Out of the posttraumatic amputees, 2 had existent lower limb affections (one ipsilateral

fracture and a contralateral diaphyseal femoral fracture) which were considered cured without sequelae during gait analysis.

Six patients have had type II diabetes for at least 8 years (SD=5.5); all of the patients have been smokers for an average time of 17.5 years (SD=7.5); five have had dislipedmic disorders; one has etanolic cyrosis; one has a coronarian stent; all have high blood pressure and two have had transient ischemic strokes. Four have had intermittent claudication for an average time of 5.3 years (SD=3.7) before amputation and two have peripheric neuropathy without ulceration. Five have had failed attempts of emergency re-vascularization. Five were at the right foot and all of the patients considered the right foot as the dominant one.

Table 1. Comparing the homogeneity of the two groups

	Age	BMI	M/F	R/L	Duration	Simple/Passive
Vascular disorder group	65.86 / 8.108	29.75 / 4.48	4	1,5	3.50 / 1.26	4
Control group	52.57 / 13.52	30.91 / 3.56	3	1,67	11.37 / 19.71	0.6

BMI – body mass index; M/F – male/female; R/L – right/left; Duration – duration of amputation in years; Prosthesis – passive: with a joint that stocks passive energy (through a spring system) and simple: with a mobile joint; M – mean value; SD – standard deviation.

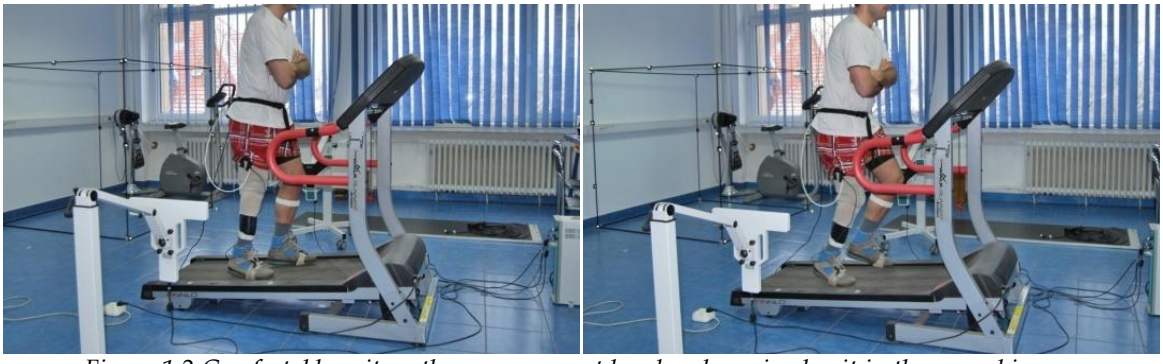


Figure 1,2 Comfortable gait on the measurement band and maximal gait in the second image

The comparison was made between the two groups, arteriopathic and posttraumatic amputees. This allowed for a "cross-sectional" type determination between two groups of patients from a rehabilitation and lump stabilization point of view. All of the patients were at a minimum duration of 2 years after amputation while the determination and gait analisys were conducted. This allowed to exclude immediate postoperative factors aswell as immediate postoperative rehabilitation. The included patients are thus valuable for theyr age groups, etiology, anatomic level, in comparison with the potential functional rehabilitation.

The evaluation comparative studies were many and covered a wide array of functional evaluation: gait anomalies surrounding the hip, the knee and the ankle, gait simmetry, straight walking and slope walking with or without shoes and a ground reaction force analisys. The statistic comparison was made using the T test.

The physiologic cost index (PCI) was introduced to estimate the energy cost during gait. The method is based upon the liniary relation between the oxygen volume and heart rate (HR) and requires only the recording of the HR at rest and during comfortable speed gait. This is why it is so sutiable for standard measurments. PCI

describes the number of extra heart beats needed for every meter the patient walks. It is calculated using the following method: mean HR during effort – mean HR at rest / walking speed [m/min].

The mean PCI values for healthy adults have been raported to exist between 0.23 and 0.42. The PCI values have been determined for other types of patients with locomotion disabilites, but they remain less studied in literature for amputees.

RESULTS

Results show a clear predominance of a metabolic and functional deficit in vascular amputees. They have a slower confortable and maximal speed, a smaller stride and a high PCI (table 2).

Table 2. Vascular amputees parametres vs. control parametres with the spatial method

Gait parameters	Vascular SD	Control SD	p
Confortable speed [m/s]	0.51±0.23	0.82±0.19	0.0074
Cadence [st/min]	33.2±4.01	38.5±5.03	0.0241
PCI	0.68±0.19	0.50±0.14	0.0402
Speed [m/s]	1,2	1,2	-
Cadence [st/min]	48.37±5.74	42.36±3.92	0.0227
PCI	0.89±0.21	0.57±0.15	0.0023
Maximum speed [m/s]	1.27±0.61	1.94±0.42	0.0179
Cadence [st/min]	60.6±4.39	57.10±3.44	0.0838
PCI	1.03±0.23	0.61±0.15	0.0004

DISCUSSIONS AND CONCLUSIONS

Patients with transtibial amputations usually have a 16% higher HR and oxygen intake than standar subjects, at a 11% lower confortable speed. There is no correlation between the weight of the prosthesis and gait efficiency, but the stump's length is indirectly proportional with the oxygen intake [Gailey].

PCI is recommended to be used as a measurement tool of the spent energy. Ijzerman et al. showed that for a confidence interval of 95%, a minimum PCI difference of 69% and a 32% difference in HR are needed. Substracting the rest HR from the PCI calculation method increases the intraindividual variability. This is why, the spent energy, calculated on the consumed oxygen is a more precise method, but which requires extra equipments [Ijzerman 2002].

Another possibility to functionally determine and measure the mobility is the 6 minute walking test. The total walking distance is significantly greater in active patients. The results match moderately with standing up from a chair, postural balance while standing and walking speed. The corelation with the autoevaluation functional scores is very low and even lower regarding the general health perception but is very easy to apply [Harada].

A solution for lowering the high metabolic costs in arteriopatic amputees could be represented by using active, bionic limbs. Unfortunately, this alternative is not

fesable at the moment. Ankle-foot prostethics can be grouped in 3 categories: simple, with passive loading and stocked energy return and active (bionic). Even with the advanced technology, the prosthetics that passively stock and release kinetic energy do not drastically reduce the energy cost.

A comparison of spent oxygen and walking patterns between transfemoral amputees that used bionic or conventional prosthetics showed that there was no difference in walking, and the efficiency of bionic prosthetics was obvious only at low walking speeds [Datta]. For transtibial amputees, the outcome of the comparison was the same. For the transfemoral ones, though, prosthetic component alignment can affect the metabolic process. All of these data can be taken out from walking parametres during sagital analysis [Schmalz].

A comparison regarding energy consume between moder prosthetic segments with passive loading and the traditional SACH model showed that the first ones did not lower the oxygen spent. The spent oxygen per walked metre is the same at both vascular and traumatic amputees but the latter ones use energy effciently, can travel at higher speed and have a better physical condition [Torburn].

Small differences in walk efficiency were noticed by other authors between the prosthetics with passive energy stock and normal ones, in posttraumatic amputees, at every speed interval and when walking on slope. For vascular patients though, these small gaps dissapear, thus, a modern prosthetic cannot be recommended with the purpose of lower metabolic costs. These patients surpass 70% of maximal frequency at a slow pace and slope walking. Thus the metabolic limits are the main mobility restrictive factors that this population has [Casillas].

In connclusion, vascular transtibial amputees have a higher degree of gait abnormality compared to the posttraumatic or tumoral ones and they use theyr metabolic resoursces significantly more inefficient, while walking at a lower comfortable and maximal speed. Although they can use the prosthetics succesfully in order to become independent, their possibilities are very low due to the weakend metabolic resources.

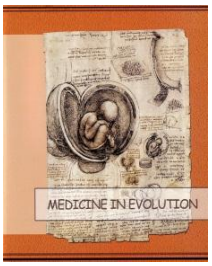
The author has gained financing through the Structural Funds POSDRU/CPP107/DMI 1.5/S/77082 "Burse doctorale de pregătire ecoeconomică şi bioeconomică complexă pentru siguranţa şi securitatea alimentelor şi furajelor din ecosisteme antropice".

REFERENCES

1. Dawson I, Keller B, Brand R, Pesch-Batenburg J, van Bockel J. Late outcomes of limb loss after failed infrainguinal bypass. J Vasc Surg 1995;21:613-22.
2. Johnson V, Kondziela S, Gottschalk F. Pre and post-amputation mobility of trans-tibial amputees: correlation to medical problems, age and mortality. Prosthet Orthot Int 1995;19:159-64.
3. Taylor, S. M., Kalbaugh, C. A., Blackhurst, D. W., et al. Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: an analysis of 553 consecutive patients. J Vasc Surg 2005 42(2): 227-35.
4. Ijzerman MJ, Nene AV. Feasibility of the physiological cost index as an outcome measure for the assessment of energy expenditure during walking. Arch Phys Med Rehabil. 2002 Dec;83(12):1777-82.
5. Schmalz T, Blumentritt S, Jarasch R. Energy expenditure and biomechanical characteristics of lower limb amputee gait: the influence of prosthetic alignment and different prosthetic

components. Gait Posture. 2002 Dec;16(3):255-63.
6. Torburn L, Powers CM, Guiterrez R, Perry J. Energy expenditure during ambulation in dysvascular and traumatic below-knee amputees: a comparison of five prosthetic feet. J Rehabil Res Dev. 1995;32(2):111–19.
7. Casillas JM, Dulieu V, Cohen M, Marcer I, Didier JP. Bioenergetic comparison of a new energy-storing foot and SACH foot in traumatic below-knee vascular amputations. Arch Phys Med Rehabil. 1995 Jan;76(1):39-44.
8. Datta D, Heller B, Howitt J. A comparative evaluation of oxygen consumption and gait pattern in amputees using Intelligent Prostheses and conventionally damped knee swing-phase control. Clin Rehabil. 2005 Jun;19(4):398-403.
9. Gailey RS, Wenger MA, Raya M, Kirk N, Erbs K, Spyropoulos P, Nash MS. Energy expenditure of trans-tibial amputees during ambulation at self-selected pace. Prosthet Orthot Int. 1994 Aug;18(2):84-91.
10. Harada ND, Chiu V, Stewart AL. Mobility-related function in older adults: assessment with a 6-minute walk test. Arch Phys Med Rehabil. 1999 Jul;80(7):837-41.

ANGIOID STREAKS COMPLICATED WITH CHOROIDAL NEOVASCULARIZATION – A CASE REPORT



ALEXANDRA DIANA VRAPCIU[1], LILIANA MARY VOINEA[2]

[1] MD, PhD stud., Assistant, Division of Anatomy, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] MD. PhD., Professor, Division of Ophtalmology, Department 12, Faculty of Medicine, „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Angioid streaks are ruptures in the Bruch's membrane. It is reported here the case of a patient (female, 54 years old) with angioid streaks and choroidal neovascularization which were treated by intravitreal injection of Bevacizumab. Fundus examination showed bilateral angioid streaks, multiple areas of "peau d'orange", small extrafoveal lesion in the right eye and large macular scar in the left eye. The best corrected visual acuity in the right eye was 20/40. Fluoresceine angiography showed subfoveal leakage with occult choroidal neovascularization in the right eye. Baseline Optical Coherence Tomography (OCT) found a choroidal neovascular membrane and a thin streak of subfoveal fluid with retinal thickness of 295 microns at the lesion (with central retinal thickness of 220 microns). Intravitreal Bevacizumab (Avastin) was injected in the right eye, under aseptic conditions. Post – injection, the best corrected visual acuity in this eye was improved to 20/30 and the retinal thickness reduced to 240 microns at one month (central retinal thickness - 166 microns). Although the diagnosis of angioid streaks is usually made on the basis of ophthalmoscopic examination, intravenous fluorescein angiography and OCT can help to report the presence of angioid streaks when the ophthalmoscopic appearance is uncertain or subtle.

Key words: *Bruch's membrane, fluoresceine angiography, Optical Coherence Tomography, choroidal neovascularization*

Correspondence to:

Alexandra Vrapciu
Address: I"Carol Davila" University of Medicine and Pharmacy, 8 Eroilor Sanitari Blvd., RO-76241, Bucharest, Romania
Phone: + 40723303926
E-mail address: vrapciualexandra@yahoo.com
www.ortopedietimisoara.ro

INTRODUCTION

Angioid streaks (AS) were first described by Robert W. Doyne, in 1889, as "irregular, jagged lines, nearly all deeply pigmented" throughout the choroid, and were presumed as resulted from the rupture of the pigment layer of the retina (Doyne, 1889). In 1917 Kofler reported that angioid streaks are changes at the level of Bruch's membrane (Kofler, 1917).

Angioid streaks are crack-like ruptures in the elastic layer of Bruch's membrane (Finger et al., 2008), localized between the retinal pigmented epithelium and the choroid, associated with atrophic changes in the overlying retinal pigmented epithelium (Georgalas et al., 2009) and the break of the choriocapillaris layer beneath AS (Federman et al., 1975). An abnormal fragility of the lamina basalis (Kanski, 2003) caused by degenerative process of elastic fibers (Georgalas et al., 2009) and calcium deposition in Bruch's membrane (Clarkson and Altman, 1982) were reported. AS are associated to various systemic diseases, such as Pseudoxanthoma elasticum, Ehler - Danlos syndrome type 6, Paget disease and sickle -cell hemoglobinophaties (Al-Rashaed and Arevalo, 2012; Bertrand et al., 1970; Clarkson and Altman, 1982; Maalej et al., 2012).

Angioid streaks are linear lesions with irregularly serrated edges lying beneath normal retinal blood vessels; they intercommunicate in a ring-like pattern around the optic disc and then radiate outwards from the parapapillary area. AS are bilateral and progressive (Yanoff and Duker, 2004). AS may associate: (i) a "peau d'orange" aspect of retin, which may antedate the appearance of the streaks (Kanski, 2003) and is most commonly found in patients suffering from Pseudoxanthoma elasticum (Yanoff and Duker, 2004), (ii) focal peripheral chorioretinal scars ("salmon spots"), (iii) optic nerve drusen and (iv) optic atrophy in patients with Paget disease (Eretto et al., 1984; Giuffre, 1986, 1987, 1988; Kamoun et al., 2006; Miller and Singerman, 2006; Munteanu and Chercota, 2007).

Most patients with angioid streaks may remain asymptomatic till development of complications and the diagnosis is made during a routine ophthalmoscopic examination of the eye (Kanski, 2003; Yanoff and Duker, 2004).

CASE REPORT

A 54 year old woman with history of angioid streaks and ocular Toxoplasmosis presented to our department for sudden and painless decreased vision in her right eye.

In the ophthalmologic exploration, the best corrected visual acuity (BCVA) in the right eye (RE) was 20/40 and counting fingers at 1meter in the left eye (LE). Intraocular pressure (IOP) and anterior pole biomicroscopy (BMC) did not reveal significant alterations.

Fundus examination (fig.1A) showed bilateral angioid streaks, multiple areas of "peau d'orange", small extrafoveal lesion in the right eye and large macular scar (fig.1B) in the left eye.

Fluoresceine angiography (FA) showed subfoveal leakage with occult CNV in the right eye (fig.1C).

Baseline Optical Coherence Tomography found a choroidal neovascular membrane and a thin streak of subfoveal fluid with retinal thickness of 295 microns at the lesion (with central retinal thickness of 220 microns)

After informed consent, 1.25 mg/0.05 ml intravitreal bevacizumab

(Avastin) was injected in the right eye, under aseptic conditions.

Post – injection, the best corrected visual acuity (BCVA) in the right eye was improved to 20/30 and the retinal thickness reduced to 240 microns at one month (central retinal thickness - 166 microns) (fig.1D).

No injection – related complications or drug related side effects were observed.

DISCUSSION

The short term results suggested that intravitreal injection of bevacizumab for the treatment of CNV in patients with AS is well tolerated and highly effective, as it was previously described (Apte, 2008; Bhatnagar et al., 2007; De Benedetto et al., 2012; Donati et al., 2009; Pedersen et al., 2007; Rinaldi et al., 2007; Sachdev et al., 2007; Salehipour et al., 2010).

Additional follow-up and large lots of patients are mandatory, to evaluate the long – term efficiency of bevacizumab.

The prognosis of AS should be approached with caution, because visual impairment occurs in over 70% of patients (Clarkson and Altman, 1982). Causes of the visual impairment are: exudative maculopathy, as a result of a subfoveal choroidal neovascular membrane (CNVM) (Lim et al., 1993; Shaikh et al., 2003), with subsequent serous and hemorrhagic detachment of the overlying neurosensory retina, foveal involvement by a streak, choroidal hemorrhage which may occur on trivial ocular trauma and result in a subfoveal hemorrhage and subsequent scarring. Because of the ocular fragility, those patients should be advised to avoid contact sports and ocular trauma.

The most frequent and serious complication is the formation of CNVM (Al-Rashaed and Arevalo, 2012; Sachdev et al., 2007; Wu et al., 2007). Patients who develop CNVM are symptomatic and their main symptoms are metamorphopsias and reduction of vision.

CONCLUSIONS

Although the diagnosis of angioid streaks is usually made on the basis of ophthalmoscopic examination, intravenous fluorescein angiography can help to report the presence of angioid streaks when the ophthalmoscopic appearance is uncertain or subtle. This investigation is also useful to confirm the presence of CNVM. On the Optical Coherence Tomography (OCT), the streaks appear like fractures at the level of Bruch's membrane (fig.2). OCT may reveal a possible CNVM and measure the central retinal thickness.

Acknowledgements

This study was supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/82839 (author #1)..

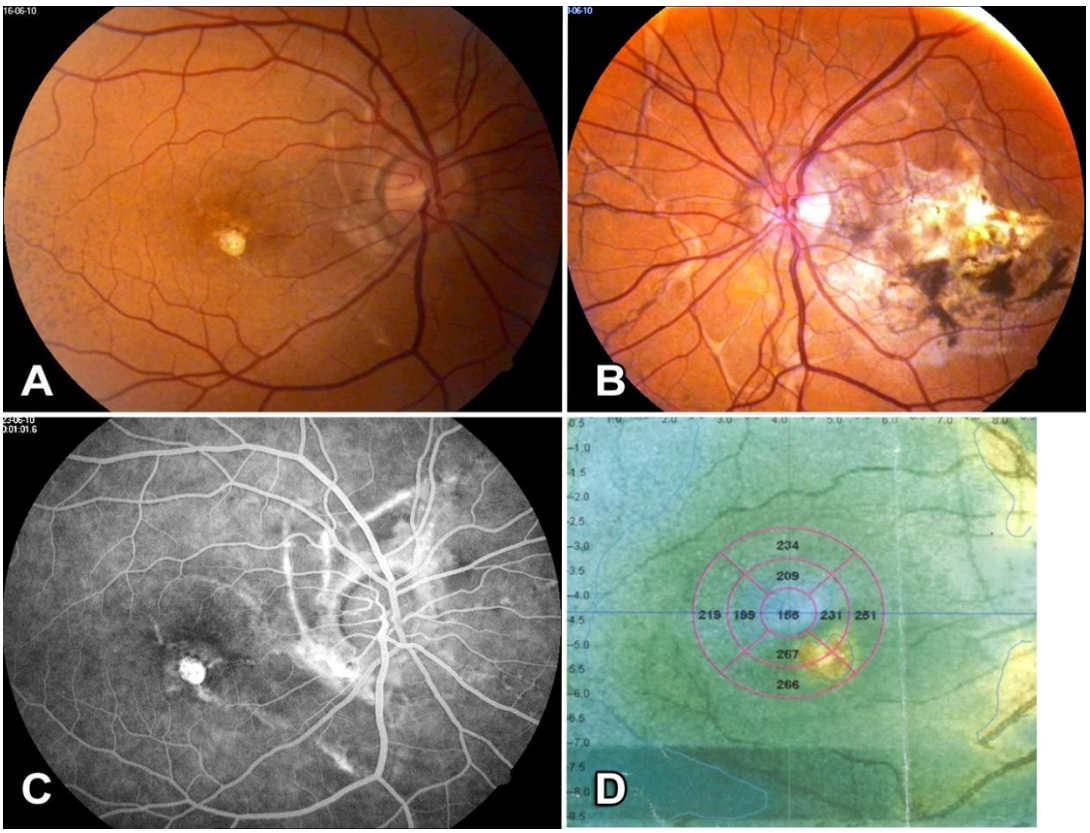


Fig. 1. A. Angioid streaks and small extrafoveal lesion in the right eye (color fundus micrograph). B. Large discoid scar in the left eye (color fundus micrograph). C. Fluorescein angiography, right eye. Subfoveal leakage with occult choroidal neovascularization. D. Optical Coherence Tomography, after Bevacizumab intravitreal injection (right eye).

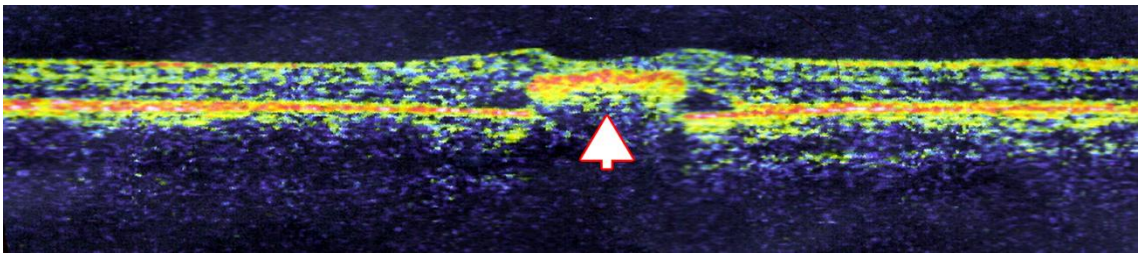


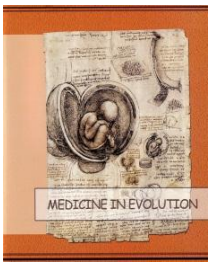
Fig. 2. OCT: the angioid streak (arrowhead) appears like a fracture of the Bruch's membrane.

REFERENCES

1. Al-Rashaed, S, Arevalo, JF. Long-term follow-up of choroidal neovascularization secondary to angioid streaks: case series and literature review. Clin Ophthalmol. 2012;6(1029-1034.
2. Apte, RS. Intravitreal bevacizumab for treatment of choroidal neovascularization secondary to angioid streaks. Eye (Lond). 2008;22(5):734-735.
3. Bertrand, JJ, Hart, ML, Voisin, J. [Angioid streaks and sickle cell anemia]. Bull Soc Ophtalmol Fr. 1970;70(12):1184-1190.
4. Bhatnagar, P, Freund, KB, Spaide, RF, Klancnik, JM, Jr., Cooney, MJ, Ho, I, Fine, HF, Yannuzzi, LA. Intravitreal bevacizumab for the management of choroidal neovascularization in pseudoxanthoma elasticum. Retina. 2007;27(7):897-902.
5. Clarkson, JG, Altman, RD. Angioid streaks. Surv Ophthalmol. 1982;26(5):235-246.
6. De Benedetto, U, Battaglia Parodi, M, Knutsson, KA, Librando, A, Bandello, F, Lanzetta, P, Iacono, P. Intravitreal bevacizumab for extrafoveal choroidal neovascularization after ocular trauma. J Ocul Pharmacol Ther. 2012;28(5):550-552.
7. Donati, MC, Virgili, G, Bini, A, Giansanti, F, Rapizzi, E, Giacomelli, G,

Menchini, U. Intravitreal bevacizumab (Avastin) for choroidal neovascularization in angioid streaks: a case series. Ophthalmologica. 2009;223(1):24-27.
8. Doyne, RW. Choroidal and retinal changes that result from blows on the eye. Trans Ophtalmol Soc UK. 1889;9(128.
9. Eretto, P, Krohel, GB, Shihab, ZM, Wallach, S, Hay, P. Optic neuropathy in Paget's disease. Am J Ophthalmol. 1984;97(4):505-510.
10. Federman, JL, Shields, JA, Tomer, TL. Angioid streaks. II. Fluorescein angiographic features. Arch Ophthalmol. 1975;93(10):951-962.
11. Finger, RP, Charbel Issa, P, Ladewig, M, Holz, FG, Scholl, HP. Intravitreal bevacizumab for choroidal neovascularisation associated with pseudoxanthoma elasticum. Br J Ophthalmol. 2008;92(4):483-487.
12. Georgalas, I, Papaconstantinou, D, Koutsandrea, C, Kalantzis, G, Karagiannis, D, Georgopoulos, G, Ladas, I. Angioid streaks, clinical course, complications, and current therapeutic management. Ther Clin Risk Manag. 2009;5(1):81-89.
13. Giuffre, G. [Angioid streaks and associated lesions: ophthalmoscopic and fluorescein angiographic interpretation]. J Fr Ophtalmol. 1986;9(12):811-824.
14. Giuffre, G. The pathogenesis of the fundus peau d'orange and salmon spots. Metab Pediatr Syst Ophthalmol. 1987;10(4):95-98.
15. Giuffre, G. The pathogenesis of the fundus peau d'orange and salmon spots. Metab Pediatr Syst Ophthalmol. 1988;11(3):141.
16. Kamoun, B, Khlif, H, Mseddi, M, Sayadi, I, Turki, H, Zahaf, A, Feki, J. [Ocular manifestations of pseudoxanthoma elasticum]. Presse Med. 2006;35(5 Pt 1):779-783.
17. Kanski, JJ, 2003. Clinical ophthalmology – a systematic approach. , 5th ed. Butterworth Heinemann, Boston.
18. Kofler, A. Beitraege zur Kennntnis der angioid Streaks (Knapp). Arch Augenheilkd. 1917;82(134-139.
19. Lim, JI, Bressler, NM, Marsh, MJ, Bressler, SB. Laser treatment of choroidal neovascularization in patients with angioid streaks. Am J Ophthalmol. 1993;116(4):414-423.
20. Maalej, A, Ouederni, M, Khallouli, A, Gabsi, S. [Angioid streaks complicated by choroidal neovascularization secondary to pseudoxanthoma elasticum: Diagnosis and treatment. Case report]. J Fr Ophtalmol. 2012;35(10):803-808.
21. Miller, DG, Singerman, LJ. Vision loss in younger patients: a review of choroidal neovascularization. Optom Vis Sci. 2006;83(5):316-325.
22. Munteanu, M, Chercota, V. [Optic nerve drusen and angioid streaks in pseudoxanthoma elasticum]. Oftalmologia. 2007;51(1):99-102.
23. Pedersen, R, Soliman, W, Lund-Andersen, H, Larsen, M. Treatment of choroidal neovascularization using intravitreal bevacizumab. Acta Ophthalmol Scand. 2007;85(5):526-533.
24. Rinaldi, M, Dell'Omo, R, Romano, MR, Chiosi, F, Cipollone, U, Costagliola, C. Intravitreal bevacizumab for choroidal neovascularization secondary to angioid streaks. Arch Ophthalmol. 2007;125(10):1422-1423.
25. Sachdev, N, Vishwanathan, K, Gupta, V, Singh, R, Gupta, A. Intravitreal bevacizumab (Avastin) in choroidal neovascular membrane in angioid streaks. Indian J Ophthalmol. 2007;55(6):457-458.
26. Salehipour, M, Vafi, N, Doozande, A, Yaseri, M. Intravitreal bevacizumab for choroidal neovascularization secondary to non-age-related macular degeneration. J Ophthalmic Vis Res. 2010;5(1):10-19.
27. Shaikh, S, Ruby, AJ, Williams, GA. Photodynamic therapy using verteporfin for choroidal neovascularization in angioid streaks. Am J Ophthalmol. 2003;135(1):1-6.
28. Wu, RA, Best, RM, Musch, DC, Johnson, MW. Surgical removal of subfoveal choroidal neovascular membranes in older patients without age-related macular degeneration. Clin Ophthalmol. 2007;1(2):157-165.
29. Yanoff, M, Duker, JS, 2004. Ophthalmology Mosby, St.Louis.

PSYCHOLOGICAL AND CLINICAL APPROACH OF HEMOPHILIC PATIENTS



HOGEA LAVINIA MARIA[1], HOGEA GHEORGHE BOGDAN[2,3], CRISTIAN OANCEA[4], ILIE ADRIAN COSMIN[2]

[1]Neurosciences Department, University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania
[2]Department of Anathomy and Embryology, University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania
[3]2nd Clinic of Orthopaedics & Traumatology Timișoara, Romania
[4]Department of Pneumology, University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania

ABSTRACT

Background. Along with the medical problems, hemophilic patients are facing a lot of psychological problems. Many of the psychological problems that the patients are dealing with are coming from pain and the impact over their physical condition.

Purpose of Study. This study aims to assess the quality of life in psychological terms of hemophilic patients. The data obtained can be useful to psycho medical staff that are working in this area and are contributing to targeting specific psychotherapeutic intervention or counseling.

Methods. The study was conducted on a sample of 200 subjects, divided into two equal groups. The control group consists of 100 individuals without hemophilia (50%) and the clinical group consists of 100 persons with hemophilia (50%), aged between 16 and 45. Data on patients were collected using the instrument to measure quality of life WHOQOL-100 and the case report forms that include data from clinical and laboratory examinations performed in each patient on admission and during hospitalization.

Results. Comparing the scores of the two groups showed differences in the psychological field against hemophiliacs, so we conclude that the hypothesis was confirmed. So can observe statistically significant differences ($p < .001$) between the two groups, chronic disease with negative consequences on the psyche of the patient. All these changes occurring in the patient's psyche affecting quality of life.

Conclusions. As you can see from these study, the medical treatement isn't enough for the improvement of life, different psyho-social problems need also dealing with reality. A multidisciplinary team is needed for helping patients in dealing with reality. This team is made up of different MD's, psichologyst and social service employees.

Key words: *hemophilic, quality of life, psyho-social problems.*

Correspondence to:

Dr. Hogea Lavinia Maria
Address: Stejarul nr. 14
Phone: 0745042035
E-mail address: laviniahogea@yahoo.com

INTRODUCTION

The modern point of view is that, health has a few dimensions very important: physical, mental, social, and each contributes to the welfare of a person's condition. To maintain good health, one needs to examine each of these dimensions and focus in the sense that it is allowed not only to live a long time, but also to enjoy as much health as possible.

The presence of hemophilia in a patient's life, compels him to face life with his body changes imposed by this disease. This life changing event can be devastating both in a physical and psychological aspectand the patient is load with a series of losses custom to this pathology: loss of independence; life style changes, uncertainty about the future, feeling of helplessness, anxiety, separation from friends, physical health changes, changes in body image. Intense and constant pain are causing to the hemophilic patient an increase in mental tension, personality introversion, bleeding injuries being more frequent and intense.

PURPOSE OF STUDY

This study aims to assess the quality of life in psychological terms of hemophilic patients. The data obtained can be useful to psycho medical staff that are working in this area and are contributing to targeting specific psychotherapeutic intervention or counseling.

MATERIAL AND METHODS

The study was conducted on a sample of 200 subjects, divided into two equal groups. The control group consists of 100 individuals without hemophilia (50%) and the clinical group consists of 100 persons with hemophilia (50%), aged between 16 and 45, that are in evidence and Clinical Assessment Treatment and Rehabilitation Center "Cristian Serban" of Buziaş.

Among the subjects surveyed, a number of 71 subjects are diagnosed with hemophilia A (35.5%) and 29 subjects are diagnosed with hemophilia B (14.5%). After the form severity there are 83 subjects diagnosed with severe hemophilia (41.5%), 13 subjects diagnosed with hemophilia average (6.5%) and 4 diagnosed with mild haemophilia (2%). In terms of age, 123 participants between 16-25 years (61.5%), 49 were aged 26-35 years (24.5%), and 28 are between 36-45 years (14%).

Data on patients were collected using the instrument to measure quality of life WHOQOL-100 and the case report forms that include data from clinical and laboratory examinations performed in each patient on admission and during hospitalization.

The WHOQOL-100 questionnaire assess individual perception on patient quality of life in the cultural and value system in which the patient lives, the expectations, concerns and objectives of each one.

The questionnaire produces a profile of quality of life, that is composed of scores of the 24 facets which are also forming six domains of quality of life (physical, psychological, level of independence, social relationships, environment, spirituality), with the overall quality of life.

RESULTS

In order to test the hypothesis that is assumed that there are significant statistical differences, regarding the quality of life from a psychological point of view ANOVA 2 X 3 factor was conducted to investigate differences between groups and interaction effect. To validate this hypothesis we relye on the following quantitative arguments for the psychological quality of life.

In Table 1 we presented averages and standard deviations for the psychological quality of life of hemophiliacs and nonhemofilici and also in age groups. At the psychological dimension of quality of life total scores ranged from 9,20 to 15,50 (M=12,26; AS= 1,31).

Table 1. 3X2 Factorial ANOVA summary table on the psychological quality of life

Source dispersion	SS	Df	MS	*F*	*P*
Lot	27,642	1	27,642	17,713**	.000**
Age	6,975	2	3,487	2,235	.110
Lot X Age	2,638	2	1,319	0,845	.431
Error	302,737	194	1,560		
Total	30428,600	200			

Note: ** p< .001; * p< .05

To test the homogeneity of variance we used the Levene test. The result is not statistically significant, which indicates that the variances are homogeneous, F (5,194) = 1,457, p>.05.

Of the three F ratios, presented in tabel , only one is statistically significant F "lot" F (1, 194)= 17,713, p < .001 (M= 11,87 versus M= 12,65). This means that there are significant differences between hemophiliacs and nonhemofilici. Hemophiliacs have a lower level of the psychological quality of life compared with nonhemofilics, because the main effect for the groups (hemophiliacs versus nonhemofilici) is presented as statistically significant.

The age variable on the variable psychological quality of life is not statistically significant F (2, 194)= 2,235, p > .05. This means that no significant differences were found between the three age groups in hemophilic subjects (M = 11.81 in the group 16-25 years, M = 12.17 in the group 26-35 years, M = 11.65 in the group 36-45 years) compared with nonhemofilic (M = 12.49 per group 16-25 years, M = 13.02 per group 26-35 years and the group M = 13.13 36-45 years).

Also, the effect of group interaction, age and the psychological quality of life is not statistically significant, F (2, 194)= 0,845, p> .05, and no interaction graph analysis do not point to an interaction of the variables under study (see Fig. 1).

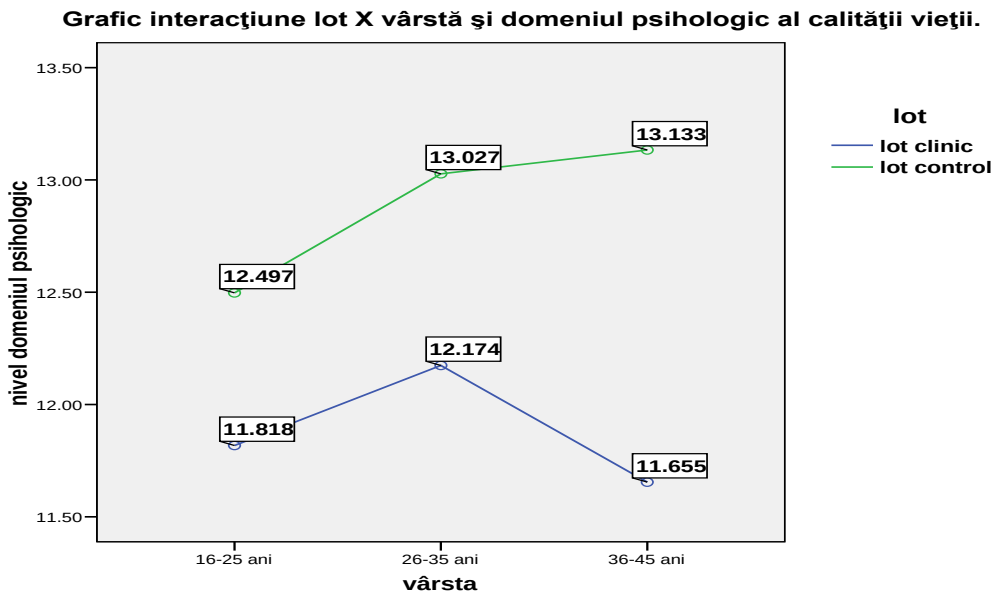


Fig. 1. Graph age X group interaction and the psychological quality of life

Although in recent years many advances have been made in the treatment of hemophilia, there are many issues still remaing unresolved, including disabling sequelae and complications of disease the risk of spontaneous bleeding, social integration, lack of preventive treatment, fear of infection through blood products, frequent hospitalizations are reflected in the psychological status of patients.

Psychological domain of the questionnaire measuring the quality of life WHOQOL-100, includes the following scale: positive feelings, thinking, learning, memory and concentration, self esteem, body image and negative feelings. Positive feelings scale explores the degree to which a person lives positive feelings (optimism, joy, contentment) to life events. Some questions of the facets are related to feelings of the future, and many people associate this facet to the quality of life.

There are studies on patients with haemophilia, using other methods of investigation, which revealed a good adaptation to the disease. (M. Canclini, 2003)

Thinking, learning, memory and concentration are investigating the ability to make decisions and opinion about how learning ways, speed and clarity of thought, memory and concentration. One can speak here of difficulties in recognizing their problems, the inability to be aware of problems in this area.

Education is an important factor on the health determinism. Educational level has the same degree of morbidity and mortality such income, both for children and adults. (R. Wilkinson, 1997) It was found that a trained person using health information and services more effectively than untrained individuals.

Self-esteem refers to feelings about themselves. Self-esteem reflects how the person is considered effective and self-satisfied. Items are aimed at education, the ability to acquire new skills, interaction with people, self acceptance, family relationships, ability to work. As noted self-esteem is closely related to other scales of psychological field, including investigating the negative feelings. (D. Watson, 2002)

Low self-esteem and appearance of a feeling of incompleteness, may be due to lack of social relationships and reduced participation in sports and recreation.

Body image and appearance is how positive or negative perceives his body, the extent of perceived bodily

changes. Body image is influenced by the attitude of others towards a person's appearance.

Body image can be modified as a consequences of haemophilia (decreased joint mobility, increase the joints, abnormal gait) on the body with negative effects on the quality of life.

Physical or functional limitations can distort body image wich forms with the onset of puberty, which may be due to shyness and embarrassment, feelings of inferiority and loss of self as teem. (Beeton et al., 2007)

The negative feelings scale concerns sadness, despair, anxiety and nervousness. Questions investigating psychological changes such as depression, mania, panic attacks, without assessing their severity.

The increased incidence of complications related to disease and treatment chronicity of disease, poor social integration and lack of social relations are consequences of various psychological disturbances in haemophiliac patients.

A study of 83 children and adolescents with hemophilia A and B, aged between 5 and 19 years, using the DSM-IV Structured interviews have noted a prevalence of major depressive disorder, a disorder of separation, anxiety disorder and suicidal behavior in children and adolescents with hemophilia. (Ghanizadeh A., 2009)

Permanent disability that a hemophiliac is subjected or a dragged organisms involves a mentally impairement with serious repercussions on the individual personality. The suffering that the patient is subjected to makes him lose his normal aggression, childhood feature, inventive spirit and his rich imagination. Shows a lack of self confidence, a diminuation of spontaneity, shyness, refuses contact with one s company, tend to separate from other children and privacy within their own family.

CONCLUSIONS AND DISCUSSIONS

Comparing the scores of the two groups showed differences in the psychological field against hemophiliacs, so we conclude that the hypothesis was confirmed. So can observe statistically significant differences ($p < .001$) between the two groups, chronic disease with negative consequences on the psyche of the patient. All these changes occurring in the patient's psyche affecting quality of life.

Hemophilia and other chronic diseases affect each person beyond physical problems. In order to optimize efforts to facilitate patients' health, it is important that with medical treatment to be offered and psychosocial care, as part of a multidisciplinary approach. Although this is not always possible due to limited financial resources, but health professionals should be aware of any problems that may occur in hemophilic patients. (Barlow et al., 2007, Beeton et al., 2007, Bossard et al., 2008; Bottle et al., 2007, Cassis, 2007; Ross, 2004).

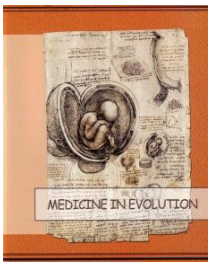
Strategies to cope with physical, mental, emotional and social education should include individual, family counseling, resources, support from the community, support from other hemophiliacs, accessibility to prophylactic treatment produced clotting factor replacement, access to physiotherapy and corrective surgery. (Bottle et al., 2007)

Psychosocial professionals can help patients learn to visualize hemophilia, their condition, more easily and be better prepared to handle this situation. They need to identify their feelings about physical changes and learn to take responsibility for themselves and for health. (Cassis, 2007).

REFERENCES

1. Barlow J.H., Stapley J., Ellard D.R., Gilchrist M. Information and self management needs of people living with bleeding disorders: a survey. Haemophilia 2007, 13 (3), 264-70.
2. Beeton K., Neal D. & Lee C. An exploration of health-related quality of life in adults with haemophilia – a qualitative perspective. Haemophilia 2005, 11, 123-132.
3. Beeton K., Neal D., Watson T. and Lee C. Parents of children with Haemophilia – a transforming experience. Haemophilia 2007, 13, 570-579.
4. Bossard D., Carrillon Y., Stieltjes N., Larbre J.P., Laurian Y., Molina V., Dirat G. Management of haemophilic arthropathy. Haemophilia 2008, 14 Suppl 4, 11-9.
5. Bottos A.M., E. Zanon, M.T. Sartori & A. Girolami. Psychological aspects and coping styles of parents with Haemophilic child undergoing a programme of counselling and psychological support. Haemophilia 2007, 13, 305-310.
6. Bullinger M., MD, PhD, Von Mackensen S., MD, and the Haemo-QoL Group. Quality of life in children and families with bleeding disorders. J. Pediatr Hematol Oncol. 2003, Volume 25, Suppl 1.
7. Bullinger M & Von Mackensen S. Quality of life assessment in haemophilia. Haemophilia 2004, 10 Suppl 1, 9-16.
8. Canclini M, Saviolo-negrin n, zanon e, et al. Psychological aspects and coping in haemophilic patients: a case-control study. Haemophilia 2003, 9(5):619-624.
9. Cassis R.M.Y. Psychosocial care for people with haemophilia. Treatment of Hemophilia, 2007, No: 44.
10. Ghanizadeh, A. & Baligh-Jahromi, P. Depression, anxiety and suicidal behaviour in children and adolescents with haemophilia. Haemophilia 2009, 15, 528-532.
11. Gregory M., Boddington P., Dimond R., Atkinson P., Clarke A. & Collins P.. Communicating about haemophilia within the family: the importance of context and of experience. Haemophilia 2007, 13, 189-198.
12. Gringeri A. & Von Mackensen S. Quality of life in haemophilia. Haemophilia 2008, 14 Suppl 3, 19-25.
13. Ioniță H., Poenaru D.V., Ritli L. O viață cu hemofilie. Editura Brumar, Timişoara, 2009.
14. Murphy B., Australian WHOQOL-100, WHOQOL-BREF and CA- WHOQOL Instruments. User's Manual and Interpretation Guide 2000, 1-4.
15. Poenaru D.V., Şerban M., Branea I.L. Artropatiile hemofilice. Editura Academiei Române, Bucureşti, 2005.
16. Ross, J. Perspectives of haemophilia carriers. Treatment of Hemophilia, 2004, No: 8.
17. Watson D, Suls J, Haig J. Global self-esteem in relation to structural models of personality and affectivity. J Pers Soc Psychol 2002, 83(1):185-197.
18. Wilkinson R.G. Socioeconomic determinants of health: Health inqualities: relative or absolute material standards? BMJ 1997; 314:591.

RELATIONSHIP BETWEEN PULSE WAVE VELOCITY AND BLOOD PRESSURE VALUES IN PATIENTS WITH CARDIOVASCULAR RISK FACTORS



IOANA SUCEAVA[1], DANIEL LIGHEZAN[2], CORINA SERBAN[3], ANCA TUDOR[4], SIMONA DRAGAN[5]

[1]Department of Internal Medicine, University of Medicine and Pharmacy "Victor Babes" Timisoara
[2]Department of Medical Semiology, University of Medicine and Pharmacy "Victor Babes" Timisoara
[3]Department of Physiopathology, University of Medicine and Pharmacy "Victor Babes" Timisoara
[4]Department of Informatics and Medical Biostatistics, University of Medicine and Pharmacy "Victor Babes" Timisoara
[5]Department of Cardiovascular Recuperation, University of Medicine and Pharmacy "Victor Babes" Timisoara

ABSTRACT

Introduction: Cardiovascular risk factors (blood pressure, atherogenic dyslipidemia, obesity) increase the likelihood of an adverse event by having a detrimental effect on the blood vessel wall. Novel imaging techniques for determination of arterial stiffness are necessary for the early assessment and management of patients with cardiovascular risk factors.

Aim: The purpose of this study is to determinate if BP influences the values on PVW in patients with cardiovascular risk factors.

Method: The study included 223 patients with cardiovascular risk factors that were divided considering the presence of coronary artery disease (CAD): 140 patients with angiographically confirmed CAD, 83 patients without CAD. The patients were compared with a control group of 74 healthy age subjects (CON). In all patients, pulse wave velocity was determined non-invasively using the Arteriograph (Tensiomed Ltd., Budapest, Hungary).

Results: The patients with CAD had significant increased values of PWV compared with patients without CAD and CON subjects (12.5±0.7 vs 10.9±0.6 vs 8.5±0.07 m/s, all p<0.001). A significant correlation between PWV and SBP (r= 0.549, p<0.001) and between PWV and DBP was found in all subjects (r= 0.540, p<0.001).

Conclusion: The study showed that blood pressure is correlated with pulse wave velocity, a classic measure of arterial stiffness in patients with cardiovascular risk factors. Arterial stiffness indicated by increased PWV may be strongly associated with endothelial dysfunction in patients with cardiovascular risk factors.

Key words: *coronary artery disease, pulse wave velocity, blood pressure, endothelial dysfunction, cardiovascular risk factors*

Correspondence to:

Corina Serban
"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
Phone: +40744142983
E-mail adress: dr.corinaserban@yahoo.com

INTRODUCTION

Arterial stiffness and endothelial dysfunction represent two interlinked pathophysiological processes. Nitric oxide is continuously released and has been shown to contribute to arterial compliance (1). Various noninvasive measures of subclinical atherosclerosis and increased arterial stiffness, such as carotid intima-media thickness (IMT), pulse wave velocity (PWV), and coronary artery calcification have been developed and commonly used (2). Noninvasive assessment of arterial stiffness has been proposed for individual cardiovascular risk evaluation and early detection of vascular damage associated with atherosclerosis (3). PWV has a potential application for screening vascular damage in large population (4).

Elastic artery stiffening, an age-related process, can be accelerated in the presence of hypertension. Hypertension may produce arterial stiffening by both functional and structural mechanisms (5). Arterial stiffness and intensity of wave reflections have evolved as major determinants of systolic blood pressure, pulse pressure, and left ventricular afterload, major players in the pathogenesis of isolated systolic hypertension and hypertrophy of the left ventricle (6).

The purpose of this study is to determinate if BP influences the values on PVW in patients with CV risk factors.

MATERIAL AND METHOD

The study included 223 patients with cardiovascular risk factors that were divided considering the presence of CAD: 140 patients were with angiographically confirmed CAD, 83 patients were without CAD and a control lot of 74 healthy age subjects. In all subjects, a full medical history was taken and a complete physical examination was performed. We recorded age, sex, smoking habits, hypertension, hypercholesterolemia, and diabetes mellitus as cardiovascular risk factors. Smokers were defined as those who were smoking at the time of enrollment or those who had stopped for <12 months.

Blood pressure (BP) was measured on the right arm using a sphygmomanometer (Riester, Germany) after 10 minutes of rest while seated, and the mean of two recordings at least 3 min apart was recorded. Hypertension was diagnosed according to ESC/ESH 2013 guidelines (7).

A fasting blood glucose concentration ≥126 mg/dl or administration of antihyperglycemic medications was defined as diabetes.

Fasting blood samples for laboratory measurements were also obtained early in the morning after overnight fasting. The parameters of lipid profile were determined enzymatically by using a COBAS integra 400 plus analyzer. LDL-C was calculated according to Friedewald's equation, valid if TG < 400 mg/dL (8).

The glomerular filtration rate was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (9).

The study protocol was approved by the local ethics committee. The study was conducted according to the Declaration of Helsinki, and the written informed consent was obtained from each subject.

Assessment of arterial stiffness

Measurement of arterial stiffness indices was done early in the morning 1 day before coronary angiography

with patients fasted and before the administration of the medications. The assessment of arterial stiffness was noninvasively performed with the Arteriograph (Tensiomed Ltd., Budapest, Hungary) by an operator who was blinded to the results of coronary angiography and other findings. All measurements were taken in the supine position in a quiet, temperature-controlled room (approximately 22 oC) after a brief period of rest in the morning before the catheterization.

Statistical analysis

Database and processing were performed using statistical software

SPSS Statistical Software Package, version 15.0 (SPSS Inc, Chicago, Illinois,

USA). Continuous data are presented as mean ± SD.

RESULTS

The clinical characteristics of the study subjects are listed in Table I. Most of the patients were women (52.2%), were smokers (62%), had hypertension (62%), had atherogenic dyslipidemia (59 %) and 40% had type 2 diabetes.

Table I. Baseline characteristics of the patients and PVW values

Parameters	Patients with CAD (n=140)	Patients without CAD (n=83)	CON (n=74)	*p*
Age	60.5±10.8	56.63±8.9	55.8±5.2	<0.001
Sex F/M (%)	51.4/48.6	51.8/48.2	54.1/45.9	0.93
AHC+ (%)	42.9	67.5	44.6	0.001
Smokers (%)	37.1	47	35.1	0.23
Systolic blood pressure (SBP) (mmHg)	154.9±20.9	157.8 ± 13.5	123.7± 6.3	<0.001
Diastolic blood pressure (DBP) (mmHg)	91.1±12.3	93.67±7.4	72.6±5.3	<0.001
Fasting glycemia (mg/dL)	117.1±44	98.7±12.1	90.9±8.7	<0.001
TC (mg/dL)	262±39.5	268.1±35.8	181.27±13.044	<0.001
TG (mg/dL)	168.3±79.2	147.3±49.6	111.9±27.8	<0.001
LDL-C (mg/dL)	145±26	126.3±23.8	115.6±18.5	<0.001
HDL - C (mg/dL)	35.9±4.3	40.5±7.5	46.7±6.4	<0.001
Serum creatinine (mg/dL)	0.9±0.3	0.8±0.1	0.7±0.08	<0.001
Blood urea nitrogen (mg/dl)	37±11.4	38.3±6.9	30.1±7	0.001
Uric acid levels (mg/dl)	6.3±1.8	5.7±1.7	4.7±1.1	<0.001
Pulse wave velocity (m/s)	12.5±0.7	10.9±0.6	8.5±0.07	<0.001

* Data are shown as mean ± SD

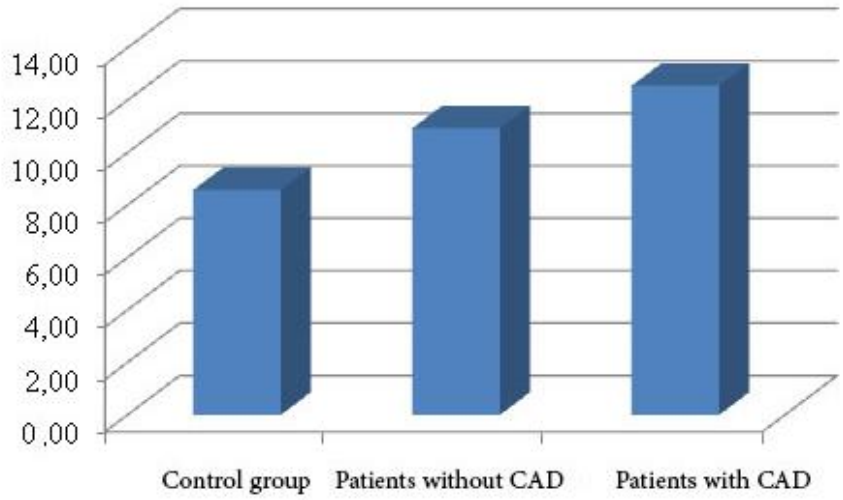


Figure 1. PVW values in three studied groups

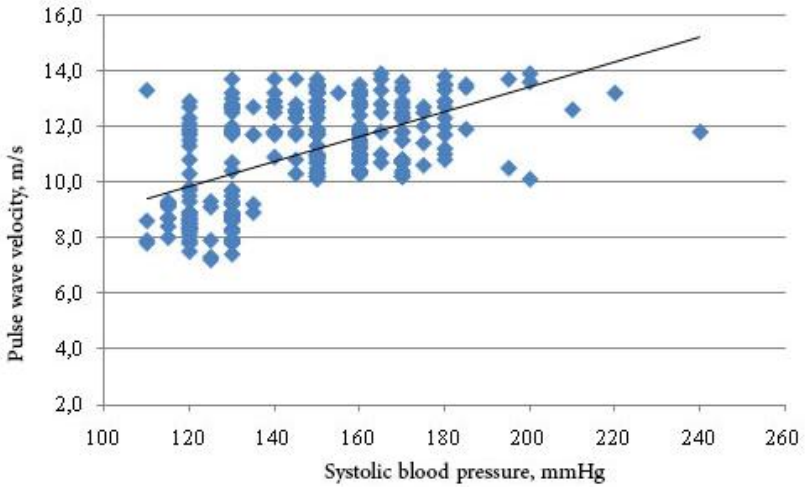


Figure 2. Correlation between PVW and systolic blood pressure (r=0.549, p<0.001)

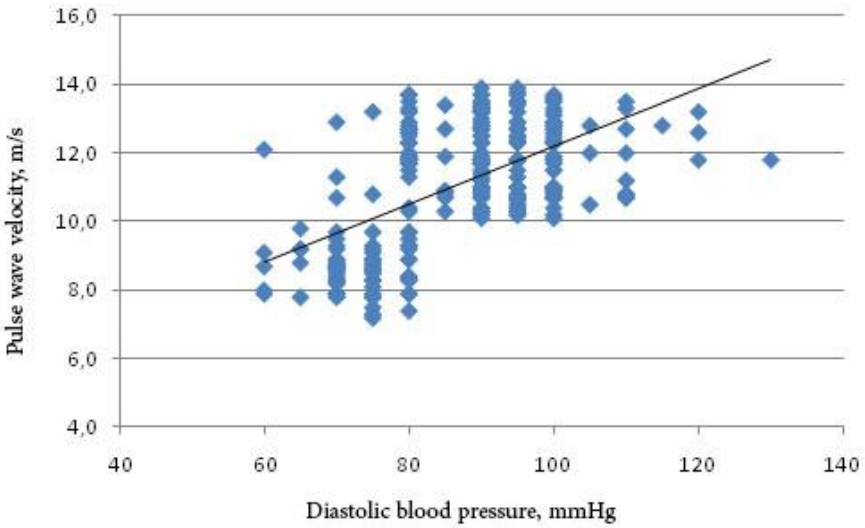


Figure 3. Correlation between PVW and diastolic blood pressure (r=0.583, p<0.001)

We obtained statistically significant differences when we compared the mean values of PWV between patients from the CAD group with patients from the group without CAD (p <0.001) and between the patients from the group without CAD and CON group (p <0.001).

It was obtained a significant direct correlation between systolic

blood pressure and pulse wave velocity in all studied groups (r=0.549, p<0.001) (Figure 2). A significant direct correlation was observed between diastolic blood pressure and pulse wave velocity in all studied groups (r=0.549, p<0.001) (Figure 3).

DISCUSSIONS

Our study showed a relationship between the values of blood pressures and arterial stiffness in patients with or without CAD, but with different CV risk factors, such as atherogenic dyslipidemia, smoking, diabetes mellitus. Our results were similar with other studies that proved a casual relationship between blood pressure and arterial stiffness (10-12).

In a recent study, a higher PWV was a predictive marker for CV events, especially ischemic stroke (13). Another study assessed the association between arterial stiffness, as determined by PWV and the extent of angiographically proved CAD in patients who visited the outpatient clinic for angina without any previous history of heart disease. PWV was an independent predictor of significant CAD, but was neither associated significantly with the extent of CAD nor with the risk of revascularization (14).

A relationship between blood pressure and arterial stiffness is difficult to ascertain because blood pressure is a major covariate in the various measurements of stiffness (15). Short-term blood pressure variability predicts cardiovascular complications in hypertension, but its association with large-artery stiffness is confounded by methodological issues related to the assessment of BP variations over 24 hour (16). Although there have been many non-invasive studies to show the relation between arterial stiffness and BP, the results are still controversial.

Competing interests

The authors declare that they have no competing interests.

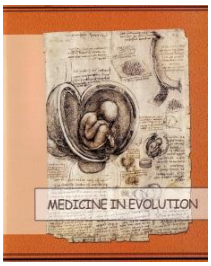
CONCLUSIONS

The study showed that blood pressure is correlated with pulse wave velocity, a classic measure of arterial stiffness in patients with cardiovascular risk factors. Arterial stiffness indicated by increased PWV may be strongly associated with endothelial dysfunction in patients with cardiovascular risk factors.

REFERENCES

1. Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, et al. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. Hypertension. 2001;38(5):1049-53. Epub 2001/11/17.
2. Rajzer MW, Wojciechowska W, Klocek M, Palka I, Brzozowska-Kiszka M, Kawecka-Jaszcz K. Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph. Journal of hypertension. 2008;26(10):2001-7. Epub 2008/09/23.
3. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2010;56(25):e50-103. Epub 2010/12/15.
4. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Validity, reproducibility, and clinical

significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertension research : official journal of the Japanese Society of Hypertension. 2002;25(3):359-64. Epub 2002/07/24.
5. Franklin SS. Arterial stiffness and hypertension: a two-way street? Hypertension. 2005;45(3):349-51. Epub 2005/02/16.
6. London GM, Pannier B. Arterial functions: how to interpret the complex physiology. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(12):3815-23. Epub 2010/10/16.
7. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Journal of hypertension. 2013;31(7):1281-357. Epub 2013/07/03.
8. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical chemistry. 1972;18(6):499-502. Epub 1972/06/01.
9. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(4):622-7. Epub 2010/03/27.
10. Asmar R, Darne B, el Assaad M, Topouchian J. Assessment of outcomes other than systolic and diastolic blood pressure: pulse pressure, arterial stiffness and heart rate. Blood pressure monitoring. 2001;6(6):329-33. Epub 2002/06/11.
11. Nar G, Soylu K, Akcay M, Gulel O, Yuksel S, Meric M, et al. Evaluation of the Relationship Between Arterial Blood Pressure, Aortic Stiffness and Serum Endothelin-1 Levels in Patients with Essential Hypertension. Clin Exp Hypertens. 2013. Epub 2013/03/28.
12. Masugata H, Senda S, Inukai M, Himoto T, Hosomi N, Imachi H, et al. Relationship between arterial stiffness and variability in systolic blood pressure during a single clinic visit in patients with hypertension. The Journal of international medical research. 2013;41(2):325-33. Epub 2013/04/10.
13. Han JY, Choi DH, Choi SW, Kim BB, Ki YJ, Chung JW, et al. Predictive value of brachial-ankle pulse wave velocity for cardiovascular events. The American journal of the medical sciences. 2013;346(2):92-7. Epub 2012/10/23.
14. Chae MJ, Jung IH, Jang DH, Lee SY, Hyun JY, Jung JH, et al. The Brachial Ankle Pulse Wave Velocity is Associated with the Presence of Significant Coronary Artery Disease but Not the Extent. Korean circulation journal. 2013;43(4):239-45. Epub 2013/05/18.
15. Anderson TJ. Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk. The Canadian journal of cardiology. 2006;22 Suppl B:72B-80B. Epub 2006/02/25.
16. Tarnoki AD, Tarnoki DL, Stazi MA, Medda E, Cotichini R, Nistico L, et al. Heritability of central blood pressure and arterial stiffness: a twin study. Journal of hypertension. 2012;30(8):1564-71. Epub 2012/06/13.



CAN ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS TREATMENT LEAD TO THE CESSATION AND REGRESSION OF THE DIABETIC RETINOPATHY?

NICULESCU N.[1], BORUGA O.[1], ZOLOG I.[1], D. BRIE[2]

[1] Ophthalmology Clinic Timişoara
[2]Institute of Cardiovascular Diseases Timişoara

ABSTRACT

Introduction . The aim of our trial was to determine on a small group of patients with diabetes mellitus type 2 and hypertension if intensive treatment to hypertension plays a role in the progression of diabetic retinopathy. A second aim was to determine whether the treatment with angiotensin-converting enzyme inhibitors - (perindopril) is superior to the treatment with calcium channel blocker (amlodipine) in preventing progression of diabetic retinopathy in patients with diabetes mellitus type 2 and hypertension.

Material and method. 231 patients with diabetes mellitus type 2 who underwent a complete eye examination at the Timisoara Clinic of Ophthalmology have been included in our trial. The ophthalmologic examination revealed that 109 patients had a degree of diabetic retinopathy (prevalence rate of ~ 47%). Of the 109 patients, 87 have been diagnosed with proliferative diabetic retinopathy (prevalence rate of 37.5%) and 22 patients with proliferative retinopathy (prevalence rate of 9.5%). Among patients with nonproliferative diabetic retinopathy (87 pts) 41 pts (18%) have a mild form, 32 pts (13.5%) a moderate form and 14 pts (6%) have a severe form. Of the 41 pts with mild non-proliferative diabetic retinopathy and 32 patients with moderate form, 40% (30 pts) have been diagnosed with hypertension. Of the 30 hypertensive patients 10 pts have a mild form and 20 have a moderate form. They have been divided into two groups A and B between which there are not significant clinical differences, each group with 15 pts (5 with mild non-proliferative diabetic retinopathy and 10 with a moderate form). All the patients included in the trial underwent a complete eye examination which has been conducted by two doctors in our clinic. Patients in group A have been treated with perindopril 5 mg / day initially, up to 10 mg / day for the BP control and patients in group B have been treated with amlodipine 5 mg / day initially, up to 10 mg / day. If needed, for the control of blood pressure, the antihypertensives have been allowed in both groups, initially diuretic, and beta blockers. The mean follow-up was of 28 ± 12 months.

Results. Blood pressure control has been achieved in 75% of cases in both groups there were no significant differences between the two groups. At first in group A the following values of systolic BP have been registered = 160 ± 12 mmHg and diastolic BP = 95 ± 4 mmHg, and in group B systolic BP = 158 ± 10 mmHg and diastolic BP = 96 ± 5 mmHg. After the follow-up period the values in group A have been systolic BP = 125 ± 9 mmHg and diastolic BP = 85 ± 5 mmHg and in group B systolic BP= 124 ± 10 mmHg, diastolic BP= 84 ± 6 mmHg, with no significant differences between the two groups (p = NS). There have been no differences between the two groups on the discontinuation of medication. During follow-up, the diabetic retinopathy rate of progression with at least one classification ETDRS scale was 23% in group A (treated with perindopril) and 24% in group B (treated with amlodipine). The diabetic retinopathy rate of progression with at least two ETDRS scales classification was 18% in group A and 17% in group B. The diabetic retinopathy rate of progression with at least three classification ETDRS scales was 7% in group A and 8% in group B. Thus, there were not statistically significant record progression of diabetic retinopathy in patients with diabetes mellitus type 2 with hypertension treated with perindopril or amlodipine. (p = NS)

Conclusions. Our trial did not reveal the reduction in the progression of diabetic retinopathy in hypertensive patients with type 2 diabetes, treated with perindopril compared to those treated with amlodipine in a follow-up period of 2 years and a half. The beneficial effects of reducing the progression and even regression of retinopathy are due to blood pressure control, and not the effect of blocking the renin angiotensin system.

Key words: *hypertension, diabetic retinopathy, angiotensin-converting enzyme inhibitors treatment, progression, regression, blood pressure control*

Correspondence to:

Nicoleta Niculescu
Address: str Fagaras nr 12, Timisoara
E-mail address: nico28niv@yahoo.com

INTRODUCTION

Many trials in recent years have launched the hypothesis that high blood pressure can lead to retinal capillary endothelial lesions in people with diabetes by increasing the blood volume. This hypothesis has been supported by observational clinical trials that have revealed an association between the high blood pressure and the presence and severity of retinopathy in people with diabetes.

While data from the observational trials suggested that hypertension is associated with diabetic retinopathy, data from the longitudinal trials have been inconsistent. The UKPDS trial showed that the incidence of diabetic retinopathy is associated with systolic blood pressure. Diabetic retinopathy does not occur in the absence of diabetes, it is the result of prolonged exposure to the toxicity caused by high levels of blood glucose. Diabetic retinopathy is a microvascular abnormality in which the capillary endothelial cell dysfunction is due to prolonged exposure to high levels of blood glucose as well as to other factors. One of them is the high blood pressure.

An important question that has not yet found the answer would be: "Some classes of drugs such as angiotensin-converting enzyme (ACE) inhibitors are effective in preventing the occurrence and progression of diabetic retinopathy compared with other classes of antihypertensive agents in patients with hypertensive diabetic?".

There is urgent need of additional medication to prevent the development and progression of diabetic retinopathy, and some clinical trials have suggested that angiotensin-converting enzyme (ACE) inhibitors (angiotensin receptor blockers) could be this medication. It is unclear whether this effect is due to the properties of angiotensin system inhibitors or to low blood pressure.

Aim

The aim of our trial was to determine on a small group of patients with diabetes mellitus type 2 and hypertension if intensive treatment to hypertension plays a role in the progression of diabetic retinopathy. A second aim was to determine whether the treatment with ACE inhibitors (perindopril) is superior to the treatment with calcium channel blocker (amlodipine) in preventing progression of diabetic retinopathy in patients with diabetes mellitus type 2 and hypertension..

MATERIAL AND METHOD

231 patients with diabetes mellitus type 2 who underwent a complete eye examination at the Timisoara Clinic of Ophthalmology have been included in pur trial. The ophthalmologic examination revealed that 109 patients had a degree of diabetic retinopathy (prevalence rate of ~ 47%). Of the 109 patients, 87 have been diagnosed with proliferative diabetic retinopathy (prevalence rate of 37.5%) and 22 patients with proliferative retinopathy (prevalence rate of 9.5%). Among patients with nonproliferative diabetic retinopathy (87 pts) 41 pts (18%) have a mild form, 32 pts (13.5%) a moderate form and 14 pts (6%) have a severe form. Of the 41 pts with mild non-proliferative diabetic retinopathy and 32 patients with moderate form, 40% (30 pts) have been diagnosed with hypertension. Of the 30 hypertensive patients 10 pts have a mild form and 20 have a moderate form. They have been divided into two groups A and B between which there

are not significant clinical differences, each group with 15 pts (5 with mild non-proliferative diabetic retinopathy and 10 with a moderate form). The clinical characteristics are shown in Table 1.

Table 1. Characteristics of the patients in group A and group B

Characteristics	Group A 15 pts	Group B 15 pts	P value
Age (years)	50±8 y	49±9 y	P=NS
Sex (Male/Female)	10/5	11/4	P=NS
IMC (kg/m ^{2})	26.5±5	27.3±6	P=NS
Diabetis lenght	7±3	6.8±3	P =NS
HbA $_{1c}$ (%)	7.2±1.3	7.1±1.7	P=NS
Creatinine (mg/dl)	0.9±0.2	0.9±0.23	P=NS
Total cholesterol (mg/dl)	178±43	175±42	P=NS
Mild non-proliferative diabetic retinopathy	5 pts	5 pts	P=NS
Moderate non-proliferative diabetic retinopathy	10 pts	10 pts	P=NS
Smokers	7 pts	8 pts	P=NS
Systolic blood pressure	160 ±12 mmHg	158 ±10 mmHg	P=NS
Diasystolic blood pressure	95±4 mmHg	96±5mm Hg	P=NS

All the 30 patients have been diagnosed with diabetes mellitus type 2 according to the criterion "World Health Organization" in 1985. All the enrolled patients had hypertension at the time of enrollement (BP s> 140 mmHg and / or BP d> 90 mmHg) and have not been administrated antihypertensive medication. Patients with known allergy to ACE inhibitors and calcium channel blockers type dihydropyridine have been excluded. Patients with a history of coronary heart disease have also been excluded (stable angina, unstable angina, acute myocardial infarction), cerebrovascular disease (transient ischemic attack, ischemic or hemorrhagic attack), hypertensive heart (left ventricular hypertrophy documented by echocardiography) chronic kidney disease, heart failure (clinical signs or treatment, LVEF <45%), chronic obliterative arterial disease. All the patients included in the trial underwent a complete eye examination which has been conducted by two doctors in our clinic.

Ophthalmologic examination included examination of the anterior pole, lens opacities, intraocular pressure measurement and photographing the retina after dilation. In order to photograph the retina we have used an optic system for digital imaging Canon CR6-45nm and a Canon EOS 10D digital camera (Canon, Tokyo, Japan). Were carried out two sets of photos for each eye, which are subject to examination by two different ophthalmologists. After dilation of the pupil a picture focused on the macula and one focused on the optic nerve have been carried out.

The retinopathy has been staged with the help of "The Modified Airlie House Classification of Diabetic Retinopathy." Examinations have been made initially and then every 6 months, 1 year and 2 years. "The Early Treatment Diabetic Retinopathy Trial (ETDRS)" has been used. 103 The severity of retinopathy has been determined using the ETDRS103 severity scale, where a scale in 23 steps is used to describe the expansion of

hypertensive retinopathy. The progression with at least two scales has been considered significant.

Patients in group A have been treated with perindopril 5 mg / day initially, up to 10 mg / day for the BP control and patients in group B have been treated with amlodipine 5 mg / day initially, up to 10 mg / day. If needed, for the control of blood pressure, the antihypertensives have been allowed in both groups, initially diuretic, and beta blockers. The mean follow-up was of 28 ± 12 months. The trial has been proposed for approval by the local ethics committee. There was no conflict of interest involving a pharmaceutical company producing drugs.

The SAS Institute software has been used for statistical analysis. Results have been expressed as mean ± standard deviation. Statistically significant differences have been expressed as $p < 0.05$.

RESULTS

Blood pressure control has been achieved in 75% of cases in both groups there were no significant differences between the two groups. At first in group A the following values of systolic BP have been registered = 160 ± 12 mmHg and diastolic BP = 95 ± 4 mmHg, and in group B systolic BP = 158 ± 10 mmHg and diastolic BP = 96 ± 5 mmHg. After the follow-up period the values in group A have been systolic BP = 125 ± 9 mmHg and diastolic BP = 85 ± 5 mmHg and in group B systolic BP= 124 ± 10 mmHg, diastolic BP= 84 ± 6 mmHg, with no significant differences between the two groups (p = NS).

There have been no differences between the two groups on the discontinuation of medication. It has been noted in two patients of Group A who have developed cough, and 2 patients in group B who have developed peripheral edema.

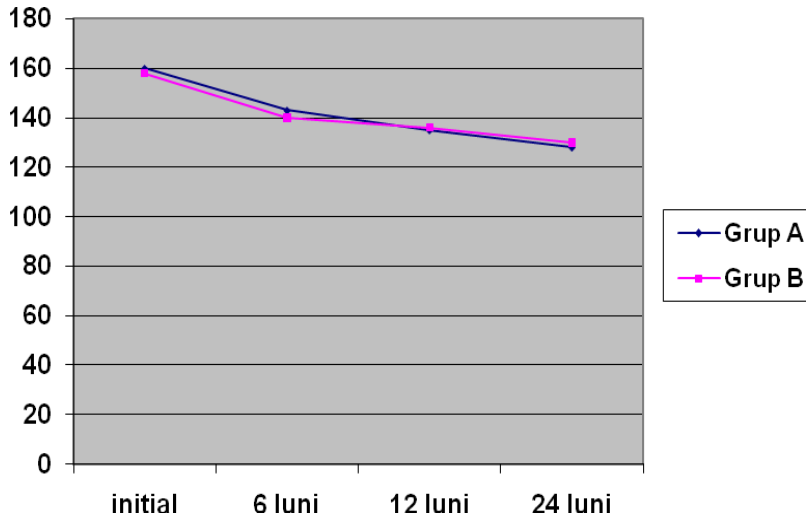


Figure 1: Systolic BP control in group A and group B

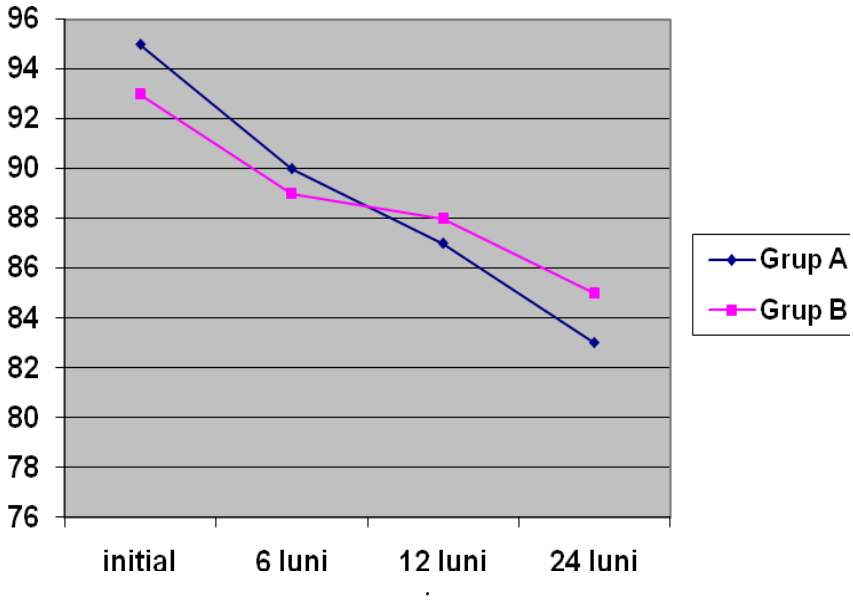


Figure 2: Systolic BP control in group A and group B

During follow-up, the diabetic retinopathy rate of progression with at least one classification ETDRS scale was 23% in group A (treated with perindopril) and 24% in group B (treated with amlodipine). The diabetic retinopathy rate of progression with at least two ETDRS scales classification was 18% in group A and 17% in group B. The diabetic retinopathy rate of progression with at least three classification ETDRS scales was 7% in group A and 8% in group B. Thus, there were not statistically significant record progression of diabetic retinopathy in patients with diabetes mellitus type 2 with hypertension treated with perindopril or amlodipine. (p = NS).

DISCUSSIONS

Both observational trials and data from clinical trials have shown that the blood pressure is an important risk factor for the development and progression of diabetic retinopathy and blood pressure decrease would reduce the incidence and progression of diabetic retinopathy.

The relationship between high blood pressure and diabetic retinopathy has been well described in an observational trial conducted in Wisconsin in patients with diabetes mellitus type 1. Increased blood pressure has been associated with an increased incidence and progression of diabetic retinopathy, the risk for developing proliferative diabetic retinopathy was 7 times higher in the hypertensive patients compared to those with normal BP. 1

A first trial was "Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID Trial Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus." This trial has investigated the effect of an inhibitor of angiotensin converting enzyme (lisinopril) on diabetic retinopathy in patients with type 1 diabetes. The trial included 530 patients aged 20 to 59 years from 15 centers in Europe who have been treated with 10 or 20 mg of lisinopril versus placebo and have been followed-up for a period of 2 years. All the patients who have been included in the trial have been normotensive and without microalbuminuria. Of the patients in the trial from the group treated with placebo the incidence of

retinopathy has been 65%, while in the group treated with lisinopril the incidence has been 59%. Results at 2 years showed no reduction in the incidence of diabetic retinopathy and a minor reduction in the progression of retinopathy (0.69 [0.30-1.59], p = 0.4) in the lisinopril-treated group compared with placebo. The real significance of this trial and its results have been weakened by differences between initial and final glycosylated hemoglobin level, which has been lower in the group treated with lisionopril.

Another trial called "The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial" was a randomized trial comparing the effect of intensive antihypertensive treatment (diastolic BP of 75 mm Hg) vs. moderate antihypertensive treatment (diastolic BP of 80-89 mmHg) on the incidence and progression of diabetes complications. Data from 470 patients with diabetes mellitus type 2 followed for a period of 5 years who have received intensive or moderate treatment using as initial medication enalapril or nisolipine following its effects on nephropathy, retinopathy and diabetic neuropathy. Additional data on the primary endpoint showed no statistically significant difference between treatment with enalapril compared to treatment with nisoldipine on the progression of diabetic retinopathy. The findings were that intensive treatment on BP in patients with diabetes mellitus reduces all the mortality causes.

A subtrial in the UK Prospective Diabetes Trial aimed to determine whether BP treatment (targeting <150 / <85 mmHg) with beta blocker (atenolol) or an inhibitor of angiotensin converting enzyme (captopril) have an advantage or a disadvantage in the treatment of micro-and macrovascular complication of type 2 diabetes. 1148 patients have been included (mean age 56 years, mean BP = 160/94 mmHg) in 20 hospitals in England, Scotland and Northern Ireland. The results of this trial showed that captopril and atenolol had a similar efficacy in reducing BP and were similarly effective in reducing the microvascular complications. In terms of diabetic retinopathy progression, the same degree of degradation was found with two points compared to the previous exploration (31% in captopril group vs. 37% in atenolol), with no statistically significant differences between the two groups.

A trial conducted in Denver, U.S.A. included 249 patients with type 1 diabetes with hypertension and diabetic retinopathy. This trial concluded that increases in diastolic blood pressure alone or in association with systolic increased BP have significantly correlated with diabetic retinopathy (p <0, 03). Also, in this trial the normal high BP has been associated with increased incidence of progression of diabetic retinopathy as well as the profession of the previous one.

A major trial published in 2008 “DIabetic REtinopathy Candesartan Trials (DIRECT)”-1 investigated the role of angiotensin receptor blocker (candesartan) in reducing the incidence and progression of diabetic retinopathy. The trial was a randomized double-blind trial vs placebo that has been conducted in 309 centers worldwide. Normotensive patients without microalbuminuria in patients with type 1 diabetes without retinopathy have been enrolled in DIRECT-Prevent 1, and those with retinopathy have been enrolled in DIRECT-Protect 1, in the first month being treated with 16mg candesartan vs. placebo, and one month later the dose of candesartan has been doubled to 32 mg. The trial enrolled 1.421 participants (aged between 18-50 years old) DIRECT-Prevent 1 and DIRECT-Protect 1 in 1905. The incidence of diabetic retinopathy was of 25% in the candesartan group and of 31% in the placebo group. The retinopathy

progression has occurred in 13% of patients receiving candesartan and in 13% in the placebo group. The hazard ratio for the retinopathy incidence (HR for candesartan vs. Placebo) was 0•82 (95% CI 0•67–1•00, p=0•0508), and for the retinopathy progression was 1•02 (0•80–1•31, p=0•85). The conclusions have been that although treatment with candesartan reduces the incidence of diabetic retinopathy, there was no effect on the progression of diabetic retinopathy.

The DIRECT-Protect 2 trial included 1905 patients (aged between 37-75 years old) with type 2 diabetes with mild to moderate diabetic retinopathy normotensive without albuminuria or hypertension who have been treated with candesartan 16 mg / day the first month and then 32 mg / day compared to placebo. The results have showed that 17% of the patients treated with Candesartan had a progression of diabetic retinopathy with at least 3 degrees at the ETDRS classification and 19% in the placebo group. The risk of progression has not been not significantly reduced in the candesartan group. However in the candesartan group, the severity of present retinopathy has been nptoced compared to the placebo group (odds 1.17, 95% CI 1.05-1.30, p = 0.003). The conclusions have been that the treatment with candesartan in patients with type 2 diabetes who have mild to moderate diabetic retinopathy can improve the degree of retinopathy.

The trial "Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes" was a double-blind multicentre randomized controlled trial vs. placebo that has been conducted in 5 centers and included 223 participants. It investigated the effect of treatment with enalapril vs. losartan vs. placebo in patients with type 1 diabetes on diabetic retinopathy and nephropathy. All the enrolled patients have been normotensive and without microalbuminuria. The findings of this trial have been that no structural and functional benefits of nephropathy after blockade of the renin angiotensin aldosterone system with ACE inhibitors (enalapril) or ARBs (losartan) in normotensive patients with type 1 diabetes without albuminuria have been noticed. In contrast to this category of patients the treatment with losartan and enalpril has been good compared to placebo in the progression of diabetic retinopathy by at least two degrees ETDRS12 classification.

The trial "Diabetic retinopathy Trial" a controlled multicenter trial, has been the first to report the effectiveness of laser photocoagulation in the treatment of proliferative diabetic retinopathy in patients with high risk for vision loss. Another trial conducted a few years later called "Early Treatment Diabetic retinopathy Trial" demonstrated the effectiveness of laser therapy in the treatment of macular edema in diabetic patients. After the results of the two trials it has been estimated that the detection and treatment of laser photocoagulation can reduce 95% of cases of vision loss due to diabetic retinopathy and macular edema. Despite both these results and the efforts to detect diabetic retinopathy, it is even today one of the leading causes of vision loss. More recent trials such as "Diabetes Control and Complication Trial" - DCCT and "United Kindom Prospective Diabetes Trial"-UKPDS demonstrated ethe effectiveness of the glycemic strict control in reducing the incidence and progression of diabetic retinopathy.

However these trials and others that have followed have shown how difficult it is in real life to get an adequate glycemic control. For these reasons attention has been given to other risk factors such as hypertension. Trials have shown that 40% of patients with type 2 diabetes are hypertensive, and the proportion increases to 60% at the age of 75 years old. Diabetic retinopathy is a microvascular complication of diabetes that does not

occur in the absence of diabetes and hyperglycemia. Is due to an endothelial dysfunction that occurs as a result of prolonged exposure to hyperglycemia. This exposure results in thinning of the capillary basement membrane, blood-retinal barrier defects and loss of pericytes. Hyperglycemia also causes disturbances in the regulation of retinal perfusion, which makes the retina susceptible in case of hypertension. Retinal hypoperfusion in hypertension in diabetic patients leads to the appearance of lesions in the retinal capillaries thus encouraging the appearance of diabetic retinopathy.

A 2011 trial conducted in the United States of America investigated the relationship between glycemic control, treatment with renin-angiotensin system blockers and the incidence and progression of diabetic retinopathy in patients with type 1 diabetes. The trial included 223 patients with type 1 diabetes with diabetic retinopathy, normotensive without microalbuminuria who received treatment with an inhibitor of angiotensin converting enzyme inhibitors (enalapril) or a angiotenine receptor blocker (losartan) compared to placebo for a period of 5 years. At the initial assessment 65.9% of the patients had diabetic retinopathy. There was no benefit of blocking the renin angiotensin system, either by enalapril or by losartan compared with placebo in patients with basal glycated hemoglobin ≤ 7.5%. On the other hand, in patients with basic glycated hemoglobin ≥ 7.5% in the group treated with a blocking renin-angiotensin system the progression of diabetic retinopathy with two or more degrees on the ETDRS scale has been found in only 27% compared to 46% for those treated with placebo ($p = 0.03$). The findings have been that the blockade of the renin angiotensin aldosterone system reduces the progression of diabetic retinopathy in patients with type 1 diabetes, normotensive without microalbuminuria and glycated hemoglobin levels ≥ 7.5%.

A 2010 trial derived from the trial the BErgamo Nephrologic Diabetes Complications Trial (BENEDICT)" investigated the effect of trandolapril an inhibitor of angiotensin converting enzyme (ACE) inhibitor on the regression of diabetic retinopathy in hypertensive patients with type 2 diabetes. The patients have been randomized to receive treatment with trandalopril, verapamil or placebo. The primary endpoint of the trial has been to assess regression of diabetic retinopathy treated with trandalopril an angiotensin converting enzyme (ACE) inhibitor compared to antihypertensive medications which does not interfere with the renin-angiotensin-aldosterone system. The effect of the treatment with trandalopril has been studied compared to placebo on the occurrence of verapamil and diabetic retinopathy in those patients who have showed no retinopathy at the initial assessment. The findings of this trial have been that the blockade of the renin angiotensin system with an ACE-inhibitor trandolapril has a benefit on the progression of diabetic retinopathy compared to a calcium blocker verapamil, benefit which is independent of reducing blood pressure or glycemic control.

Our trial did not reveal the reduction in the progression of diabetic retinopathy in hypertensive patients with type 2 diabetes, treated with perindopril compared to those treated with amlodipine in a follow-up period of 2 years and a half. The beneficial effects of reducing the progression and even regression of retinopathy are due to blood pressure control, and not the effect of blocking the renin angiotensin system.

CONCLUSIONS

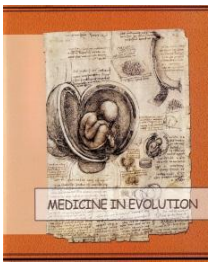
Recent and even older trials have shown that there is a positive relationship between high blood pressure and the incidence and progression of diabetic retinopathy in patients with type 2 diabetes. Our trial did not reveal the reduction in the progression of diabetic retinopathy in hypertensive patients with type 2 diabetes, treated with perindopril compared to those treated with amlodipine in a follow-up period of 2 years and a half. The beneficial effects of reducing the progression and even regression of retinopathy are due to blood pressure control, and not the effect of blocking the renin angiotensin system.

REFERENCES

1. Kohner EM. Diabetic retinopathy. Br Med Bull 1989;45:148–73
2. Davis MD. *Diabetic retinopathy, diabetic control, and blood pressure.* Transplant Proc 1986;18:1565–*8*
3. Chase HP, Garg SK, Jackson WE, et al. Blood pressure and retinopathy in type 1 diabetes. Ophthalmology 1990;97:155–*9.*
4. Gillow JT, *Gibson JM, Dodson PM. Hypertension and diabetic retinopathy – what's the story?* Br J Ophthalmol 1999;83:1083–*7.*
5. *Teuscher* A, Schnell H, Wilson PWF. Incidence of diabetic retinopathy and relationship to baseline plasma glucose and blood pressure. Diabetes Care 1988;11:246–51
6. Kostraba JN, Klein R, Dorman JS, et al. The Epidemiology of Diabetes Complications Trial. IV. Correlates of diabetic background and proliferative retinopathy. Am J Epidemiol 1991;133:381–91.
7. Klein R, Klein BEK. Vision disorders in diabetes. In: Hammon R, Harris MWH, eds. Diabetes in America, Diabetes Data Compiled 1984. Bethesda, MD: US Public Health Service, NIH Publication No 85-1468. Chapter XIII, August 1985:1–36
8. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. Diabetologia 2001;44:156–63.
9. World Health Organization: *Diabetes Mellitus: Report of a WHO Trial.* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
10. Klein R *et al.* Is blood pressure a predictor of the incidence or progression of diabetic retinopathy? *Arch*
11. *Intern Med* 1989; 149: 2427–2432.
12. UK Prospective Diabetes Trial Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998; 317: 703–713.
13. Chaturvedi N, Sjolie A-K, Stephenson JM, Abrahamian H, Keipes M, Castellarin A *et al*. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. *Lancet* 1998; 351: 28–31.
14. Estacio RO, Gifford N, Jeffers BW, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetic Care* 2000; 23(suppl.2): B54–B64
15. UK Prospective Diabetic Trial Group. Efficacy of atenolol and captopril in reducing risk of both macrovascular and microvascular complications in type 2 diabetes (UKPDS39). BMJ 1998; 317: 713-720.
16. Chase HP, Garg SK, Jackson WE, et al. (1990) Blood pressure and retinopathy in type 1 diabetes. Ophthalmology 97:155–159.
17. Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, Bilous R, Sjølie AK; DIRECT Programme Trial GroupEffect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet. 2008 Oct 18;372(9647):1394-402. doi: 10.1016/S0140-6736(08)61412-9. Epub 2008 Sep 25
18. Klein R, Klein BE, Magli YL, et al. An alternative method of grading diabetic retinopathy. Ophthalmology 1986;93:1183-118
19. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T *et al*.

Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009; 361: 40–51.
20. Diabetic Retinopathy Trial Research Group. Preliminary report on effect of photocoagulation therapy. Am J Ophtalmol 1976; 81:383-96.
21. ETDRS Research Group. Photocoagulation for diabetic macular edema. Arch Ophthalmo 1985; 103:1796-806.
22. American Diabetes Association. Diabetic retinopathy. Position Statement. Diabetes Care 1998;21:157-9.
23. The Diabetic Control and Complications Trial Resarch Group. The effect of intensive treatment of diabetes on the development and progression of long-term complication. N Engl J Med 1993; 329:977-86.
24. UK Prospective Diabetes Trial Group. Intensive blood-glucose control with sulphonylureas or insulin compared with convetional treatment and risk of complication in patients with type 2 diabetes. Lancet 1998; 352:837-53.
25. UK Prospective Diabetes Trial Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. BMJ 1998; 317:703-13.
26. Sullivan PM, Davies EG, Caldwell G. Retinal blood flow during hyperglycemia. Invest Ophthalmo Vis Sci 1990; 31:2041-5
27. Harindhanavudhi T, Mauer M, Klein R, Zinman B, Sinaiko A, Caramori ML; Renin Angiotensin System Trial (RASS) group. Benefits of Renin-Angiotensin blockade on retinopathy in type 1 diabetes vary with glycemic control. Diabetes Care. 2011 Aug;34(8):1838-42.
28. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *New England Journal of Medicine*. 2004;351(19):1941–1951.
29. Piero Ruggenenti, Ilian Iliev, Marco Filipponi et al. Effect of Trandolapril on Regression of Retinopathy in Hypertensive Patients with Type 2 Diabetes: A Prespecified Analysis of the Benedict Trial. J Ophthalmol. 2010; 2010: 106384.

PLATELET CONCENTRATES TRANSFUSION ASSOCIATED BACTERIAL INFECTION



PATRICIA URTILA[1,2], MARGIT SERBAN[2], FLORIN URTILA[1,3], SMARANDA ARGHIRESCU[1,2]

[1]University of Medicine and Pharmacy „Victor Babes" Timisoara
[2]Children's Emergency Hospital "Louis Turcanu" Timisoara
[3]City Emergency Hospital Timisoara

ABSTRACT

The presence of bacteria in cellular blood products is one of the most common microbiological causes of transfusion-associated morbidity and mortality. This potentially preventable complication is underrecognized and underreported.

Causes of transfusion-associated bacterial infection are reviewed. Despite the introduction of new methods of bacteria detection in blood components, reports about severe infections or sepsis prove the persistence of this threat. Therefore physicians should be aware about this risk and should monitor, recognize and treat the transfusion related reactions.

Key words: *platelet transfusion, bacterial infection, contamination of blood products, children*

Correspondence to:

Patricia Urtila
Address: "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania
Phone: 0753957777
E-mail address: patriciaurtila@yahoo.com

INTRODUCTION

Bacterial infection transmitted by blood products has been reported at the advent of the transfusion medicine and still continue to remain a major problem in the present. Its incidence is probably around 1 per 50,000 platelet units transfused. The connection of infection to the transfused platelets has been for a long time ignored. The underdiagnosis of platelet transfusion-associated infections is still actual. It is also due to the fact that most of the recipients are frequently immunosuppressed or leukopenic, developing an atypical expression even of severe infections [1].

THE PREVALENCE OF CONTAMINATED PLATELET CONCENTRATES

The prevalence of contaminated platelet concentrates is variable, but most of the reports concluded that 1:2,000 to 1:3,000 platelet concentrates (apheresis and random donor platelets) are bacterial contaminated. This type of contamination is greater than that of viral infections currently known to be transfusion transmitted [1]. The detection effects of human immunodeficiency virus, hepatitis B and C viruses, human T-cell lymphotrophic virus and more recently of West Nile virus and prions are extensively presented in the literature

SOURCES OF BACTERIAL CONTAMINATION

There are many sources of bacterial contamination in platelet components: blood donor it self, blood collection, processing, storage and its transportation procedures.

1.1. Blood donor

Blood donors with asymptomatic bacteremia, recovering from bacterial infections, those with ENT (ear-nose-tonsils), periodontal diseases or dental procedures can be a potential source of platelet concentrates contamination. Therefore in the majority of blood centers, the candidates for donation are subject of accurate health control, they being asked to answer questionnaires regarding their health status; those questionnaires are lacked of significant sensitivity [2].

2.2.Blood collection procedures

Most of bacteria detected and reported as the cause of transfusion-associated infection are those which belong to the normal skin flora. A sterile venipuncture is not always performed. It is known that the human skin is richly colonized, that the commensal bacteria is present in the superficial layer of epidermis, but also in the deeper layers colonizing sebaceous glands, hair follicles and sudoriferous glands; organisms present in skin fragment may be drawn into the blood component product. The bacteria most commonly contaminating platelet products is Staphylococcus epidermidis. Table 1 shows bacteria detected in infected platelet concentrates [3].

It is important that the skin be disinfected correctly; it should be performed in at least two stages. In many blood centers it is recommended to use two different disinfection agents. There are some studies available connecting skin disinfection techniques with the frequency of platelet contamination. A survey regarding the methods and the type of the product used for disinfection and the bacterial contamination rates of platelets components is given in Table 2 [4]

Table 1. Bacteria and their percentage in infected platelet concentrates

Blood component	Bacteria	Percentage of detected bacteria that caused complications
Platelet concentrate	*Staphylococcus epidermidis*	25%
	Salmonella choleraesuis	13,5%
	Serratia marcescens	9,6%
	Staphylococcus aureus	9,6%
	Bacillus cereus	3,8%
	Streptococcus viridians	5,8%
	Other bacteria	36,5%

Table 2. Comparison of effectiveness of skin preparation methods

Method	No. of platelet components tested	Platelet contamination rate (% culture positive of tested component)
Ethanol + chlorhexidine	650	0
Ethanol + ethanol	1,040	0
Ethanol*	500	0-0,2
PVP-I + PVP-I	9,000	0,05
Quaternary ammonium salts**	10,000	0,05-0,13
PVP-I	2,000	0,17-0,89
PVP-I***	1,500	0,95
Ethanol or PVP-I****	560	1,2

* Administered one or more times

** Administered three times

*** Open system

**** One blood center in this country uses PVP-I; the remaining use ethanol

PVP-I, Providone-Iodine, also known as Iodophor

No standard methodology for using disinfection products is established. The process of skin disinfection could be better understood if qualitative analysis would be made about the duration, type and efficacy of currently used methods. But, without any doubts the utmost importance of high accuracy of this procedure is generally accepted.

2.3. Blood processing procedures

Single-donor platelets are obtained by a process called apheresis in which donor whole blood is collected then anticoagulated by means of a centrifugal apheresis system. The leucocytes, erythrocytes and plasma are reinfused into the circulation of the donor during cytapheresis. This technique collects the equivalent of a pool of four to five random donor platelets. Assessing a higher number of platelets, cytapheresis is an highly appreciated procedure, with elevated effectively but more expensive than centrifugation method (pooled random donor).

Leukocyte filtration of blood products is an additional methodology mainly recommended for severe hematological patients, candidates for hematopoietic stem cell transplantation. Several studies showed that this technique can reduce the rate of bacterial contamination; this is due to the particularity of leukocyte that can withdraw the bacteria from the blood product unit [4].

2.4. Blood storage and transportation procedures

Transfusion associated sepsis due to contaminated platelet product concentrates is more frequent that due to contaminated red blood cells. Platelet concentrates prepared by centrifugation techniques or apheresis (single donor platelets) of whole blood are stored under special and well-established conditions: room temperature 20- 24 C, on a constant agitator which prevents agglutination and platelet inactivation. On this temperature the bacteria can proliferate. This growth occurs for both gram-negative and gram-positive

organisms, even there is a low inoculum- 1 organism per mL [5]. In most of the countries, also our country, the storage time for platelet products (apheresis and random platelet pools) is 5 days.

The relative frequent transmission of bacteria by room-temperature-stored platelets was evident by 1986, but it was not until 18 years later (2004) that the routine bacteriologic testing was introduced in the United States. Based on the functional quality of the platelets in 1984 the Unites States Food and Drug Administration (FDA) extended the storage of whole-blood-derived platelets from 5 to 7 days. But septic episodes related to platelets transfusion occurred, so in 1986 the FDA mandated the reduction of interval back to 5 days [6]. In Germany the shelf life has been reduced since 2008 to 4 days [7].

Transportations condition should be respected in all the situations. A special box that can keep optimal temperature for platelets concentrates should be used.

DETECTION OF BACTERIAL CONTAMINATION

Bacteriological testing of blood components are performed in Blood centers. In the modern transfusion medicine new techniques for detecting the blood contamination have been developed and implemented trying to prevent the transfusion related risk.

The BacT/ALERT system an automatic method, able to detect the presence of bacterial growth by a precocious change in color of culture bottle (colorimetric technology), is largely recommended. Every culture bottle (aerobic, anaerobic and pediatric) contains a colorimetric carbon dioxide sensor that changes the color when there is a high carbon dioxide level [8]. Positive bottles receive a gram stain and a manual culture prompting to withdraw of the contaminated platelet concentrates samples. Unfortunately the BacT/ALERT system is not able to detect all the contaminated blood products [9]. A positive bacterial culture after routine platelet donation is the first sign of an occult infection and obliges accurate medical evaluation, if it has already been transfused.

OTHER FACTORS THAT CAN INFLUENCE THE SEVERITY OF PLATELET TRANSFUSION TRANSMITTED INFECTION

Contaminated platelet concentrates transfusion can produce severe bacterial infection, even death, especially on immunocompromised patients (on chemotherapy, aplastic anemia or receiving transplantation). For those patients a small inoculum of bacteria can be fatal.

Septic transfusion reactions to platelet transfusion were estimated to occur with approximately 1:25,000 transfusions before 2004. Actual contamination rates were measured to be higher, 1:2,000 to 1:3,000 platelet product transfused. Despite the maintenance of the diagnosis difficulties determinates by pathological background-immunosupression, neutropenia, concomitant antibiotic therapy, this important difference has become possible due to increased awareness and vigilance for early diagnosis [10].

CLINICAL INVESTIGATION OF TRANSMITTED TRANSFUSION INFECTION

During the transfusion or within 4 hours after, the sepsis signs that can occur are: fever, tachycardia, dyspneea and vomiting or nausea. The patients receiving transfusions with high levels of endotoxin released from Gram-negative organisms may develop disseminated intravascular coagulation and shock. All units infused within the 4 hours preceding the onset of symptoms must be sent for laboratory testing. An institutional developed clinical treatment strategy is required to the particularly situation for patient already receiving antibiotics [11].

When evaluating a transfusion reaction is important to know that several viral infectious diseases can be transmitted by infusion of blood components and be taken into consideration in diagnosis level. Table 3 summarizes the agents and the disease related [11].

Table 3. Transfusion-transmitted infection

Agent	Disease
Human Immunodeficiency Virus 1 / 2	HIV disease
Hepatitic Viruses (A, B, C, G)	Hepatitis (A, B, C, G)
Cytomegalovirus	Cytomegalovirus disease
Parvovirus	RBC aplasia
Epstein-Barr virus	Mononucleosis
HHV-6	possible Roseola
Cytomegalovirus	CMV disease
West Nile Virus	Febrile, meningoencephalitis
HHV-8	Febrile, Kaposi sarcoma
Chikengunya Virus	Febrile, arthalgia
Yersinia	Sepsis
XMRV	Chronic fatigue syndrome
Parasite (*Plasmodium malariae*)	Malaria
Tripanosoma cruzi	Chagas disease
Tick Borne (Babesia)	Babesiosis
Borrelia	Lyme disease
Leishmania	Leishmaniasis
Prions	Variant Creutzfeldt-Jakob disease

HHV-6, human herpes virus 6
HHV-8, human herpes virus 8
XMRV, xenotropic murine leukemia virus

CONCLUSIONS

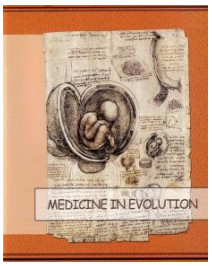
The infection risk reduction related to transfusion is a realistic problem in clinical setting and preclinical medicine. The highest danger is correlated with platelet products. Their storage conditions are connected with the bacterial proliferation. At present no platelet bacterial screening technology is perfectly sensitive. Therefore, in the future, specific and rapid methods of bacterial contamination are needed in order to improve the bacteriologic safety of blood products.

REFERENCES

1. Morris A. Blajchman, Mindy Goldman. Bacterial Contamination of Platelet Concentrates: Incidence, Significance, and Prevention. Sem. in Hem. 2001; 38: 20-26.
2. Mark E. Brecher, Shauna N. Hay. Bacterial Contamination of Blood

Components. Clin. Microbiol. Rew. 2005; 18:195-204.
3. Fernandez R. Severe Sepsis and Sepsis Shock- Understanding a serious killer. InTech; 2012.Feb.10; Available from www.intechopen.com.
4. Stephen J. Wagner, Leonard I. Friedman. Transfusion-associated bacterial Sepsis. Clin. Microbiol. Rew.1994; 7:290-302.
5. B.B.Barett, J.W. Andersen. Strategies for the avoidance of bacterial contamination of blood components. Transf. 1993; 33:228-233.
6. Mark E. Brecher, Morris A. Blajchman. Addresing the risk of bacterial contamination of platelets within the United States: a history to help illuminate the future. Transf. 2013: 53:221-231
7. M. M. Mueller. M. K. Hourfar. Oxygen measurements in platelet fluids- a new non-invasive method to detect bacterial contaminations in platelets. Transf. Med. 2012; 22:211-216
8. P.A.W.te Boekhorst, E.A.M. Beckers. Clinical significance of bacteriological screening in platelet concentrates. Transf. 2005; 45:514-519
9. Roslyn A. Yomtovian, Elisabeth L. Palavecino. Evolution of surveillance methods for detection of bacterial contamination of platelets in a university hospital, 1991 through 2004. Transf. 2006; 46:719-730.
10. Anne F. Eder, Jean M. Kennedy, et al. Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: the American Red Cross experience (2004-2006). Transf. 2007; 47:1134-1142.
11. Anne F. Eder and Mindy Goldman.How do I investigate septic transfusion reactions and blood donors with culture-positive platelet donations? Transf. 2011; 51:1662-1668
12. Jeffrey McCullough. Transfusion Medicine, third edition, Wiley-Blackwell 2012; from: ePDF 9781444398717

THE DEVELOPMENT OF INFERIOR TURBINATE SURGERY



ISABELLA POSTOLACHE

University of Medicine and Pharmacy "CAROL DAVILA", Bucharest - Institute of Phono-Audiology and Functional Surgery, ENT Department, "Prof. Dr. D. Hociota" Bucharest

ABSTRACT

Purpose of the study: The purpose of this study is to emphasize the major role of the inferior turbinate pathology within the nasal obstruction syndrome, as it is shown by the large and continuously increasing number of surgeries.

Material and methodology: The research group was made of patients with inferior turbinate pathology, who underwent various surgeries with Section III of IPAFS ENT over a period of 10 years (January 2001 – December 2010).

The methodology was based on working grids for each individual case considered in this study.

Results: The increase of inferior turbinate surgeries, diversification of surgical techniques and procedures, the use of modern technology.

Conclusions: The appearance and the development of advanced technologies allowed the more frequent diagnosis of this pathology, as well as the possibility to operate on it in optimal intra operatory circumstances and with a quick recovery period.

Key words: *Inferior turbinates, nasal obstruction, surgical technologies*

Correspondence to:

Isabella Postolache, MD
University of Medicine and Pharmacy "CAROL DAVILA", Bucharest
Institute of Phono-Audiology and Functional Surgery, ENT Department, "Prof. Dr. D. Hociota" Bucharest
E-mail: octavian.postolache@yahoo.com

INTRODUCTION

The inferior turbinate is the largest of the three nasal turbinates; it derives from the jawbone [1] and it is a stand-alone bone. The angle between the inferior turbinate and the lateral wall of the nasal cavity [2] largely varies from 20° to 90°; it is an important angle to be considered when determining the inferior turbinate surgery plan. The cavernous parenchyma of the inferior turbinate is better developed than with the other turbinates. When it is congested, its volume may increase 3 to 4 times [3], so that it can completely obstruct the nasal fossa.

The turbinate mucosa varies in terms of cilia and glandes; it contributes mainly to the humidification, warming and filtering of the air we breathe.

There have been at least 13 methods of operating on the inferior turbinate pathology over the last 130 years; some of these methods are still used today, others were abandoned.

MATERIAL AND METHOD

The research group was made of patients that underwent inferior turbinate surgery solely or in association with other nasal and sinus segments, if they caused nasal obstructions. The research was conducted on 6274 cases of patients admitted to Section III - IPAFS ENT; it covers a period of 10 years.

The methodology was based on grids for each case that was part of the research.

This is a retrospective research, based on individual case study; it consists of casuistry analysing and statistical interpretation.

Grid 1. Ways of establishing the inferior turbinate pathology;

Grid 2. Inferior turbinate surgeries associated or not with other causes of nasal obstruction syndrome;

Grid 3. Surgical techniques and technologies.

RESULTS

By applying Grid 1, the diagnostic certainty and the surgical indications were determined by flexible or rigid endoscopy (fig. 1) corroborated with imaging.

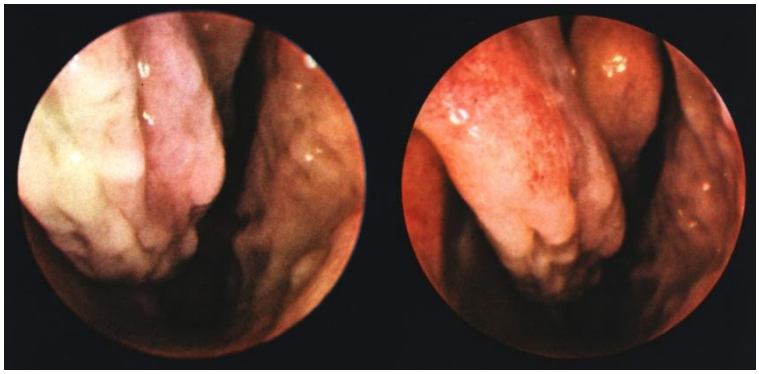


Figure 1: Mulberry-like degeneration of inferior turbinate head.

When the endonasal pathological processes obstruct the nasal fossae to a high degree and even using the 2.7mm fibre is impossible, we chose the retrograde flexible endoscopy for the calm patients (fig. 2). The contra oral

insertion of the fibre allowed the visualisation of the cavum, choanae and turbinate heads.

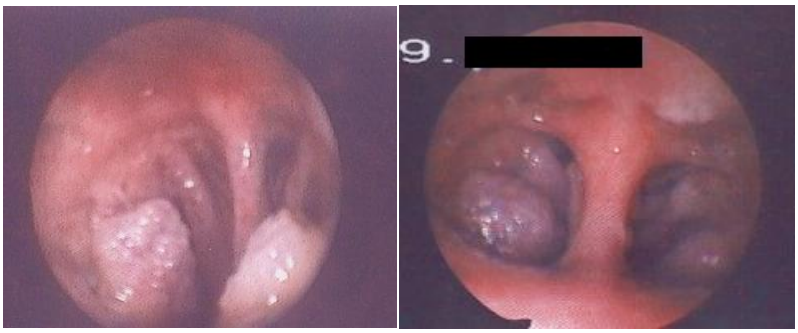


Figure 2: Retrograde endoscopy of the pharynx and choanae: mulberry-like degeneration (4th degree) of turbinate heads

By applying Grid 2, we grouped the nasal obstruction syndrome surgeries as follows:

- endonasal surgeries, solely localized at the level of nasal fossae; they may regard the septum, the turbinates, the nasal valve;
- nasal and sinus surgeries associated with various surgeries of the paranasal sinuses.

The comparative numerical development of the main nasal obstructive syndrome surgeries is presented in figures 3 and 4.

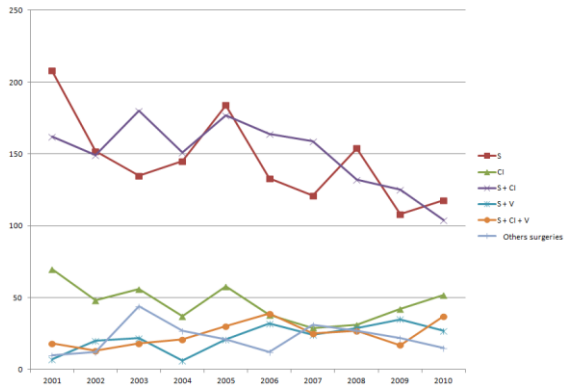


Figure 3: Yearly numerical development of the main endonasal surgeries (S - septum; CI - inferior turbinate; CI - inferior turbinate; V - valve)

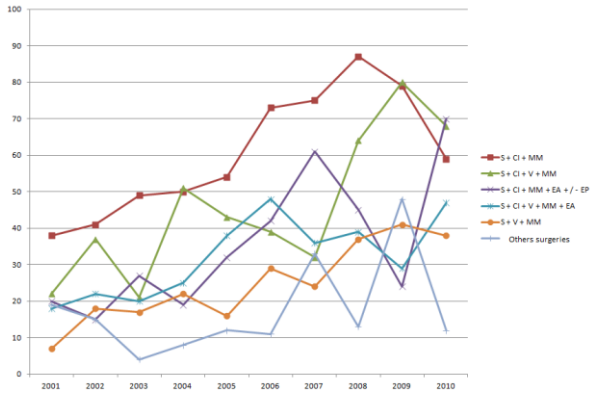


Figure 4: Yearly numerical development of the main nasal and sinus surgeries (S - septum; CI - inferior turbinate; MM –middle meatus; V – valve; EA – anterior ethmoid; EP –posterior ethmoid)

Table 1. The yearly numerical distribution of inferior turbinate surgeries. The P_values obtained by comparing distributions using the chi-square test

	NO. OF INFERIOR TURBINATE SURGERIES		TOTAL NO. OF SURGERIES	
	Endonasal Surgery	Nose and Sinus surgery	Endonasal Surgery	Nose and Sinus surgery
2001	257	98	475	124
2002	230	115	394	148
2003	276	117	455	138
2004	215	145	387	175
2005	286	167	491	195
2006	273	202	418	242
2007	237	204	389	261
2008	219	235	400	285
2009	219	212	349	301

	NO. OF INFERIOR TURBINATE SURGERIES		TOTAL NO. OF SURGERIES	
	Endonasal Surgery	Nose and Sinus surgery	Endonasal Surgery	Nose and Sinus surgery
2010	220	242	353	294
Total	2432	1739	4111	2163

P_value=0.000000000 P_value=0.000000000

P_value=0.7902487

P_value=0.95196456

A probability value smaller than 0.05 (p_value < 0.05) means that distributions differ from a statistic point of view.

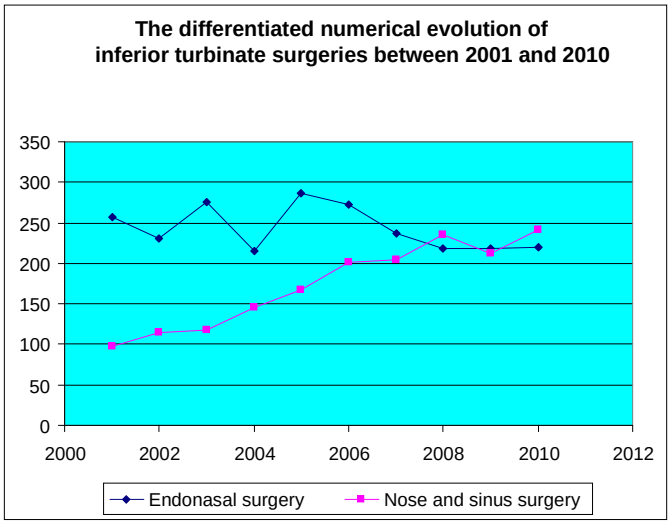


Figure 5: The comparative evolution of inferior turbinate surgeries within endonasal and nose and sinus surgeries

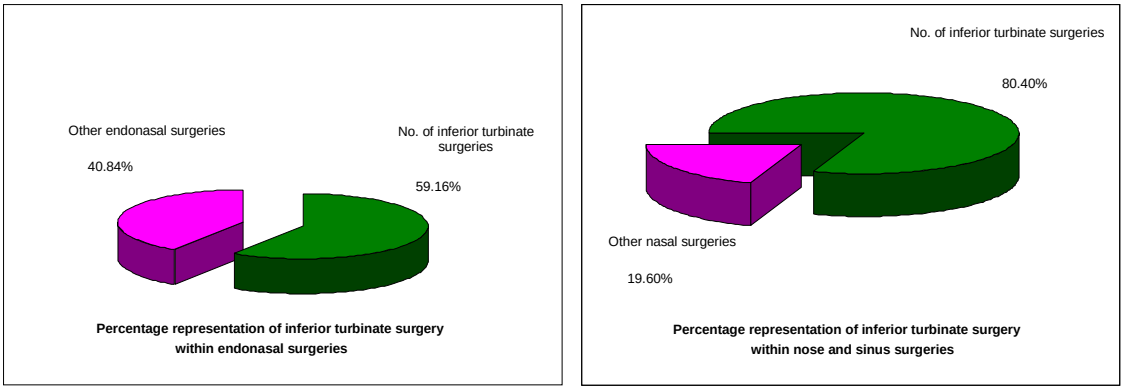


Figure 6: The percentage representation of inferior turbinate surgeries within endonasal and nose and sinus surgeries

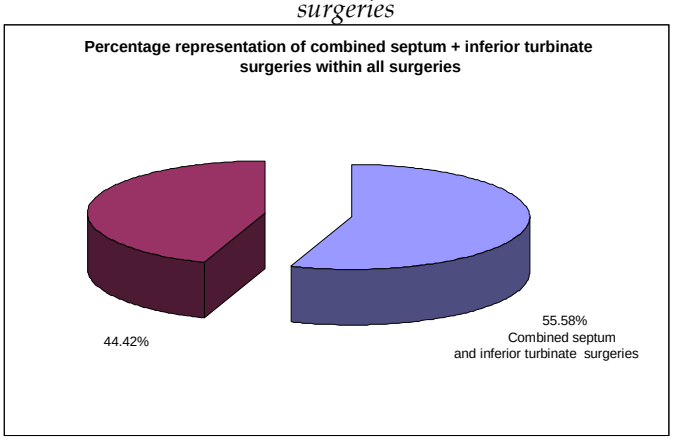


Figure 7: Weight of combined surgeries (septum + inferior turbinate) within the research group

By applying Grid 3, we were able to list the main inferior turbinate surgeries with IPAFS ENT between 2001 and 2010 as it follows:

a. Volumetric reduction of soft tissue hypertrophy with the bipolar electrocautery, endoscopically assisted or not;

b. Volumetric reduction of the localized hypertrophy of turbinate heads (partial mucotomy) with cold instruments (ansa-snare, Heymann scissors) endoscopically assisted or not [2];

c. Volumetric reduction of the generalized hypertrophy of inferior turbinate heads soft tissue (radical mucotomy) with cold instruments (Heymann scissors, scalpel) endoscopically assisted or not;

d. The fracturing and lateralization of the inferior turbinates is more frequent as associated to other turbinate surgeries than as a unique procedure aiming to permeabilize the nasal fossae.

e. Volumetric reduction of the hypertrophy of inferior turbinate tissues using radiofrequency [2, 4, 5, 6] endoscopically assisted, which proved to be the most modern and effective treatment (fig. 8);

f. Submucous resection of localized or generalized inferior turbinate hypertrophies using the endoscopically assisted microdebrider (fig. 9) was another frequent technique with our clinic, as the technology and the accessories were available;

g. Volumetric reduction of the inferior turbinate hypertrophy using Laser is a method which we do not use a lot at our clinic;

h. Submucosal turbinoplasty endoscopically assisted or not is the chosen method for the inferior turbinate bone hypertrophies.

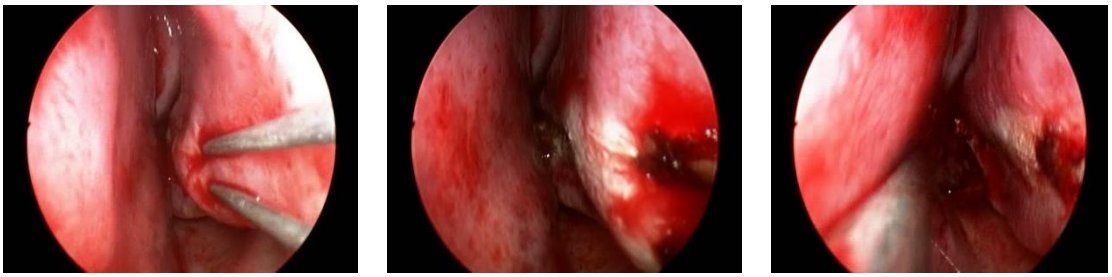


Figure 8: Intra operatory elements: volumetric reduction of inferior turbinates using radiofrequency – bipolar electrode

DISCUSSIONS

The total number of inferior turbinate surgeries, both as unique and combined procedures, has been constant in endonasal surgery, but there was a large increase in nose and sinus surgery (table I, fig. 5). The reasons for the increase of the total number of inferior turbinate surgeries are:

- more frequent diagnosis of this pathology (especially of the inferior turbinate head hypertrophy) by using more often endoscopy as means of diagnosis;
- the appearance and the development of surgical technologies for the various volumetric reductions of the inferior turbinate hypertrophic tissue (Laser, ultrasounds, radiofrequency, microdebrider) having the following advantages:
  - o surgeries can be made with local anaesthesia and therefore a larger number of older patients or patients having other conditions for which general anaesthesia would be contraindicated could be operated on;

o intra and post operatory bleeding is reduced when using this technology, compared to the classic methods of turbinate volumetric reduction, therefore the body is less stressed; this is another reason for the increase of patients undergoing this type of surgery;

o reduced postoperative recovery, with patients spending less time in the hospital; thus the bed usage parameter increases, with a higher number of patients for the same time period.

The double surgical reduction, both of the septum and the inferior turbinates is one of the most frequent multiple purpose surgeries; it represents the main purpose and the base time of these surgeries (fig. 7).

CONCLUSIONS

Evaluating one of the surgical techniques of inferior turbinate volumetric reduction consists of comparing two elements:

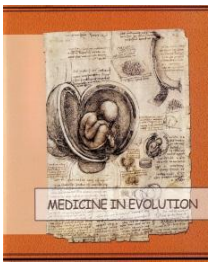
- improving symptoms (respiratory obstruction, rhinorrhea, sneezing, headaches);
- keeping the inferior turbinate function by preserving the mucosa as much as possible.

The inferior turbinate surgery, both as unique and multiple purpose, is a frequent surgery both with endonasal (59.16 %, p_value = 0.7902487) and nose and sinus surgeries (80.40 %, p_value = 0.95196456) (fig. 6).

REFERENCES

1. Theissing J, Rettinger G, Werner JA. ENT – Head and Neck Surgery: Essential Procedures. New York: Thieme, 2010.
2. Huizing EH, De Groot JA. Functional Reconstructive Nasal Surgery. Stuttgart: Georg Thieme Verlag, 2003.
3. Berger, Gilead et al. Histopathology Of The Inferior Turbinate With Compensatory Hypertrophy In Patients With Deviated Nasal Septum. Laryngoscope 2005; 111(12):2100-2105.
4. Back et al. Submucosal Bipolar Radiofrequency Thermal Ablation Of Inferior Turbinates: A Long-Term Follow-Up With Subjective And Objective Assessment, Laryngoscope 2003; 112(10):1806-1812.
5. Marinescu A. Innovative Bipolar Radiofrequency Volumetric Reduction With "Orl-Set" For Treatment Of Habitual Snorers. Laryngorhinootologie 2004; 83:610-6.
6. Blumen MB, Chalumeau F, Gauthier A. Comparative Study Of Four Radiofrequency Generators For The Treatment Of Snoring. Otolaryngology Head Neck Surgery 2008; 138:294-299.

THE SURGICAL TREATMENT OF BRONCHIECTASIS



ADINA MAGDALENA TURCANU[1,2], TRAIAN MIHAESCU[1,2], CRISTIAN COJOCARU[1,2]

[1]University of Medicine and Pharmacy "Gr. T. Popa" Iasi, Facultaty of General Medicine, Pneumology Discipline
[2]The Pneumology Clinic Hospital Iasi

ABSTRACT

The Surgical Treatment of Bronchiectasis. The surgical treatment of bronchiectasis represents, in most of the cases a curative method, as the patients become asymptomatic. Recent studies have shown the benefice of different surgical techniques and the low rates of mortality and morbidity. The aim of this article is to underline the most important aspects connected to the post-surgical evaluation of the patients who had to undergo surgical resections with the objective of removing the bronchiectasis.

Key words: *bronchiectasis, surgical treatment, mortality, resection*

Correspondence to:

Dr. Turcanu Adina Magdalena
Address: Clinic of Pulmonary disease, Str. Cihac nr. 30, Iasi, Jud. Iasi
Phone: 0745099456
E-mail address: adinagheorghita@yahoo.com

INTRODUCTION

The bronchiectasis was described for the first time in 1819 by Laenec and before the antibiotics era it was considered an ailment with high degree of mortality due to the respiratory insufficiency and of the complications. Together with the discovery of antibiotics and with their correct administration the disease evolution and the life quality of the patients were significantly improved. However, there are cases where the anti-microbial treatment (even the chronic one) it is no longer efficient for controlling the disease and as a therapeutic purpose it is imposed the surgical treatment. The decision to make a surgical intervention in order to remove the bronchiectasis varies and includes a series of indications such as repeated haemoptysis, reduced efficiency of the therapy with antibiotics, recurrent pulmonary infections, chronic cough with expectoration, etc.

The surgical treatment of bronchiectasis is improving the symptomatology, especially to the patients where it is practiced the total resection. This approach does not influence the respiratory function. The results of a study published by Prieto and collaborators which had included a number of 119 patients with bronchiectasis (71 women, 48 men), the average age of 42.2 years old, have demonstrated that after a total resection which was performed to a percentage of 91% of the patients (using different techniques which have included lobectomy, segmentectomy, pneumonectomy, bilobectomy), the symptoms have disappeared in a percentage of 68%, were improved in a percentage of 31% and for only 3.7% we have encountered a deterioration of the situation; as well, the respiratory function, evaluated by the FEV1 parameter had remained steady. The post-operational mortality was 0% and the morbidity 15%.

A study developed by Gursoy and collaborators published in 2010 is confirming the favorable results of the surgery in the therapeutic treatment of this illness. There were analyzed a number of 92 patients (54 women, 38 men), the average age 38.7±14.3 years old, who have undergo lobectomy (36 patients), lobectomy and segmentectomy (32 patients) or pneumonectomy (10 patients), as the rest of the patients needed a combinations of these techniques as the illness was more advanced; it was observed a wider expansion of the disease as compared to the HRCT images and the surgical intervention had included the new lesions identified intra-operator. The left lung was the most frequently involved (78% of the cases), the resection was performed most frequently to the left inferior lobe and the number of the surgical removed segments for each patient was in between 1 and 11. After the surgical intervention there were followed only 75 out of all 92 patients and it was observed that 84% of them were asymptomatic, 10.7% have presented a clearly improved symptomatology and only 5.3% did not experienced any modification as compared to the pre-operator moment. The registered mortality was of 1% and the morbidity 15%..

RESULTS

The results of a retrospective study made for a period of eight years were published in 2008. A number of 45 patients (21 men, 41 women), average age 42 years old, were subjected to different surgical interventions (23 lobectomies, 11 lobectomies associated with

segmentectomies, 2 bilobectomies, 9 segmentectomies, 12 thoracoscopies cu 10 lobectomies of the medium lobe and two segmentectomies of the lingula) with curative purpose. For a following period of time, an average of 47 months, there was noticed that 32 of the patients were asymptomatic, 10 have presented a significant improvement of the symptomatology, and for 2 of the patients there were present the same constant symptoms before the surgical intervention. As for the respiratory function, we could notice a decrease of the FEV1 post-surgical parameter as compared to the pre-surgical parameter (80.9"16.9% versus 89.9"16.3%).

A recent study achieved by Bagheri and collaborators, whose results were published in 2010, had analyzed a number of 277 patients with bronchiectasis (72.2% men and 27.7% women), the average age of the lot 34.7 years old, subjected to surgical interventions for remedial motivation. To a number of 62 patients there were noticed bilateral localization, but the most frequent setting was noticed at the level of the left inferior lobe. The most frequent used surgical technique was the lobectomy (42.2%) and the unilateral lobectomy with segmentectomy at the level of the other lung (to the patients with bilateral bronchiectasis). The mortality was 0.7% and the morbidity 15.8%. The patients were followed for a period of 4.5 years and it was noticed that a percentage of 65.8% were asymptomatic, 23.8% have presented a significant improvement of the symptoms and to a percentage of 7.5% the symptomatology had remained constant.

The results of a retrospective analysis upon a lot of 790 patients with bronchiectasis (466 men, 266 women), the average age 41.6 years old, who have underwent surgical interventions for removing the bronchiectasis were published in 2010 by Zhang and collaborators. They have noticed that from the total of the surgical techniques 62.9% were lobectomies, 4.7% segmented resections, 11.3% pneumonectomies, 7.1% bilobectomies and 14% lobectomies with segmentectomies. There were registered 9 deceases during the post-surgical period. Afterwards the patients were followed for an average period of 4.2 years and it was noticed that 60.5% were asymptomatic, 14.1% have presented an improvement of the symptomatology and 14.8% have had the same symptoms or confirmed a worsening status.

The surgical treatment of bronchiectasis is recommended mainly when the treatment based on drugs is becoming insufficient and the patient's life quality is prejudiced. From the presented studies we can observe that most of the treated patients are male patients.

In most of the studies there was detected the predominance of the bronchiectasis at the level of the left inferior lobe, and the most used ablation technique was the independent lobectomy or associated with segmentectomy. The chosen surgical technique had depended also of the intra-surgical detected lesions as there were identified more lesions than those diagnosed through the imagistic method. The pneumonectomy is rarely used and applied only to the patients with expanded bronchiectasis or with other adjacent lesions (such as the neoplasm).

At the same time we can observe the fact that the complete resections of the bronchiectasis present the best result, most of the patients (over 60%) of each study becoming asymptomatic and another significant percentage presenting a noteworthy improvement of their symptomatology. As regarding the respiratory function, it is not evaluated but in some of the studies recently developed, but it seems that there is a decrease of the FEV1 post-surgical parameter as compared to the pre-surgical one.

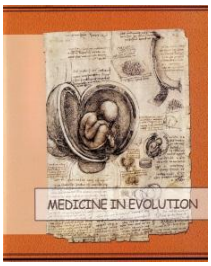
The post-surgical mortality remains under 1% and the morbidity varies. Therefore the surgical treatment of bronchiectasis can be done to the patients receiving this indication, no matter the age, as long as the morbidity and mortality rate remain low and it is recommended the total resection in order to obtain the best control of the symptomatology.

ACKNOWLEDGEMENTS

The authors wish to thank to AMPOSDRU for the financial support within the project called "Parteneriat interuniversitar pentru cresterea calitatii si interdisciplinaritatii cercetarii doctorale medicale prin acordarea de burse doctorale-DocMed.net"(POSDRU/107/1.5/S/78 702)."

REFERENCES

1. Prieto D., Bernardo J, João Matos M et al. Surgery for Bronchiectasis. *Eur J Cardiothorac Surg*. 2001;20:19-24.
2. Gursoy S, Ozturk AA, Ucvet A et al. Surgical Management of Bronchiectasis: The Indications and Outcomes. *Surg Today*.2010; 40:26-30.
3. Giovannetti R, Alifano M, Stefani A et al. Surgical Treatment of Bronchiectasis: Early and Long-Term Results. *Interact Cardiovasc Thorac Surg*. 2008; 7: 609–612.
4. Bagheri R, Haghi SZ, Fattahi Masoum SH et al. Surgical Management of Bronchiectasis: Analysis of 277 Patients. *Thorac Cardiovasc Surg*. 2010; 58:291-294.
5. Zhang P, Jiang G, Ding J et al. Surgical Treatment of Bronchiectasis: A Retrospective Analysis of 790 Patients. *Ann Thorac Surg*. 2010; 90: 246–250.



A THOROUGH RESEARCH REGARDING THE EFFECTIVENESS OF MEDICAL REHABILITATION TREATMENT BY USING MEDICAL AND ECONOMIC INDICATORS

DAN SURDUCAN[1], DAN NEMEŞ[1,2], MIHAI DRĂGOI[1,2]; DANIEL POPA[1,2]; ELENA AMĂRICĂI[1]; CRISTINA POPA[1,3]

[1]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[2]City Emergency Hospital Timisoara –Rehabilitation and Rheumatology Department, Timisoara, Romania
[3]"Louis Turcanu" Children Emergency Hospital, Timisoara, Romania

ABSTRACT

Aims and objective: Assessment on the effectiveness of a complex treatment for vertebral-peripheral arthrosis with or without associated soft-tissue inflammatory rheumatic disease.

Material and method: 223 patients underwent medication and medical rehabilitation treatment. We carried out 2 assessments using the Modified Physical Performance Test and a questionnaire based on Short Form (SF-36) Health Survey. We evaluated medication, average number of electrotherapy procedures on an articular region, treatments effectiveness, outcome of cost-effectiveness analysis and the influence of kinetic therapy.

Results: The treatment associating medication, electrotherapy (up to 2 procedures for an articular region), manual and kinetic therapy had the highest effectiveness. The patients had better results if the kinetic therapy was part of their previous medical rehabilitation treatments.

Conclusions: As for the medical rehabilitation treatment, the kinetic therapy is the most important mean. An objective and subjective assessments can be used for cost-effectiveness analysis.

Key words: *objective assessment, subjective assessment, cost-effectiveness analysis*

Correspondence to:

Dan Surducan
PhD Student
Adress: "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
Phone: +40.744.647.287
E-mail adress: surducan_dan@yahoo.com

INTRODUCTION

Arthrosis or osteoarthritis is a degenerative rheumatic disorder with high social impact due to the possibility of causing physical disability. The main symptoms are pain and joint stiffness. Medication, preventive measures and medical rehabilitation treatment are part of the therapeutic approach (1). Medical rehabilitation treatment encompasses electrotherapy, manual therapy and kinetic therapy. Scapulohumeral periarthritis is a soft-tissue rheumatic disorder. Pain and a limited mobility are part of the symptoms. Myofascial pain syndrome involves chronic pain in specific anatomic regions of the body. The treatment of these 2 disorders also includes medication, electrotherapy, manual therapy and kinetic therapy. (2).

The Physical Performance Test (PPT) is a useful tool for the assessment of functional capacity, 9 items being part of this test. The Modified – Physical Performance Test (MPPT) also encompasses 9 items, 7 items being part of PPT. PPT and MPPT can be used for degenerative rheumatic disorders (3). The reliability of data achieved by PPT and MPPT is already proved (4).

The Short Form (SF-36) Health Survey is a questionnaire used to measure general health status without age, disease or treatment specificity. SF-36 includes 36 questions in 8 scales. Information regarding the reliability of data provided by SF-36 are available in literature (5).

The cost-effectiveness analysis takes into account treatment cost and outcome. This analysis is carried out when decision makers want to find out the best therapeutic approach with a limited budget. Outcomes of different treatments can be evaluated by different measures (diminishing the level of cholesterol, days free of symptoms or years of life gained). A simple ratio between the cost and outcome of a treatment would lead to a comparison between a treatment and the absence of a treatment ("do-nothing option"). A comparison between different treatments of a disorder can be accomplished by using ICER (incremental cost-effectiveness ratio), comparison being achieved in terms of cost and outcome (6).

Aims and objectives

The present paper presents the assessment on the effectiveness of a complex treatment of vertebral-peripheral arthrosis with or without associated soft-tissue rheumatic disease. The objective, subjective evaluations as well as the cost of the treatment are taken into account.

MATERIAL AND METHOD

We carried out a study on 223 patients. Their diagnosis was spine and peripheral osteoarthritis (SPO) with or without associated soft-tissue rheumatic disease (myofascial syndrome or tendinitis or scapulohumeral periarthritis). The patients were split into 2 groups: Group 0 (only SPO, 165 patients) and Group 1 (SPO and myofascial syndrome or tendinitis or scapulohumeral periarthritis, 58 patients).

The aforementioned patients went through 2 assessments. An objective assessment was accomplished by using the Modified Physical Performance Test (MPPT in results). The subjective assessment was based on Short Form (SF-36) Health Survey, 31 questions out of 36 were used, this new questionnaire being referred to as SF in the results section. We used the

objective and subjective assessment twice, at the beginning of the treatment and after 7, 8 or 9 days. The Modified Physical Performance Test encompasses the following items: standing static balance (1), chair rise (2), lift a book and put it on a shelf (3), put on and remove a jacket (4), pick up a coin from the floor (5), turn 360 degrees (6), 50-foot walk test (7), climb one flight of stairs (8), climb stairs (9). The SF questionnaire is based on Short Form (SF-36) Health Survey and it has 31 questions. The questions refer to the patient's opinion regarding: vigorous activities (1), moderate activities (2), lifting or carrying groceries (3), climbing several flights of stairs (4), climbing one flight of stairs (5), bending and kneeling (6), walking more than one kilometer (7), walking few hundred meters (8), walking 100 meters (9), bathing or dressing yourself (10), amount of time spent on work or other activities (11), the accomplishment of activities (12), limitation of work or other activities (13), difficulty in performing the work or other activities (14), bodily pain (15), influence of pain on work (16), influence of physical health on social activities (17), amount of time spent on social activities (18), own mood (19), feeling of nervousness (20), feeling of sadness (21), feeling of calmness (22), own energy (23), feeling of discouragement (24), feeling of weariness (25), feeling of happiness (26), feeling of tiredness (27), possibility of getting sick easier (28), own health (29), possibility of health getting worse (30), existence of excellent health (31).

All of the patients underwent a complex treatment: medication (M), electrotherapy (E), manual therapy (TM) and kinetic therapy (K). As for the number of electrotherapy procedures, we split the treatments in: M_3-5E_TM (1), M_6-9E_TM (2), M_3-5E_TM_K (3) and M_6-9E_TM_K (4). 3-5E means a number of electrotherapy procedures between 3 and 5, whereas 6-9E means a number of procedures between 6 and 9. For each patient, the daily cost of treatment was calculated according to the prices available in our department. We evaluated medication, average number of electrotherapy procedures on an articular region and treatment effectiveness. Effectiveness of the 4 aforementioned treatments was achieved by using the daily improvements found upon objective assessment (D_MPPT_ZI) and subjective assessment (D_SF_ZI). The difference between the final score (MPPT_F, SF_F) and the initial score (MPPT_I, SF_I) in both assessments was divided to the number of days between assessments. The daily improvement values were therefore obtained. We also performed a comparison between the daily improvements for each treatment and group.

The treatments were ranked according to their effectiveness provided by the objective assessment (D_MPPT_ZI) in each group. A ratio between cost and effectiveness was calculated. The ICER index was also calculated as the ratio between the differences in cost and effectiveness, respectively. As we already pointed out, the effectiveness was provided by the objective assessment (D_MPPT_ZI). In the end, for each group, we evaluated the influence of kinetic therapy on the evolution of patients with previous medical rehabilitation treatment. We evaluated the influence of kinetic therapy on the evolution of patients undergoing the first medical rehabilitation treatment as well.

RESULTS

The average age of patients in group 0 was 62.430 years. In group 1, the average age was 61.120 years. The women represented 63.64% (105

patients) whereas the men 36.36% (60 patients) in group 0. 74.14 (42 patients) was the percent of women in group 1, the percent of men was 25.86 (15 patients).

As for the outcomes of the objective (D_MPPT_ZI) and subjective assessments (D_SF_ZI), the patients had better outcomes after the treatment encompassing kinetic therapy. Moreover, the kinetic therapy led to a lower number of electrotherapy procedures for an articular region in group 0. Nonsteroidal anti-inflammatory drugs were part of the treatment in both groups. Trophic medication was useful in group 0. The analgesic medication was useful in group 1 (Table I).

Table I. Outcomes in groups 0 and 1 (D_MPPT_ZI – daily improvement of objective assessment, D_SF_ZI – daily improvement of subjective assessment, K – kinetic therapy, NSAID – nonsteroidal anti-inflammatory drug, ANT – analgesic medication, M – muscle relaxant, T – trophic medication, No. el. – average number of electrotherapy procedures, No. art. – average number of painful articular regions, El./art. – average number of electrotherapy procedures on an articular region, Pat. – patients)

K	D_MPPT_ZI	D_SF_ZI	NSAID %	ANT %	M %	T %	No. el.	No. art.	El. / art.	Pat.
No	0.306	1.139	93.37	21.93	39.79	21.43	5.367	2.718	1.974	77
Yes	**0.560**	**1.861**	96.67	29.39	37.27	41.62	5.496	2.893	1.899	88
	p<0.01	**p<0.01**	**Group 0**							
No	0.287	1.007	100	40.83	50.83	85.00	5.608	3.908	1.435	22
Yes	**0.578**	**1.914**	93.75	47.91	50.00	41.66	5.624	3.624	1.551	36
	p<0.01	**p<0.01**	**Group 1**							

A correlation between D_MPPT_ZI and D_SF_ZI was pointed out in group 0 even if the correlation coefficient was not so high (R-squared=0.14, correlation coefficient=0.37, $p<0.01$). The correlation encountered in group 1 was stronger (R-squared=0.41, correlation coefficient =0.64, $p<0.01$).

In terms of both assessments, M_3-5E_TM_K (3) and M_6-9E_TM_K (4) led to better outcomes than M_3-5E_TM (1) and M_6-9E_TM (2). The treatments 3 and 4 demonstrated the best effectiveness within both groups. The effectiveness was highlighted by higher values encountered upon the objective (D_MPPT_ZI) and subjective assessments (D_SF_ZI), as well as by a lower ratio between cost and effectiveness (D_MPPT_ZI). A lower ratio meant a higher effectiveness for a lower cost. In terms of ICER, treatment 3 turned out to be the most efficient because ICER had the lowest value. A lower value of ICER meant a higher increase in effectiveness with a lower increase of cost. A lower number of average electrotherapy procedures on an articular region were emphasized in group 1 (around 1.2) as compared with batch 0 (around 1.7). This was due to the higher number of painful joint areas as a consequence of associated soft-tissue rheumatic disease in group 1 (Table II).

Table II. Cost-effectiveness analysis (Tr. – treatment, Cost – daily cost, RON – Romanian currency, Cost / eff. – ratio between cost and effectiveness, Pat. - patients)

Tr.	Cost (RON)	D_MPPT_ ZI	D_SF_ ZI	No. el.	El. / art.	Cost / eff.	ICER	Pat.
Group 0								
1	21.39	0.288	1.103	4.306	1.540	74.270	-	49
2	29.02	0.337	1.202	6.428	2.433	86.112	155.714	28
3	29.27	**0.552**	**1.883**	4.509	**1.710**	**53.025**	**1.162**	55
4	36.32	**0.573**	**1.826**	6.484	**2.057**	**63.385**	335.714	33
Group 1								
1	22.06	0.250	0.982	4.416	1.127	88.240	-	12
2	31.52	0.331	1.037	6.800	1.743	95.226	116.790	10
3	29.17	**0.555**	**1.813**	4.333	**1.181**	**52.558**	**-10.491**	12
4	38.35	**0.589**	**1.965**	6.916	**1.930**	**65.110**	270.000	24

In both groups, the patients without previous kinetic therapy showed lower values following the objective and subjective assessment (D_MPPT_ZI, D_SF_ZI), whereas the patients undergoing previous treatment including kinetic therapy had higher values. As for the patients undergoing kinetic therapy as part of previous treatments, better initial and final outcomes in both assessments (MPPT_I, MPPT_F, SF_I, SF_F) were emphasized as well. The kinetic therapy undergone in the past led to an improvement of patient functional capacity (Table III).

Table III. Evolution of the patients with previous medical rehabilitation treatment (Pat. – patients)

Kinetic therapy	MPPT_I	MPPT_F	D_MPPT_ZI	SF_I	SF_F	D_SF_ZI	Pat.
No	21.26	23.77	0.299	74.85	83.64	1.082	53
Yes	**21.92**	**26.06**	**0.514**	**75.46**	**89.20**	**1.710**	50
Group 0			**p<0.01**			**p<0.01**	
Kinetic therapy	MPPT_I	MPPT_F	D_MPPT_ZI	SF_I	SF_F	D_SF_ZI	Pat.
No	20.56	23.00	0.294	69.63	78.38	1.061	16
Yes	**21.53**	**26.57**	**0.624**	**73.23**	**90.53**	**2.133**	26
Group 1			**p<0.01**			**p<0.01**	

CONCLUSIONS

The assessment of patients led to a variety of results. However, a correlation was encountered. Owing to this correlation, the assessment by using Modified Physical Performance Test and the questionnaire based on Short Form (SF-36) Health Survey can be undertaken in cost-effectiveness analysis.

As for the outcomes, a complex treatment encompassing a nonsteroidal anti-inflammatory drug, up to 2 electrotherapy procedures on an articular region, manual therapy and kinetic therapy led to the best results. The trophic medication proved to be useful on patients without associated soft-tissue rheumatic disease, whereas the analgesic medication was useful on patients with associated soft-tissue rheumatic disorder.

DISCUSSIONS

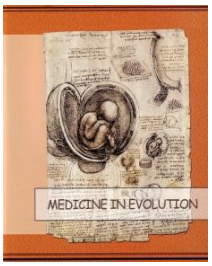
In terms of medical rehabilitation treatment, the kinetic therapy stands out as the main therapeutic mean. The medication and the number of

electrotherapy procedures should be carefully selected in order to achieve a better effectiveness of treatment. Osteoarthritis with or without associated soft-tissue rheumatic disease has to be diagnosed as early as possible. Moreover, the sooner patients undergo a proper treatment the better outcomes are noticed. When kinetic therapy is included in the treatment regimen a better evolution is achieved.

The cost-effectiveness analysis is still a useful tool for the health system. Thorough objective and subjective assessments can be undertaken to emphasize the effectiveness of a treatment. The usefulness of the cost-effectiveness analysis is proven when the health system resources are limited and the best treatment should be chosen.

REFERENCES

1. Bredveld FC. Osteoarthritis – the impact of a serious disease. Rheumatology. 2004;43(Suppl.1):i4-i8
2. Frontera WR, Silver JK, Rizzo TD. Essentials of Physical Medicine and Rehabilitation. Second edition. Philadelphia: Saunders Elsevier. 2008:745-750 (Osteoarthritis-chapter130), 71-81 (Rotator Cuff Tendinits-chapter 14), 529-35 (Myofascial pain syndrome-chapter96)
3. Hayes KW, Johnson ME. Measures of Adult General Perform ance Tests. Arthritis Care & Research; 2003 October;vol.49,no.5S;S28-S42
4. Freiberger E, de Vreede P, Schoene D, Rydwik E, Mueller V, Fraendin K, Hopman-Rock M. Performance-based physical function in older community-dwelling persons: a systematic review of istruments. Age Ageing. 2012 Nov;41(6):712-21
5. Busija L, Pausenberger E, Haines TP, Haymes S, Buchbinder R, Osborn RH. Adult Measures of General Health and Health-Related Quality of Life. Arthritis Care & Research. 2011 November;vol.63,no.S11:S383-412
6. Drummond MF. Cost-effecteveness analysis (chapter 5). In: Drummond MF, Schulpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. Third Edition. New York: Oxford University Press; 2005.130-133.



COMPLEX APPROACH ON THE MEDICAL REHABILITATION OF LUMBAR SPINAL DISC HERNIATION IN YOUNG ACTIVE ADULTS

GEORGE PUENEA[1], DAN NEMES[1,2], LAVINIA BUSESCU[2], ROXANA BALACESCU[2] ,LILIANA CATAN[1]

[1]University of Medicine and Pharmacy „Victor Babes" Timisoara, Romania
2City University and Emergency Hospital, Timisoara, Romania-Rehabilitation and Rheumatology Department

ABSTRACT

Introduction: Around 80-85% of the general population develops at least on episode of lower lumbar pain at some moment in life (6-8). The aim of the study: To early identify lumbar spinal disc herniation symptoms in young active adults, using modern assessment methods and to establish a correlation between the assessed parameters, involved in highlighting the role of specific medical rehabilitation therapy, associated to early and sustained complex medication, in regaining functionality and increasing life quality.

Material and method: During a 3 years period, 296 young, active patients diagnosed with lumbar disc herniation were monitored, being classified into 3 homogeneous groups and receiving different therapies/group. Each patient was subjected to 6 complex evaluations consisting of: a complex clinical examination, assessment of the daily activity using the Lequesne functional index, life quality using the SP12-HSQ12 questionnaire and an innovative, non-invasive method – Actigraph, by which the intensity and character of pain were assessed, by determining certain functional parameters.

Results: The comparison between the 3 group-differentiated therapies shows statistically significant differences regarding: the Lequesne score ($F(2.293)=226.94$, $p<0.001$), the HSQ score ($F(2.293)=239.51$, $p<0.001$), the number of awakenings/night ($F(2.293)=260.39$, $p<0.001$), the number of steps ($F(2.293)=123.50$, $p<0.001$) and the cardiac rate ($F(2.293)=103.1$, $p<0.001$). Upon all the 6 assessments, positive and statistically significant correlations between the Lequesne and HSQ scores, number of awakenings, cardiac rate (CR) and significant but negative correlations to the number of steps were found. Using multiple regression, the prediction equation of the Lequesne score was obtained: Lequesne score at 12.5 months = - 47.90 + 0.23 x BMI + 2.08 x intial HSQ.

Conclusions: The early diagnosis, complex assessment and adequate therapeutic approach have a positive impact on the functionality and life quality in young, active adults with lumbar spinal disc herniation.

Key words: *spinal disc herniation, young adult, assessment, life quality*

Correspondence to:

George Puenea
University of Medicine and Pharmacy "Victor Babes"Timisoara, Romania
Phone: 0722438747
E-mail address: george.puenea@cardinalmed.ro

INTRODUCTION

During recent years, lumbar-sacral pain has become increasingly frequent among young people, having a strong impact on their daily activity and social life.

An adequate knowledge of this condition and its treatment, together with an active involvement in making decisions for the therapeutic management may help patients with a chronic, disabling disease to make decisions which will allow them to improve their life quality in terms of needs, purposes and circumstances.

The socio-economic costs generated by the late diagnosis of these diseases are much higher than those imposed by diagnosing it as early as possible and introducing an aggressive treatment during the onset stage of the disease.

The complex assessment of young, active patients with lumbar sacral pain is crucial for diagnosing incipient spinal disc herniation and for monitoring various forms of treatment.

For this purpose, a large number of variables, some anatomic and others functional or of medical imaging, suited to measure various aspects of the disease were elaborated.

THE AIM OF THE STUDY

1. Early identification of lumbar disc herniation symptoms in young, active adults, using a non-invasive and inexpensive method (ActiGraph), correlated to specific indexes for evaluating functionality (Lequesne Index) and life quality (Health Status Questionnaire - SP12-HSQ12);

2. Establishing a correlation between the assessed parameters, depending on the therapeutic approach, with the possibility to contribute to decreasing social and economic costs, by decreasing the number of expensive investigations, early diagnosis, as well as by early implementation of an adequate therapy, thus increasing the functionality and life quality of these patients;

3. Highlighting the role of specific medical rehabilitation therapy, including a programme of kinetic therapy at home, associated to the complex, early and constantly administered medication, for recovering functionality and increasing life quality of young patients with occupational lumbar sacral pain, induced by lumbar spinal disc herniation;

4. Assessing the way the kinetic therapy programme influences the patient's life quality and compliance to treatment.

MATERIAL AND METHOD

During the period between January 2010 – December 2012, in the Clinic for Physical Medicine and Balneology Timisoara and in the CARDINAL MED Medical Centre Timisoara, 296 young, active patients diagnosed with lumbar spinal disc herniation and secondary lumbar sacral pain, aged between 26-45 years, 147 men (49.7%) and 149 women (50.3%), 189 urban (63.9%) and 107 rural (36.1%) residents were included in the study.

The 296 patients were classified into 3 homogeneous groups depending on the type of treatment they received previously, the clinical-functional status, but especially on the patient's compliance to treatment and differentiated therapies were administered to each group:

- group 1- 98 patients, received a complex medication (analgesics: Piafen

500mg/day, Gabapentin 300mg/day; NSAI: Celebrex 200mg/day, Meloxicam 15mg/day, Ketoprofen 200mg/day; myorelaxants: Mydocalm 150mg/day) in repeated courses and, whenever required, additional lumbar sacral orthosis (lombostat);

- group 2- 98 patients, idem group 1 + periodic medical rehabilitation treatment: 3 courses of 10 daily sessions at 6 months intervals (initial, after 6 and 12 months, respectively) consisting of manual masage, electric and kinetic therapy, with the following objectives: decreasing the pain, improving the body posture and orientation, improving functionality and reeducating the performance of occupational and daily activities (fig.1)

- group 3 – 100 patients, idem group 2 + individualised, home adapted kinetic therapy programme.

Each patient benefited from 6 complex assessments: initial (before adopting the therapeutic programme), after 2 weeks (after receiving medication – group 1 and after the first course of 10 rehabilitation sessions – groups 2 and 3), after 6 months (before the second course of therapy), after 12 months (before the third course of therapy) and after 12.5 months (after the third course of therapy), consisting of: complex clinical examination, assessment of the daily activity using the Lesquene functional index (1-4) (we interpreted: 0=no disfunction, 1-4=slightly affected, 5-7 moderately affected, 8-10=severely affected, 11-13=very severely affected, ≥14=extremely severely affected), life quality using the Health Status Questionnaire: SP12-HSQ12 (5) (our interpretation: 0=not affected, 1-7=slightly affected, 8-13=moderately affected, 14-18=severely affected, 19-24=very severely affected, ≥25=extremely severely affected) and an innovative, non-invasive method – Actigraph (6-10), by which we assessed the degree and character of pain depending on the number of awakenings per night (our interpretation: normal: 0-3, slight discomfort: 4-6, moderate discomfort: 7-10, severe discomfort: 11-15, very severe discomfort: 16-20, extremely severe discomfort: ≥21), number of steps/day (our interpretation: normal: >3000 steps/day, slight deficit: 1000-3000 steps/day, moderate deficit: 500-1000 steps/day, severe deficit: 200-500 steps/day, very severe deficit: 100-200 steps/day, extremely severe deficit: <100 steps/day and cardiac rate (our interpretation: normal: 60-80 beats/minute, slightly increased rate: 81-85 beats/minute, moderately increased rate: 86-90 beats/minute, severely increased rate: 91-95 beats/minute, very severely increased rate: 96-100 beats/minute, extremely severely increased rate: ≥101 beats/minute).

The Actigraph was used in all cases by attaching it to the wrist and wearing it for 24 hours for each assessment, with the patient performing normal daily activities, and not taking the device into consideration, while the recorded data were saved and used for statistical analysis..

Fig. 1. Specific medical rehabilitation treatment (1a-d. Kinetic therapy, 1 e, f. analgesic electrotherapy, g, h. Relaxing massage) – personal collection; patient's consent granted.

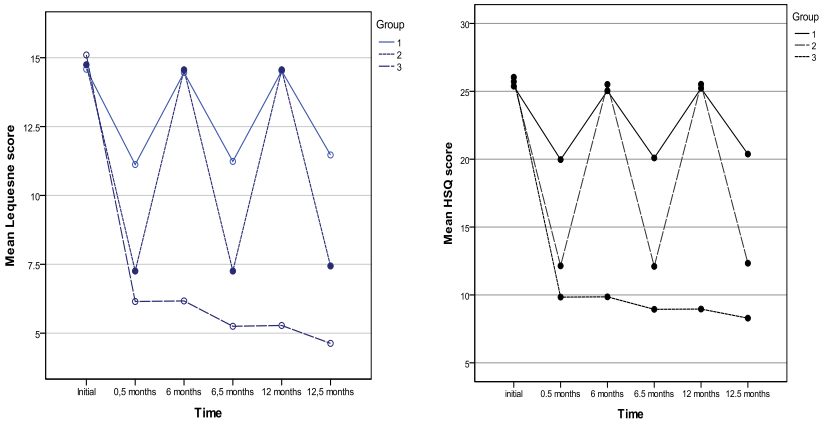
RESULTS

A mixed variance analysis was performed between groups and between serial investigations, in order to establish the impact of the 3 types of interventions (therapies) on the average value of the Lequesne score measured initially, and then after 2 weeks, 6 months, 6 months and 2 weeks, 12 months and 12 months and 2 weeks. The comparison between the 3 types of therapies shows:

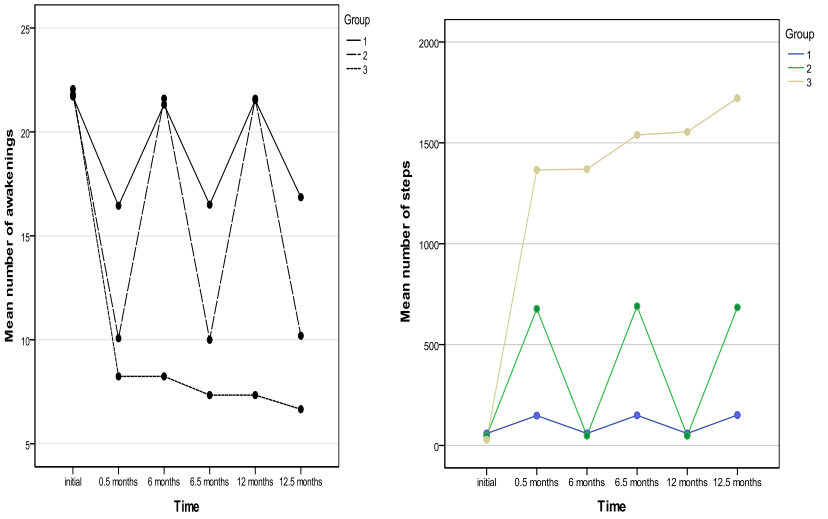
- statistically significant differences between therapies regarding the Lequesne score, $F(2.293)=226.94$, $p<0.001$. Thus, between group 1 and 2 an average difference of 1.92 may be observed between scores, between groups 2 and 3 the difference is 3.87, and between groups 1 and 3 there is a difference of 5.80, all the differences being statistically significant, $p<0.001$. (Graph 1)
- statistically significant differences for the HSQ score between therapies, $F(2.293)=239.51$, $p<0.001$. Thus, between groups 1 and 2 an average score difference of 3.79 may be observed, between groups 2 and 3 the difference is 6.89, and between groups 1 and 3 there is a difference of 10.69, all these differences being statistically significant, $p<0.001$. (Graph 2)
- statistically significant differences between therapies regarding the number of awakenings, $F(2.293)=260.39$, $p<0.001$. Thus, between groups 1 and 2 an average difference of 3.18 may be observed between the number of awakenings, between groups 2 and 3 the difference is 5.89, and between groups 1 and 3 there is a difference of 9.08, all these differences being statistically significant, $p<0.001$. (Graph 3)
- statistically significant differences between therapies regarding the number of steps, $F(2.293)=123.50$, $p<0.001$. Thus, between groups 1 and 2 an average difference of 261.59 may be observed between the number of steps, between

groups 2 and 3 the difference is 897.13, and between groups 1 and 3 the difference is 1158.72, all these differences being statistically significant, p<0.001. (Graph 4)

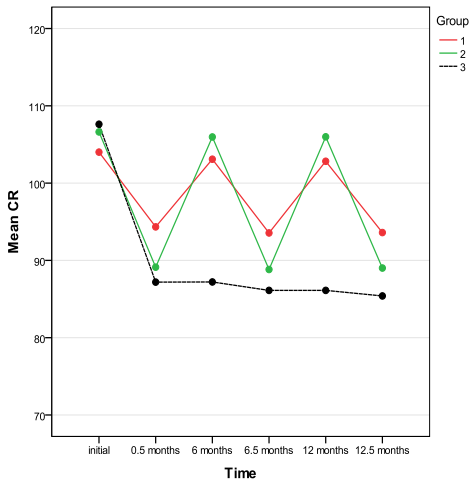
- statistically significant differences of CR between therapies, F(2.293)=103.1, p<0.001. Thus, between groups 1 and 2 an average CR difference of 0.98 may be observed, which is not statistically significant, p>0.05. The other differences, of 7.64 between groups 2 and 3 and of 8.62 between groups 1 and 3, are statistically significant, p<0.001. (Graph 5).



Graph 1-2. Evolution of the average Lequesne score (1) and HSQ (2)



Graph 3-4. Evolution of the number of awakenings/night (3) and steps/day (4) – Actigraph method



Graph 5. Evolution of the average cardiac rate – Actigraph method

Upon all 6 assessments, we found positive and statistically significant correlations between Lequesne scores and HSQ, number of awakenings, CR, and significant but negative correlations with the number of steps.

Upon the assessment at 12.5 months:

- In group 1 we found positive and statistically significant correlations between the Lequesne score and HSQ τ=0.81, p<0.01, number of awakenings τ=0.76, p<0.01, CR τ=0.61, p<0.01, and significant but negative correlations with the number of steps τ=-0.65, p<0.01.
- In group 2 we found positive and statistically significant correlations between the Lequesne score and HSQ τ=0.92 p<0.01, number of awakenings τ=0.88, p<0.01, CR τ=0.75, p<0.01, and significant but negative correlations with the number of steps τ=-0.71, p<0.01.
- In group 3 we found positive and statistically significant correlations between the Lequesne score and HSQ τ=0.95 p<0.01, number of awakenings τ=0.92, p<0.01, CR τ=0.86, p<0.01, and significant but negative correlations with the number of steps τ=-0.86, p<0.01.

Using only data from patients in group 3, we used multiple regression in order to assess the capacity of 6 parameters (age, gender, body mass index (BMI), initial HSQ score, initial number of steps and initial number of awakenings) to predict the Lequesne score at 12.5 months.

Prediction equation

Lequesne score at 12.5 luni = - 47.90 + 0.23 x BMI + 2.08 x initial HSQ

CONCLUSIONS

Global and specific evaluation systems, repeatedly used in the 296 patients, allowed an objective assessment of the clinical, paraclinical and functional status, of disease activity, and last but not least, of the life quality of these patients. The complex evaluation (clinical, paraclinical, functional, life quality assessment) of young, active patients with cronic lumbar sacral pain secondary to lumbar spinal disc herniation is imperative for establishing an adequate therapeutic approach and in assessing its effectiveness, as illustrated by the comparative results obtained by us in dynamics, throughout the three years of study.

In order to early identify the symptoms accompanying lumbar spinal disc herniation in young, active adults, together with complex clinical and paraclinical examinations, other methods, using last generation non-invasive equipments for the early detection of symptoms, such as the Actigraph, become mandatory.

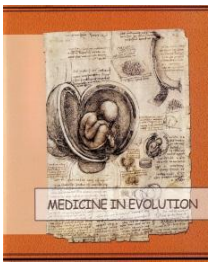
1. The young adult should be made aware of the need to use ergonomic work equipments, but also of healthy lifestyles, including an adequate hygiene and diet regimen to be constantly folowed, as well as quitting sedentarism and maintaining the body weight within normal limits.
2. Preventing lumbar sacral pain secondary to lumbar spinal disc herniation in young, active adults is an extremely important aspect for performing optimal longterm occupational or recreational activities, with multiple advantages.
3. Complex medication, associated to specific medical rehabilitation and to an individualised home-adapted kinetic therapy programme, in the 100 cases of group

3, significantly improves life quality and functionality of these patients, as shown by the progressively favourable evolution of all the assessed parameters, in all cases, even obtaining the decrease/elimination of medication doses.

REFERENCES

1. Lequesne M Mery C et al. Indexes of severity for osteoarthritis of the hip and knee. Scand J Rheumatology. 1987; Supplement 65: 85-89.
2. Lequesne M. Indices of severity and disease activity for osteoarthritis. Seminars in Arthritis and Rheumatism. 1991; 20 (supplement 2): 48-54.
3. Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. J Rheumatol. 1997; 24: 779-781.
4. Lequesne M, Samson M, Ge´ rard P, Me´ ry C. Indices algo-fonctionnels pour le suivi des arthroses de la hanche et du genou. Rev Rhumatisme 1990; 57:32–6.
5. Barry TL, Kaiser KL, Atwood JR., Reliability, validity, and scoring of the Health Status Questionnaire-12 version 2.0., J Nurs Meas. 2007;15(1):24-35.
6. ActiGraph Applications - www.theactigraph.com
7. Pigot, Hélène; Bernard Lefebvre, Jean-Guy Meunier, Brigitte Kerhervé, André Mayers, Sylvain Giroux (2003). The role of intelligent habitats in upholding elders in residence (PDF). Canada: Département de mathématiques et d'informatique, Université de Sherbrooke. Retrieved 2008-01-22.
8. K.Y. Tang, Nicole; G. Harvey, Allison (2004). "Correcting distorted perception of sleep in insomnia: a novel behavioural experiment?". Behaviour Research and Therapy (Elsevier) (42): 27–39.
9. Google Scholar; keyword: actigraph+sleep; 10.3k results as of September 2011
10. Jean-Louis, G., von Gizycki, H., Zizi, F., Spielman, A., Hauri, P., & Taub, H. (1997). The actigraph data analysis software: I. A novel approach to scoring and interpreting sleep–wake activity. Perceptual and Motor Skills, 85, 207–216.

EPIDEMIOLOGICAL ASPECTS OF ACUTE SUBSTANCES ASSOCIATION POISONINGS IN ARAD COUNTY DURING 2000-2004



GLIGOR ŞERBAN[1]

[1]West University, Faculty of Physical Education and Sports, Kinesytherapy Department, Timisoara

ABSTRACT

Acute poisonings are a serious health problem, being responsible for increasing number of hospitals admitted cases.

The aim of this study is to analyze the epidemiological features and the management of acute substances combinations poisoning, both in adults and children, recorded in Arad county during a five years period.

Methods: For this, a retrospective study of such poisoning cases, admitted in Arad County Hospital between 01.01.2000 to 31.12.2004, was done.

Results: In the reported period there were 71 cases of acute poisoning with substances combinations, representing 5.8% of total poisoning (1232 cases), and resulting in an average incidence of 3.040/0000 in that span. Substances combinations poisonings were more than twice as common in males than in females (67.6% and 32.4%) and were mostly voluntary (81.7%), the main association was between drugs and alcohol, chemical substances and alcohol respectively; most poisonings occurred in May (14.3%) and December (12.5%). Treatment of such poisoning has been applied differently depending on patient age, associated pathology, investigations results and present symptoms.

Conclusion: Although these poisonings represent a small proportion of total poisonings, they are an important issue because of their gravity (resulting from the different substances combination) and of their predominant effect on younger ages.

Key words: *substances combination, acute poisoning, epidemiological characteristics*

Correspondence to:

Serban Gligor
MD, PhD, Lecturer
West University, Faculty of Physical Education and Sport, Kinesytherapy Department
Phone: .+40256592.129
Fax: +40256592129
E-mail adress: gligor_serban@yahoo.com

INTRODUCTION

Acute poisonings are serious health problems, medical emergencies which cause a significant increase of hospitalized patients. These poisonings are caused by adsorption of

a high dose of toxic agents or repeated adsorption of small doses over short time causing acute poisonings which in some cases may end with the death of the patient (1,2,3)

A particular category of poisonings are caused by association of substances (drugs, chemicals, alcohol, and mushrooms a.a). In general, the toxic effects of some poisonings are similar in adults and children. However, there are differences in terms of absorption, distribution, metabolism and elimination of these toxic substances. (4)

In adolescents and adults predominate voluntary intoxication, and in children the unintentionally. Substances commonly involved in intoxication in children are household chemicals, medication and plants, with caustics, insecticides, herbicides, dietary supplements, ethnic remedies etc. (4,5)

Poisoning treatment involves supportive care, prevent further absorption of toxic (gastrointestinal decontamination, gastric lavage and administration of activated charcoal, producing vomiting, administration of purgatives a.a), favoring removing toxic, administering antidotes (if it exists). (4)

Often, there is a direct relationship between the amount of toxic consumption and the risk of serious side effects, though, both in adults and especially in children, is difficult to assess the exact toxic dose consumed. (4)

Aim

The aim of this study is to analyze the epidemiological features and the management of acute substances combinations poisoning, both in adults and children, recorded in Arad County during the time period 2000-2004.

MATERIAL AND METHOD

The research was based on a retrospective study of such poisoning cases, admitted in Arad County Hospital, Clinic 1 and the 2 Pediatric Departments between 01.01.2000 to 31.12.2004, was done.

The main criteria for this study was the diagnostic of acute poisoning caused by association of chemicals and a minimum hospitalization for 24 hours.

The clinical studies were based on the observation charts of patients with acute poisonings caused by substance association.

Statistical method

The statistics were based on the observation charts with the EPIINFO software, version 6.0 used by the Center of Disease Control and Prevention from Atlanta, USA applied to medical statistics. Also the chi2 test was used.

RESULTS AND DISCUSSION

Osteosclerosis was possible and For the above mentioned time frame, 71 cases of acute poisoning caused by substances association were recorded, representing 5,8% of the total cases of acute poisoning (1232), the average occurrence being 3.04 0/0000. This kind of poisonings occurred twice as frequent in male subjects compared to female subjects (table I), the gender ration male/female subjects being 1/3 in adults and 3.5/1 in children.

Table I. Occurrence of acute poisonings caused by association of substances on genders

Gender	Adults			Children			Total		
	Nr.	%	‰	Nr.	%	‰	Nr.	%	‰
Female subjects	16	25.8	1.64	7	77.8	2.95	23	32.4	1.90
Male Subjects	46	74.2	5.26	2	22.2	0.80	48	67.6	4.27
	62	**87.3**	**3.35**	**9**	**12.7**	**1.85**	**71**	**5.8**	**3.04**

The occurrence of acute poisonings caused by substances association was significantly higher in adults (3.35%000) than in children (1.85 %000), twice more frequent in male subjects (4.27%000) than in female subjects (1.9 %000). ($p<0.001$).

In adults the occurrence was 3.2 times higher in male subjects (5.26%000) than in female subjects (1.64%000) ($p<0.02$) and in children the occurrence was 3.7 times higher in girls than boys (2.950/0000, compared to 0.800/0000) ($p<0.001$).

The distribution of these intoxications according to the living environment showed a ratio urban/rural of 2/1, this ration being the same in adult as well as in children subjects (table II). The occurrence of these poisonings were 1.8 times more frequent in urban cases than in rural ones ($p<0.02$).

The occurrence of these intoxications in rural children was half than in adults subjects and in urban cases the occurrence was 1.6 times less frequent ($p<0.05$).

It was found that almost 60% of these cases occurred at the age of 18-47 years (59.1%). The highest occurrence of the acute poisonings involving substances associations was at the age 15-17 years followed by the age group 28-37 years (table III).

Most of these cases occurred after voluntary intoxications (81.7%) and not by accidental exposure to substances (only 18.3%). In adults the voluntary ingestion of substances was 4.2 more frequent than the accidental exposures and in children the voluntary exposures were 8 times more frequent than the accidental ones (table IV).

The associated pathology occurred at 65 patients (91.5%) of the cases of poisonings caused by association of substances; the morbidity cases were 93.5% in adults cases and 77.8% in children cases.

In our research series the most frequent case was the digestive pathology (40%) and the neuropsychiatric ones (36.9%). The digestive pathology was more frequent in adults and the neuropsychiatric one was more frequent in children.

Almost 55% of the total poisonings were caused by association of drugs with alcohol (54.9%) , both in adults cases (54.8%) and children cases (55.6%) (table V).

Over one quarter of the total patients (26.8%) associated chemicals with alcohol (27.4% in adult cases and 22.2% in children cases) and only a small percentage of patients associated drugs with chemicals (11.3% adults and 11.1% children) (table V).

Almost 80% of the patients arrived at the hospital in the first 6 hours from the ingestion of the substances 31.1% arrived in the first 3 hours. In case of children 71.4% were brought to the hospital in the first 3 hours after the ingestion of the substances and only 23.7% of the adults were brought in the first 3 hours (table VI).

The occurrence of poisonings caused by association of chemicals had a sinusoidal distribution, the most frequent being recorded in June (14.3%) and December (12.5%) (table VII).

The occurrence of these poisonings was almost equal in the 4 seasons (table VIII).

Table II. Occurrence of acute poisonings caused by substances association according to the living environment

Living environment	Adults			Children			Total		
	Nr.	%	‰	Nr.	%	‰	Nr.	%	‰
Rural	21	33.9	2.41	3	33.3	1.20	24	33.8	2.14
Urban	41	66.1	4.19	6	66.7	2.54	47	66.2	3.87

Table III. Occurrence of acute poisonings cases caused by substances association on age

	Age group	Nr.	%	‰
Children	0-6 months	-	-	-
	6 months-1 year	-	-	-
	1-3 years	-	-	-
	4-6 years	-	-	-
	7-10 years	1	1.4	0.97
	11-14 years	3	4.2	2.39
	15-17 years	5	7.0	5.15
Adults	18-27 years	14	19.7	3.99
	28-37 years	15	21.1	4.21
	38-47 years	13	18.3	4.13
	48-57 years	11	15.5	3.63
	58-67 years	5	7.0	2.06
	68-77 years	4	5.6	2.01
	>77 years	-	-	-

Table IV. Type of acute poisonings caused by substances association

Type	Adults			Children			Total		
	Nr.	%	‰	Nr.	%	‰	Nr.	%	‰
Accidental	12	19.4	0.65	1	11.1	0.21	13	18.3	0.56
Voluntary	50	80.6	2.70	8	88.9	1.65	58	81.7	2.48

Table V. Occurence depending on substances

Asociated substances	Adulți		Copii		Total	
	Nr.	%	Nr.	%	Nr.	%
Alcohol + i.v. air	-	-	1	11.1	1	1.4
Mushrooms+alcohol	4	6.5	-	-	4	5.6
Drugs + alcohol	34	54.8	5	55.6	39	54.9
Drugs + chemicals	7	11.3	1	11.1	8	11.3
Chemicals + alcohol	17	27.4	2	22.2	19	26.8

Table VI. Hospitalization time after ingestion

Hospitalization time	Adults		Children		Total	
	Nr.	%	Nr.	%	Nr.	%
<1h	3	7.9	1	14.3	4	8.9
1-3h	6	15.8	4	57.1	10	22.2
3-6h	20	52.6	1	14.3	21	46.7
6-12h	3	7.9	0	0,0	3	6.7
12-24h	5	13.2	0	0,0	5	11.1
>24h	1	2.6	1	14.3	2	4.4
	38	**61.3**	**7**	**77.8**	**45**	**63.4**

Table VII. Monthly occurrence of acute poisonings caused by substances association

Month	Adults		Children		Total	
	Nr.	%	Nr.	%	Nr.	%
Ianuary	5	10.2	2	28.6	7	12.5

Month	Adults		Children		Total	
	Nr.	%	Nr.	%	Nr.	%
February	3	6.1	0	0.0	3	5.4
March	5	10.2	0	0.0	5	8.9
Aprilie	3	6.1	0	0.0	3	5.4
May	7	14.3	1	14.3	8	14.3
June	4	8.2	1	14.3	5	8.9
July	3	6.1	0	0.0	3	5.4
August	5	10.2	1	14.3	6	10.7
September	1	2.0	0	0.0	1	1.8
Octomber	4	8.2	0	0.0	4	7.1
November	5	10.2	1	14.3	6	10.7
December	4	8.2	1	14.3	5	8.9
	49		**7**		**56**	

Table VIII. Occurrence according to the season

Season	Adults		Children		Total	
	Nr.	%	Nr.	%	Nr.	%
Winter	12	24.5	3	42.9	15	26.8
Spring	15	30.6	1	14.3	16	28.6
Summer	12	24.5	2	28.6	14	25.0
Autumn	10	20.4	1	14.3	11	19.6

The most frequent symptoms were the neuropsychiatric ones (74.6%) and the digestive ones (56.3%) followed by cardiovascular symptoms (465%) and coetaneous symptoms (45.1%). In adults the most frequent symptoms were the neuropsychiatric symptoms (71%) followed by cardiovascular symptoms (50%) and digestive symptoms (50%). In children 77.8% skin symptoms were recorded.

The treatment for acute poisonings was chosen according to the pathology, age, investigation and tests results and symptoms. (3)

In children, beside the symptomatic treatment (with anticoagulants – 22%, sedatives 22.2%, hepatoprotectives 22.2% and NSAI-22.2% and vitamins 22.2%) hydro electrolitical balance was induced (100%), forced dieresis (77.8%), stomach cleaning (44.4%), and cardio-respiratory rescue (6.5%) was used.

Antidote administration was done for 10 adult patients (16.1%), psychiatric therapy was necessary for 24.2% of adults and 11.1% of children. The average hospitalization period was significantly higher in adults than in children ($p<0.05$) (table IX).

Table IX. Average hospitalization period

	Adults	Children	Total
Period (days)	1-18	1-4	1-18
AHP	3.3 ± 1.4	2.2 ± 1.0	3.1 ± 1.3

DISCUSSIONS

In our case, the majority of intoxication were voluntary (81.7%), for suicidal purposes, mainly by the association of alcohol with various drugs or chemicals. This is explained by the higher incidence of voluntary intoxication in adults than children.

Similar results (78.94% poisonings) in terms of the proportion of voluntary intoxication in adults has obtained Özköse Z. (6), who made a one year retrospective study on acute poisoning cases admitted to the emergency center at University

Hospital in Ankara, Turkey. In our study the majority (60%) of patients were aged between 18-47 years. Similar results, but with a preponderance of teenagers and young adults have had Cengiz M. et al. (56.9% aged between 15-24 years) and Özköse Z. (63.6% aged under 25 years). (6,7) The study by Chen F. et al. (8) on epidemiology and characteristics of patients with acute intoxication treated in Emergency Center of Fujian Provincial Hospital, China, in 2004-2009, showed that most patients (76.39%) were aged between 18 and 40 years. In these studies, the major cause of acute poisoning in adults were drug overdoses (analgesics respectively benzodiazepines, antidepressants and analgesics). Second place was inhaling gas (17.6% in Özköse Z. study) or agricultural chemicals - insecticides, pesticides, rodendicides (37.2% in Cengiz M. study). (6,7) Leading cause of acute poisonings in Chen F. et al. study was alcohol poisoning (54.55%), followed by medication poisoning (25.95%) and pesticide poisoning (5.65%). (8)

As in our study (patient ratio from urban area/rural area - 2:1), in the 3-year retrospective study (2002-2005) conducted by Cengiz M. et al. on acute poisoning cases admitted to ICU-Harran University Hospital, Turkey, most patients (81.3%) were from urban area. Unlike studies of Özköse Z. and Cengiz M., in our study, the majority of adult patients with acute substances association poisonings (3.35%000 vs 1.85 %000, $p<0.02$) were male (6,7); in the case of acute poisoning in children, the majority of patients were female.

CONCLUSIONS

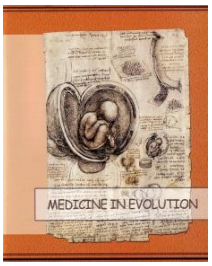
- Acute poisonings involving association of substances is a small part of the total poisonings cases but it is a major pathology problem because of the complex symptoms and possibilities
- The acute poisonings caused by the association of substances was 3.040/0000, higher in male subjects (compared to female subjects) and higher in urban cases than in rural ones; also the occurrence of these cases was 1.8 times more frequent in adults than in children
- Most of these poisonings occurred voluntarily, the main causes being the association of drugs with alcohol or other chemicals with alcohol
- The distribution of the occurrence is almost equal during the 4 seasons
- The main symptoms are neuropsychiatric, digestives (both in adults and children) and cardiovascular symptoms
- The main treatment methods involved both in adults and children cases, restablishing the hydro-electrolitical balances, stomach cleaning, forced dieresis, activated carbon administration and symptomatic treatment.

REFERENCES

1. Bălălău D, Baconi D. - *Toxicologie generală*, Ed. Tehnoplast Company SRL, Bucureşti, 2005
2. Ab Rahman AF - *Drug and chemical poisoning admissions at a teaching hospital in Malaysia*. Hum. Exp. Toxicol. 2002; 21: 377-381.
3. Ramisetty-Mikler S, Mains D, Rene A. *Poisoning hospitalizations among Texas adolescents. Age and gender differences in intentional and unintentional injury.* Tex. Med., 2005; 101(5): 64-71
4. Meyer S., Eddleston M., Bailey B., et al. – *Unintentional household poisoning in children*, Klin. Pädiatr., 2007, 219: 254-270
5. Watson WA, Litovitz TL, Rodgers GC, et al. – *2004 Annual report of the*

American Association of Poison Control Centers Toxic Exposure Surveillance System, Am. J. Emerg. Med., 2005, 23: 589-666

6. Özköse Z. – *Etiological and demographical characteristics of acute adult poisoning in Ankara, Turkey*, Human & Experimental Toxicology, 1999, 18(10): 614-618
7. Cengiz M., Baysal Z., Ganidagli S., Altindag A. – *Characteristics of poisoning cases in adult intensive care unit in Sanliurfa, Turkey*, Saudi Med. J., 2006, 27(4): 497-502
8. Chen F., Wen J-p, Wang X-p, et al. – *Epidemiology and characteristics of acute poisoning treated at an emergency center*, World J. Emerg. Med., 2010, 1(2): 154-156



IMPACT OF MULTIPLE ASSOCIATED PATHOLOGIES ON THE COMPLEX SPECIFIC AND INTERDISCIPLINARY APPROACH OF INFLAMMATORY RHEUMATIC DISEASES

RADU PETROMAN[1], DAN NEMES[1,2], MIHAI DRAGOI[1,2]; DANIEL POPA[1,2]

[1]University of Medicine and Pharmacy „Victor Babes" Timisoara
[2]City Emergency Hospital, Timisoara, România – Department of Rehabilitation, Physical Medicine, Balneology, Rheumatology

ABSTRACT

Aim and objectives: Implementing an interdisciplinary monitoring protocol for the identification and surveillance of complications/co-morbidities affecting the treatment and evolution of early diagnosed and therapeutically approached rheumatic diseases, in order to decrease the influence of the first upon the manner treatment is conducted and, implicitely, on the prognosis of the main disease.

Material and method: A number of 203 early RA, AS and PsA patients were evaluated, on whom a monitoring protocol was implemented regarding the activity of the main disease, pain and the general health status, as well as an interdisciplinary monitoring (regarding the occurence of possible complications and/or aggravating associated pathology).

Results: In the 190 subjects who remained in the study, the associated pathology influenced in various manners the evolution of scores monitoring the level of disease activity and the life quality of these patients with RA, AS and PsA, those with associated cardio-respiratory diseases still presenting the lowest level of improvement in all scores, regardless of the main rheumatic disease.

Conclusions: Novel positive diagnostic criteria and the careful and early interdisciplinary monitoring using a standardised protocol, allowed the implementation of an effective treatment, as shown by the effective control of the main disease, with the improvement of life quality on the concerned subjects and a lower number of lately diagnosed comorbidities, which might have by themselves aggravated the general prognosis of these patients, thus increasing the difficulty of implementing a correct treatment.

Key words: *multiple associated pathology, early interdisciplinary approach, standardised protocol*

Correspondence to:

Dr. Radu Petroman, PhD student
Address: "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania
Phone: 0720036805
E-mail address: petromanradu@yahoo.com

INTRODUCTION

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are long term evolving rheumatic inflammatory diseases, marked by certain complications occurring during activity periods and by various co-morbidities associated to the main disease (cardio-vascular, respiratory, gastro-entero-hepatic, metabolic, etc.) already existent or highly probable during the evolution of the disease. These, in their turn, influence the response to treatment as well as the prognosis of the subjects in question, increasing by themselves the morbidity and mortality rates, as well as the difficulty in establishing an adequate therapeutic control over the main disease, this involving a severe influence upon life quality and important socio-economic costs, thus justifying to monitor these patients as completely as possible.

Aim and objectives

The study aims to correct the deficiencies in the interdisciplinary approach regarding the identification and surveillance of complications/co-morbidities which affect the treatment and evolution of early diagnosed and therapeutically approached RA, AS and PsA and to reduce the degree in which associated multiple pathology affects the course of a complex treatment (medication and rehabilitation) and implicitly the prognosis of these rheumatic inflammatory diseases, also pursuing the implementation of a monitoring chart, as complete as possible, for these subjects, containing a clear protocol for following up disease activity and the patient's life quality.

MATERIAL AND METHOD

During the period between January 2010 – July 2013, a total of 203 patients with the above mentioned rheumatic inflammatory diseases were monitored, these patients being early approached therapeutically (hygiene-diet and life regimens, orthopedic hygiene measures, 10 days courses of complex rehabilitation treatment, periodically instituted, as well as personalized medication – symptomatic, DMARD and biologic – with staged implementation depending on the stage of the main disease and on the presence and severity of associated pathology, in concordance with present consensus therapeutic protocols). In order to establish the early positive diagnosis the new ACR – EULAR (American College of Rheumatology - European League Against Rheumatism) diagnostic criteria of 2010 were used for early defined RA [1], and the ASAS (Assessment of SpondyloArthritis International Society) criteria of 2009 for early SA and PsA, respectively [2,3].

After obtaining the informed consent at the moment of diagnosis, each patient was interdisciplinary and rheumatologically monitored for 24 months, recording all complications and co-morbidities detected throughout the entire follow up period, these being mentioned upon the 5 overall assessments, the first being recorded at the time of diagnosis, and the other 4 at 6 month intervals each. On these assessments, the evolution of laboratory parameters, disease activity indexes (DAS28 - Disease Activity Score 28 [4] - in the case of RA, and BASDAI - Bath Ankylosing Spondylitis Disease Activity Index [5] - in the case of AS and PsA, respectively), the EQ-5D-5L (EuroQuol) general health index [6] (considered a direct index of life quality and an indirect index for the assessment of disease activity, containing answers on five severity

levels to questions on mobility, self-care capacity, ability to perform daily life activities, pain/discomfort, anxiety/depression) and the visual analog scale - VAS [7] - which measures the intensity of pain experienced by the patient (from 0 = no pain to 10 = maximal possible pain, as an average between the values provided by physician and patient), were also evaluated, the therapeutic approach being adjusted depending on all these factors.

Patients who passed away during the monitoring period were excluded from the study, as were those who did not attend each of the 5 evaluations, and those subjects who did not adhere to the therapeutic protocol according to the recommendations made by the physician.

The most important complications and/ or co-morbidities of RA, AS and PsA were included into statistical analysis, these being included into groups (spectra) of associated pathology. Thus, spectrum 1 (cardio-circulatory) included high blood pressure, ischemic heart disease, congestive heart failure +/- events such as myocardial infarction, pericarditis, stroke and peripheral vascular disease, spectrum 2 (respiratory) contains bronchial asthma, chronic obstructive pulmonary disease and other respiratory diseases – sleep apnea, interstitial fibrosis, pleurisy, etc., and spectrum 4 included other diseases than cardio-circulatory or respiratory (digestive, hepatic, renal, neurological, ophtalmologic, as well as associations of previously mentioned autoimmune rheumatic diseases with hyperlipidemia, obesity, type 2 diabetes mellitus, and osteoporosis). Regarding spectrum 3 (cardio-respiratory), it reunites patients with associated pathology contained both by spectrum 1 and spectrum 2.

The statistical analysis of data was performed using the MedCalc programme, version 12.4.0, with further data processing by the STATA programme, version 9.2. The Student and paired T tests were used, values of $p < 0.05$ being considered as statistically significant.

RESULTS

Of the total of 203 monitored patients, data from 190 cases could be correctly collected and interpreted, including subjects of both genders (63 men and 127 women), coming both from urban (133) and rural (57) areas, aged between 17 and 73 years, of whom 93 had RA, 57 AS and 40 PsA, respectively.

After the analysis of cumulative data from the moment of diagnosis to the end of the assessment period, we detected the following numeric and percent values (adjusted to one decimal digit) representing the weight of complications/co-morbidities detected in the group followed up by us, separated in groups of associated multiple pathology, in the three sub-groups of analysed rheumatic inflammatory diseases, namely RA, AS and PsA, the results being presented below, in figure 1.

S	RA	AS	PsA
0	N = 27 (29 %)	N = 18 (31.6 %)	N = 8 (20 %)
1	N = 37 (39.8 %)	N = 16 (28.1 %)	N = 15 (35.7 %)
2	N = 4 (4.3 %)	N = 6 (10.5 %)	N = 3 (7.5 %)
3	N = 9 (9.7 %)	N = 4 (7 %)	N = 4 (10 %)
4	N = 16 (17.2 %)	N = 13 (22.8 %)	N = 10 (25 %)
Total	N = 93 (100%)	N = 57 (100%)	N = 40 (100%)

Figure 1: Evolution of numeric values (N = number of patients) and percent values (%) representing the weight of complications/co-morbidities detected in the group followed up by us, depending on S = spectrum of associated pathology (0,1,2,3,4), throughout the 24 months period of treatment and monitoring, for each of the inflammatory rheumatic disease (RA, AS, PsA)

Regarding the changes in the used scores, it may be stated that these had an overall progressively decreasing character throughout evaluations, the best evolution being observed in the sub-groups of patients without multiple associated pathology (spectrum 0), and the most severe impairment occurring in patients of the sub-group with associated cardio-respiratory pathology (spectrum 3) in the 3 analysed rheumatic diseases, even though all the sub-groups included into the study started from sensitively similar average scores at the moment of diagnosis.

There were also certain particularities of the 3 rheumatic diseases in terms of evolution of the other 3 sub-groups of patients, i.e. those with associated cardio-circulatory (spectrum 1), pulmonary (respiratory) (spectrum 2) and with other co-morbidities than cardio-circulatory and respiratory (spectrum 4) diseases. Thus, in the case of AR, the best evolution of the disease index (DAS28) at the end of the 24 months of treatment and monitoring was observed in subjects with pulmonary impairment (spectrum 2) with an average score of 3.08, followed by those with other diseases associated to the main disease, excepting cardio-respiratory diseases (spectrum 4) with a score of 3.10, the weakest control of the main disease being observed in the sub-group with associated cardio-circulatory pathology (final average of 3.29), as shown in figure 2. Given the different specificities of AS patients, they evolved worse in the sub-group with associated respiratory pathology (average final BASDAI = 2.91), with slightly improved values in those with cardio-circulatory impairment (final average value = 2.83) and significantly better in subjects included in spectrum 4 (final average value = 2.65) – figure 3. Regarding PsA, with the exception of patients in spectra 0 and 3 who evolved similarly to those in the respective groups of AS and RA patients, the weakest control of the main disease was observed in the sub-group with associated cardio-circulatory pathology (BASDAI final average value of 2.80), with a comparatively modest improvement in the sub-group with respiratory pathology (final average value of 2.73) and a more significant one in the case of subjects with other associated pathologies than cardio-respiratory diseases (spectrum 4) with a final average of 2.61 – figure 4.

S	Moment 1			Moment 2			Moment 3			Moment 4			Moment 5		
	DAS	EQ-5D	VAS	DAS	EQ-5D	VAS	DAS	EQ-5D	VAS	DAS	EQ-5D	VAS	DAS	EQ-5D	VAS
0	7.36	5.74	6.67	6.48	4.70	5.86	6.17	4.33	5.69	4.44	3.22	4.20	2.79	1.44	2.04
1	7.39	5.62	6.75	6.65	4.46	5.75	6.15	4.21	5.43	5.08	3.59	4.58	3.29	1.83	2.71
2	7.38	6.00	7.12	6.81	5.00	6.52	6.42	5.00	6.17	4.87	3.25	4.55	3.08	1.75	2.52
3	7.40	6.33	7.24	6.84	5.22	6.35	6.52	5.00	6.05	5.65	4.66	5.22	3.50	2.55	3.16
4	7.38	5.75	7.01	6.47	4.56	6.18	6.08	4.18	5.73	5.03	3.75	4.68	3.10	1.93	2.71

Figure 2: Evolution of average values of DAS28, EQ-5D and VAS scores upon the 5 monitoring moments (every 6 months) starting from diagnosis (Moment 1) to the end of the evaluation period (Moment 5), depending on S = spectrum of associated pathology (0, 1, 2, 3, 4) in the group diagnosed with AR

S	Moment 1			Moment 2			Moment 3			Moment 4			Moment 5		
	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS
0	6.90	5.55	6.76	6.29	4.55	6.02	5.88	4.38	5.76	4.50	3.44	4.59	2.48	1.38	2.43
1	6.96	5.62	6.93	6.28	4.62	6.13	5.93	4.43	5.84	4.75	3.50	4.55	2.83	1.75	2.66
2	6.97	5.00	6.75	6.34	3.83	5.88	5.94	4.16	5.60	4.42	3.66	4.30	2.91	1.66	2.86
3	7.00	6.00	6.85	6.60	5.00	5.70	6.30	5.00	5.37	4.90	4.00	4.52	3.32	2.00	3.15
4	6.93	5.92	6.89	6.32	5.00	6.07	5.98	5.00	5.87	3.95	3.23	4.01	2.65	1.61	2.56

Figure 3:Evolution of average values of BASDAI, EQ-5D and VAS scores upon the 5 monitoring moments (every 6 months) starting from diagnosis (Moment 1) to the end of the evaluation period (Moment 5), depending on S = spectrum of associated pathology (0, 1, 2, 3, 4) in the group diagnosed with AS

S	Moment 1			Moment 2			Moment 3			Moment 4			Moment 5		
	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS	BAS DAI	EQ-5D	VAS
0	6.52	5.25	6.57	5.75	4.75	5.72	5.25	4.12	4.96	4.39	3.50	4.12	2.38	2.00	2.33
1	6.56	5.40	6.79	5.82	5.00	5.76	5.19	4.53	5.17	4.42	3.86	4.26	2.80	2.46	2.64
2	6.55	5.33	6.66	5.6	4.66	5.56	4.60	4.33	4.66	3.93	3.66	4.00	2.73	2.33	2.50
3	6.60	5.25	6.85	5.62	5.00	5.72	4.66	4.50	4.77	4.25	4.25	4.32	3.00	2.50	2.82
4	6.56	5.10	6.75	5.61	4.50	5.87	4.93	3.90	5.09	3.82	3.20	3.81	2.61	2.20	2.56

Figure 4 Evolution of average values of BASDAI, EQ-5D and VAS scores upon the 5 monitoring moments (every 6 months) starting from diagnosis (Moment 1) to the end of the evaluation period (Moment 5), depending on S = spectrum of associated pathology (0, 1, 2, 3, 4) in the group diagnosed with PsA:

The results are statistically significant ($p < 0.001$) in all the studied rheumatic diseases, correlations being recorded (correlation coefficient = $r > 0.50$) between the evolution of disease activity scores (DAS28, and BASDAI, respectively) and VAS scale, as well as with EQ-5D, especially in AS ($r = 0.52$) and PsA($r = 0.68$).

DISCUSSIONS

Even if genetic factors determining the occurrence of co-morbidities and of certain complications could not be controlled, and the influence on environmental triggering factors was neglectable, an important decrease may be observed in the prevalence (incidence) of complications/co-morbidities, in our group of patients (values in figure 1) as

compared to literature data [8, 9, 10], most probably due to the early diagnosis and interdisciplinary approach, before the alteration of these patients' general state of health.

Different decreasing evolutions of the scores recording the activity level of the rheumatic disease and life quality in these patients were observed, despite the fact that these started from approximately equal values at the moment of diagnosis, the most prominent decrease being visible in patients without co-morbidities (spectrum 0) of the three groups – RA, AS and PsA – the complex treatment applied leading to the best results, due to it being wisely conducted, without influence from associated multiple pathology. Subjects with associated cardio-respiratory pathology at any moment after the diagnosis (spectrum 3) had a lower improvement in all scores calculated throughout the evaluations, which leads to the idea that this type of multiple pathology most severely influenced the capacity to implement the rehabilitation treatment and medication, with a lower control of the main disease and a worse medium and long term prognosis.

We state the necessity and we propose the use of the above mentioned patient approach algorithm with the data to be entered in an individual follow up and treatment chart, justified by the fact it offers the practitioner a more accurate score including all the health problems of the patient, thus facilitating a improved overall evaluation and a better therapeutic approach of all his/her diseases.

This chart, initiated on the date of the positive diagnosis and updated every 6 months, will include the diagnosis (clinical, staged, functional) and the treatment of the main disease, values of disease activity indexes (DAS28 [4], in the case of AR and BASDAI [5] for AS and PsA, respectively), general state of health index EQ-5D-5L [6] and the pain score as experienced by the patient (VAS) [7], as well as complications and co-morbidities, presented in detail in terms of staging and therapeutic approach. The information will be made available for the general practitioner, treating physician and for the other specialists involved, the therapeutic strategy being adjusted after a thorough analysis of all these factors, in order to obtain the best possible control of the main disease and co-morbidities, avoiding unwanted interactions.

Also, the careful screening for the early detection of complications and co-morbidities allows their early and effective therapeutic approach, decreasing their influence on the evolution and treatment of the main disease, as well as on the overall impairment of the patient's life quality.

CONCLUSIONS

The early diagnosis and focused therapeutic approach, as well as the focused and rapid interdisciplinary clinical-biological and imaging investigation, determined a good control on the activity of the rheumatic disease, reflected by the progressively decreasing results of evaluation scores (DAS28 [4], and BASDAI [5], respectively), also correlated to a decrease/elimination of painful stress/experienced pain factor (decrease indicated by the VAS scale [7]), even in cases without early established aggressive medication (especially biological) thus creating the possibility to importantly decrease the unwanted side effects of medication.

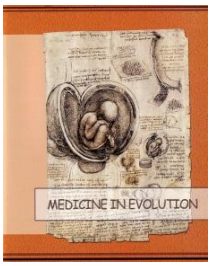
Last but not least, an improvement in the life quality of these patients has been observed (as demonstrated by the gradual decrease of cumulative values of the EQ-5D score [6]), also due to the decrease in

the number of co-morbidities and late diagnosed complications, in advanced stages, which might have aggravated by themselves the prognosis of these patients, also increasing the effort to control the main disease by medication and rehabilitation treatment.

REFERENCES

1. Aletaha D, Neogi T, Silman SJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*.2010;62(9): 2569-2581.
2. Rudwaleit M, van der Heijde D, et al. The development of Assessment of SpondyloArthritis International Society(ASAS) classification criteria for axial spondyloarthritis(Part II): validation and final selection. Annals of Rheumatic Diseases 2009; 68: 777 – 783.
3. Sieper J., Braun J. Ankylosing Spondylitis in clinical practice. Ed. Springer-Verlag London Limited . 2011. p18-96
4. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38:44–8.
5. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994 Dec;21(12):2286-91
6. Rabin, R., & de Charro, F. EQ-5D: a measure of health status from the EuroQol Group. Annals of Medicine, 2001, 33: 337–343
7. Collins S., Moore R., McQuay H. The visual analogue pain intensity scale: what is moderate pain in millimeters? Pain 1997; 72:95-7
8. Norton S, Koduri G, Nikiphorou E et al. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Oxford Journal of Rheumatology 2013; 52 : 99-110
9. Kang J-H, Chen Y-H, Lin H-C. Comorbidity profiles among patients with ankylosing spondylitis: A nationwide population-based study. Annals of Rheumatic Diseases 2010; 69: 1165 – 1168
10. Husted J A, Thavaneswaran A, Chandran V et al. CardioVAScular and other comorbidities in patients with psoriatic arthritis: A comparison with patients with psoriasis. Arthritis Care & Research, December 2011, Vol.63, No. 12, pp 1729-1735

CROSS-SECTIONAL SURVEY ON THE INFLUENCE OF SUGARS CONSUMPTION ON DMFT SCORE



DENIS ȘERBAN[1], ANCUȚA BANU[2], COSTELA ȘERBAN[3], IOANA TUȚĂ-SAS[4], BRIGITHA VLAICU[4]

[1] University of Medicine and Pharmacy Timișoara, Department of Microbiology
[2] Clinical Emergency City Hospital Timișoara, Department of Oro-Maxilo-Facial Clinic
[3] Statistică Medicală Dr. Șerban Freelance
[4] University of Medicine and Pharmacy Timișoara, Department of Hygiene

ABSTRACT

The scope of this paper is to analyze the contribution of frequency of sugars consumption to the burden of oral health pathologies.

Material and method WHO STEPS questionnaire for oral health was applied to our study group that included 80 patients. As measures of oral health we used DMFT score.

Results and conclusions We found a relationship between high number of sugar teaspoons consumed per day and high frequency of sweets intake with the measures of oral health.

Key words: *sweets, oral health, DMFT*

Correspondence to:

Denis Șerban
MD, PhD student
University of Medicine and Pharmacy "Victor Babes"Timisoara, Department of Microbiology
Adress: 16 Victor Babes Str, 1st floor, Timisoara, Romania
Phone: +40723.169.089
E-mail address: denis.serban@umft.ro

INTRODUCTION

The high quantity and high frequency of consumption of sugars has been related to oral pathologies such as dental cavities. Although dental pathologies are not directly life-threatening, they have a major contribution to quality of life with impact on self-esteem, eating and speaking ability. Dental decay can evolve to tooth loss which reduces the ability to eat and to socialize [1-3].

Dental caries occur because of demineralization of enamel and dentine by organic acids formed by bacteria in dental plaque through the anaerobic metabolism of sugars derived from the diet [4].

The scope of this paper is to analyze the contribution of frequency of sugars consumption to the burden of oral health pathologies, quantified as DMFT score (decayed, missing filled teeth) as calculated by dentists in a group of patients with a CI over 1.

MATERIAL AND METHODS

The study group included 80 patients selected in a prior visit that had a calculus index (CI) over 1, as calculated by dentist. Patients responded to a questionnaire based on the WHO STEPS questionnaire STEPwise approach to surveillance (STEPS) for oral health, developed by the WHO programme for oral health [5]. For this article we used data referring to the frequency of sweets consumption and the number of sugar teaspoons used per day to sweeten tea and coffee. The prevalence of dental caries was assessed using WHO criteria and the calculated as DMFT score for each tooth [6].

Patients were included after they expressed their consent, and the study was performed respecting the Declaration of Helsinki.

Data were processed using IMB SPSS version 18 (2010). For the comparisons of ordinal and non-parametric data we used Kruskal-Wallis and Mann-Whitney tests and for correlations we used Kendall test. For the prediction of DMFT score we have used hierarchal multiple regression. The level of statistical significance was set at 0.05, unless otherwise specified, after applying the Bonferroni correction.

RESULTS

Females represented 52.5% of total study population. Age range was between 20 and 65 years. Mean group age is 42.74 +/- 12.38 years, with median at 45 years. Mean DMFT score for the whole group was 21.3 +/- 4.94, with a minimum of 9 and a maximum of 28.

The mean number of teaspoons of sugar consumed per day was 4.3 teaspoons with a SD of 4.2. Correlation between DMFT score and the number of teaspoons of sugar consumed per day was positive and statistical significant $\tau=0.343$, $p<0.001$, $r2=0.12$, indicating a small size association (Figure 1).

15.0% (12) of the responders indicated a frequency of consumption for sweets of 2 or more times per day, and 33.8% (27) eat sweets one time per day. The rest of the patients indicated a less frequent consumption: 26.3% (21) consume sweets 4-6 times per week, 13.8% (11) consume sweets 1-3 times per week and 11.3% (9) declare non-consumption. Significant differences were found between mean DMFT score

among sweets frequency consumption groups, H(4)=17.03, p<0.01. We investigated further, applying the Mann-Whitney test and Bonferroni correction, though the level of significance was set to 0.016. Significant differences were found between the group that consumes 2 or more times per day when compared to the group that consumes sweets 4-6 times per week or never U=61.5, z=-2.42, p<0.01 and respective between those that consume once a day when compared to those that consume 1-3 times per week or seldom U=71.5, z=-2.48, p<0.01. The rest of the differences are not statistically significant, p>0.016 (Figure 2).

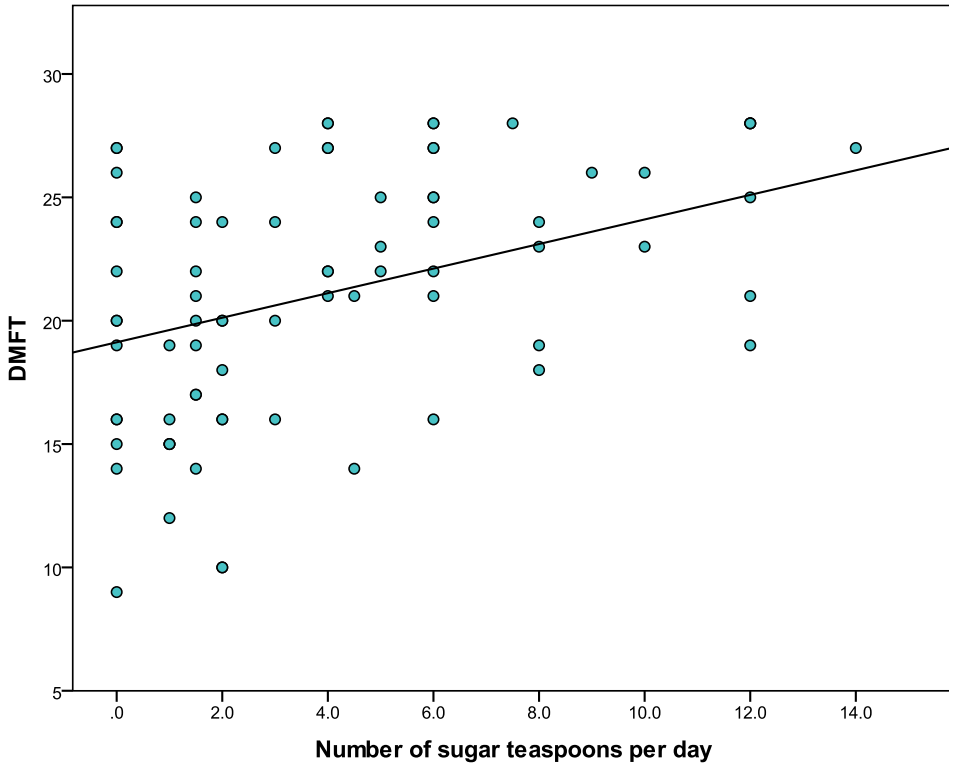


Figure 1. Correlation between the number of sugar teaspoons consumed per day with the DMFT score

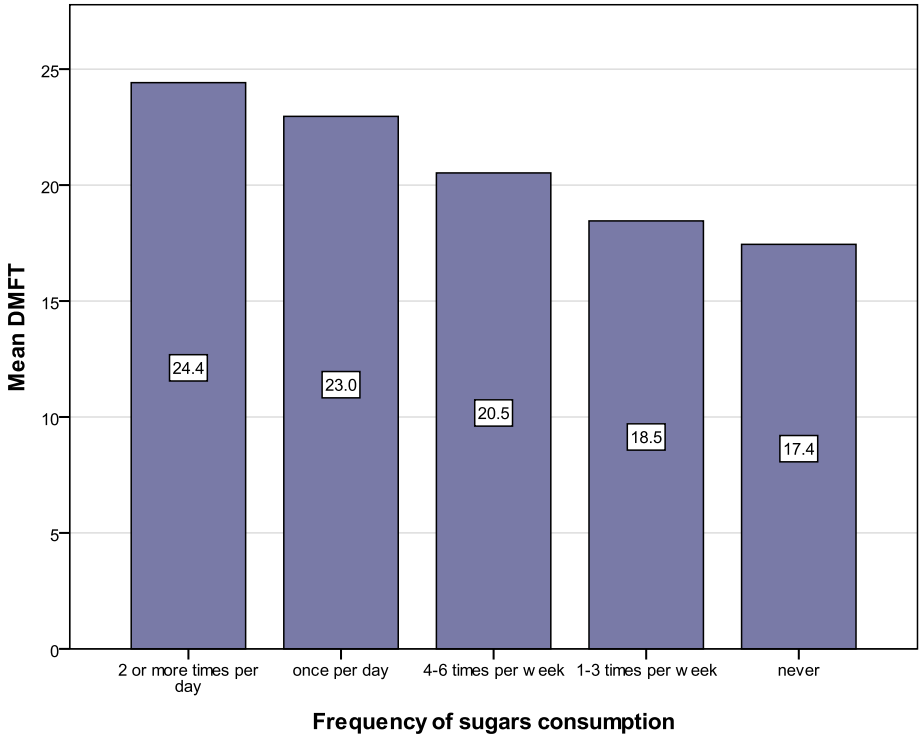


Figure 2. The distribution of mean DMFT score with the frequency of sugars consumptio

Multiple hierarchical regression was used to assess the ability of 2 measures (the frequency of sweets consumption and the number of sugar teaspoons) to predict the DMFT score, after controlling for the influence of total gender and age. Preliminary analyses were conducted in order to ensure no violation of the assumptions of normality, multicollinearity, homoscedasticity. In the first step, gender and age were included and the model containing these variables was not statistically significant. In the second step, besides gender and age we introduced the frequency of sweets consumption and the number of sugar teaspoons. This model as a whole explains 25,9% of the variance of DMFT score $F(4,79)=7,91$, $p<0,001$. The frequency of sweets consumption has the highest beta value (beta=-0,36, $p<0,01$), followed by the number of sugar teaspoons with beta=0,28, $p<0,01$. The unique variance explained by the significant predictors was 32,9% for frequency of sweets consumption, and 25,9% for number of sugar teaspoons.

Gender and age and did not contribute significantly to the model (Table 1).

Prediction equation

DMFT = 22,41 - 1.46 x frequency of sweets consumption + 0.33 x number of sugar teaspoons per day

Table 1. Regression coefficients for the prediction of DMFT score

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	19.557	2.061		9.491	.000
	Gender	1.291	1.111	.131	1.161	.249
	Age	.025	.045	.062	.552	.582
2	(Constant)	22.410	2.199		10.190	.000
	Gender	.119	.982	.012	.122	.904
	Age	.032	.039	.081	.830	.409
	Number of sugar teaspoons per day	.331	.124	.285	2.672	.009
	Frequency of sweets consumption	-1.468	.432	-.359	-3.401	.001

DISCUSSIONS AND CONCLUSIONS

For our study group we have demonstrated a positive relationship between high number of sugar teaspoons consumed per day and high frequency of sweets intake with the high DMFT score.

In univariate analysis the correlation between DMFT score and sugar teaspoons was positive, with a small magnitude of the relationship. The mean DMFT score was higher is high frequency consumers, when compared with low frequency consumers of sweets.

In multivariate analysis, when controlling the effects of age and gender, the number of sugar teaspoons consumed per day and the frequency of sweets consumption explained 25,9% of the variance of DMFT score.

According to our results, other authors had found positive correlations with the number of teacups drunk per day and the DMFT score, but also between the number of sugar teaspoons consumed per day and the DMFT score [7-9].

Proofs of association between sweets consumption and the risk of dental cavities was investigated and demonstrated during the last century. After 1950, interventional studies offered proofs of this relationship [10,11]. Studies performed more recently in Western Europe where the fluoridation is performed at population

level, demonstrated a significant relationship between sweets consumption and dental cavities, but the size of the relationship is weaker than before the fluoridation campaigns [12-14].

Longitudinal studies [15,16] that monitored the alterations in time of carious experience relationed to diet factors had offered the strongest proofs. It was proven that when the sugar consumption per person exceeds 15 kg per year (or 40 g per person per day), the incidence of dental cavities increases with the rise in sugar intake. When the sugar consumption is under 10 kg per person per year (or 27 g per person per day), the dental cavities incidence is very low [17,18] . The exposure to fluorides is increasing the safety limit to sweets.

Cross-sectional studies should be carefully interpreted because dental cavities are developing gradually, in time and for the correct measure of association is necessary the quantification of overall diet, because the diet from past several years is responsible of the actual level of oral health. Sundin [19] concluded that nowadays the consumption of sweets and other sugary products does not seem to be a strong factor for the occurrence of caries. However, for subjects with a combination of poor oral hygiene, the consumption of sweets has been shown to be particularly harmful.

REFERENCES

1. http://www.who.int/dietphysicalactivity/publications/trs916/en/gsfao_dental.pdf, accessed at July 16th 2013
2. http://www.who.int/oral_health/media/orh_socio_beh_risks_CDOE2005.pdf, accessed at July 16th 2013
3. Burt BA, Pai S, 2001, Sugar Consumption and Caries Risk:A Systematic Review, *Journal of Dental Education October* 1, 2001 vol. 65 no. 10 1017-1023
4. Arens U, ed, 1999, Oral health --- diet and other factors: the Report of the BritishNutrition Foundation's Task Force. Amsterdam, Elsevier Science PublishingCompany, 1999.
5. http://www.who.int/chp/steps/riskfactor/en/index.html, accessed at June 5th 2012
6. Romanul IM, 2010, Medicina Dentara Preventiva – Îndrumător de lucrări practice, Universitatea de Medicină şi Farmacie Timişoara, Facultatea de Medicină Dentară, ISBN 978-976-759-415-0
7. Jamel HA, Sheiham A, Watt RG, Cowell CR, 1997, Sweet preference, consumption of sweet tea and dental caries; studies in urban and rural Iraqi populations. Int Dent J. 1997 Aug;47(4):213-7.
8. Watt RG, Rouxel PL, 2012, Dental caries, sugars and food policy *Arch Dis Child* archdischild-2012-301818Published
9. Ceylan S, Açikel CH, Okçu KM, Kiliç S, Tekbas OF, Ortakoğlu K, 2004, Evaluation of the dental health of the young adult male population in Turkey. Mil Med. 2004 Nov;169(11):885-9.
10. Gustafsson BE et al. The Vipeholm dental caries study. The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for 5 years. Acta Odontologica Scandinavica, 1954, 11:232-364.
11. Scheinin A, Makinen KK, Ylitalo K. Turku sugar studies. V. Final report on the effect of sucrose, fructose and xylitol diets on the caries incidence in man. Acta Odontologica Scandinavica, 1976, 34:179-198.
12. Angelillo IF, Torre I, Nobile CG, Villari P, 1999, Caries and fluorosis prevalence in communities with different concentrations of fluoride in the water. Caries Res. 1999;33(2):114-22.
13. ***, 2007, A systematic review of the efficacy and safety of fluoridation, Australian Government, National health and Medical Research Council, http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/eh41_1.pdf

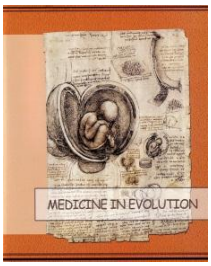
14. Shekar C, Cheluvaiah MB, Namile D, 2012, Prevalence of dental caries and dental fluorosis among 12 and 15 years old school children in relation to fluoride concentration in drinking water in an endemic fluoride belt of Andhra Pradesh, Indian Journal of Public Health, 2012 Volume 56 Issue 2 Page 122-128
15. Burt BA et al. The effects of sugars intake and frequency of ingestion on dental caries increment in a three-year longitudinal study. Journal of Dental Research, 1988, 67:1422-1429
16. Rugg-Gunn AJ et al. Relationship between dietary habits and caries increment assessed over two years in 405 English adolescent schoolchildren. Archives of Oral Biology, 1984, 29:983-992
17. Ruxton CH, Garceau FJ, Cottrell RC. Guidelines for sugar consumption in Europe. Is a quantitative approach justified? European Journal of Clinical Nutrition, 1999, 53:503-513.
18. Rodrigues CS. Dietary guidelines, sugar intake and caries increment. A study in Brazilian nursery school children [Thesis]. London, University of London, 1997.
19. Sundin B, 1994, Dental caries and sugar-containing products. Thesis. Malmö, Lund University.

Centrele de Cercetare blend-a-med și Oral-B

Este nevoie de efort - zi de zi - pentru a îmbunătăți cu adevărat sănătatea orală a pacienților. De aceea, P&G Oral Health, cu Centrele sale de Cercetare blend-a-med și Oral-B îi susține pe medicii dentiști atât în cabinet, cât și prin extinderea influenței lor dincolo de unitul dentar. Când pacienții părăsesc cabinetul de medicină dentară, produsele și serviciile noastre sunt un sprijin pentru ei.

blend-a-med RESEARCH CENTERS Oral-B

P&G Oral Health



CYTOLOGICAL LANDMARKS FOR DIFFERENTIAL DIAGNOSIS THROUGH FINE-NEEDLE ASPIRATION CYTOLOGY (FNAC) OF SKELETAL AND EXTRA-SKELETAL SARCOMAS

ADRIAN NICOARĂ[1], LILIANA VASILE[2], FELICIA STREIAN[1], EMILIA IANEŞ[1]

[1]University of Medicine and Pharmacy „Victor Babes" Timisoara, Romania, Department of Oral and Maxillofacial Surgery
[2]University of Medicine and Pharmacy „Victor Babes" Timisoara, Romania, Department of Histopathology and Cytology

ABSTRACT

Aim and objectives: This article presents the cytological landmarks used by the pathologist in cytological diagnosis of sarcomas using FNAC.

Material and methods: Between 1999-2013, 259 oncology patients have been investigated. The samples were obtained using classical FNAC, in some cases under laparoscopic control or using touch-print cytology.

Results: We present the cell type found and the landmark used by an experienced cytopathologist to establish the cell type and grading of the sarcoma, and the differential diagnosis of soft tissue sarcomas with other types of lesions, ascertaining the category of benign, malignant or inconclusive.

The lesion screening through FNA and cytology in our study has permitted the determination of the mesenchymal nature of a malignant tumor in 84% of cases.

Conclusions: Specific cytological diagnosis of the soft and skeletal tissue tumors is very difficult and an experienced cytologist is needed. Subgrouping the sarcomatose lesions can be very useful, because cytological diagnosis can determine the early phases of therapy and the prognosis.

Key words: *fine-needle aspiration cytology, cytological landmarks, differential diagnosis.*

Correspondence to:

Adrian Nicoară
Address: str. Albinelor 55A, Timişoara, 300244
Phone: 0723969298
E-mail address: adinicoara@gmail.com

INTRODUCTION

Fine-needle aspiration cytology is a preferential procedure for preliminary diagnosis of soft-tissue tumors, having a high degree of accuracy especially in differentiating malignant and benign tumors. This method has the advantages of a relatively low cost, it is quick and well accepted by the patient, and has a low morbidity associated with the procedure.

Nevertheless, the specific cytological diagnosis of the soft and skeletal tissue tumors is very difficult.

The main factors that could make diagnosis by FNAC difficult are: the heterogeneity of the cells within the tumor or that are part of the reactive population of the tumor, the presence of hemorrhage, necrosis, mucoid and inflammatory tissue on the smear, and the matrix tissue material included in ice or paraffin.

Within hard tissue, the sarcomas develop in patterns similar to the ones in soft tissue, thus standing as proof for the mesenchymal-fibroblast-like filiation.

The following entities are considered to be soft tissue tumors: tumors of the connective tissue proper and specialized connective tissue, tumors of the peripheral nervous system, and tumors of mesothelial and paraganglionic tissue.

Aim and objectives:

The present article presents the cytological landmarks used by the pathologist in the cytological diagnosis of the tumors using FNAC. Whenever a tumor is investigated, the following algorithm is applied:

- Establishment of the cell type and grading of the sarcoma, which is essential in appreciating the prognosis and therapeutic method (surgery, radiotherapy or chemotherapy).
- Differential diagnosis of the soft tissue sarcomas with other types of lesions, also having in mind the clinical and evolutionary aspects.
- Ascertaining the category of benign, malignant or inconclusive

MATERIAL AND METHOD

The hystopathological sample of investigation between 1999-2013 includes patients aged 5 to 74, both male and female, presenting tumors of the soft and hard tissue, localized as follows: head and neck region (n=108); limbs (n=98 – subcutaneous, intramuscular); trunk (n=10 – interscapular, presternal); retroperitoneal (n=39); mezenteric (n=4);

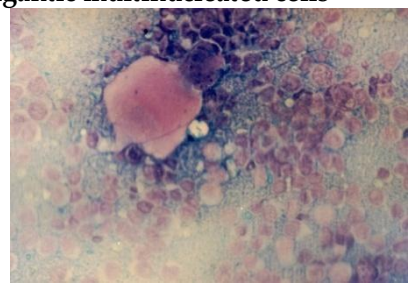
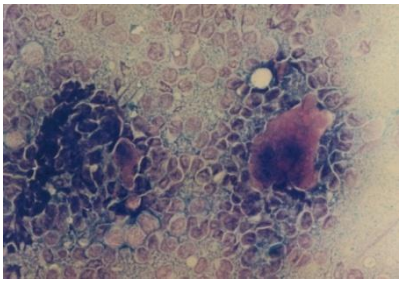
The patients were investigated it the Oral and Maxillofacial Surgery Clinic, in the Oncology Clinic and General Surgery Clinic of the Municipal Hospital of Timişoara, and the samples were analyzed in the Pathological Anatomy Laboratory of the Municipal Hospital, and at the Histology Department at the University of Medicine and Pharmacy "V. Babes" of Timişoara.

The samples were obtained using classical FNAC, in some cases under laparoscopic control or using touch-print cytology. The fixation of the material was made for the original APT-Drăgan and Giemsa coloration, and by using Resofix, Cytofix Merck for the Papanicolau coloration.

RESULTS

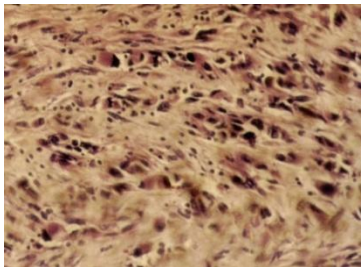
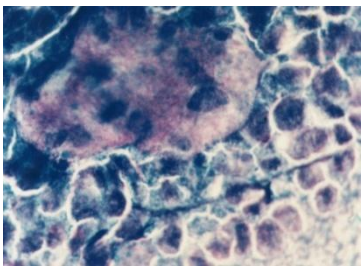
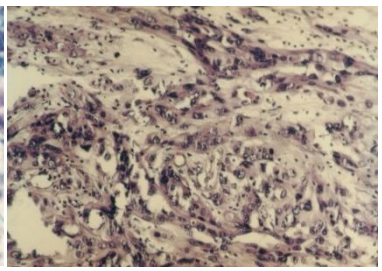
The cell types identified using FNAC in the investigated samples are

1. **Gigantic multinucleated cells**

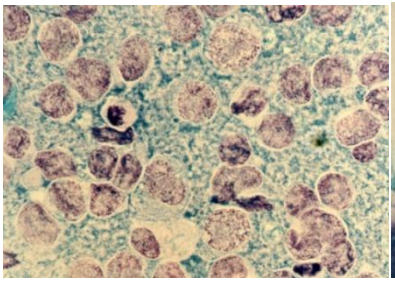
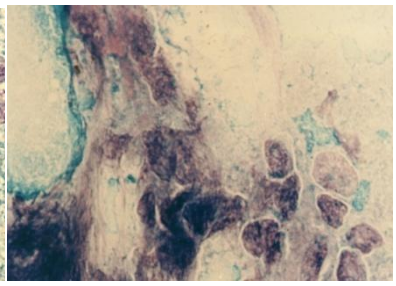



a. monomorphic:

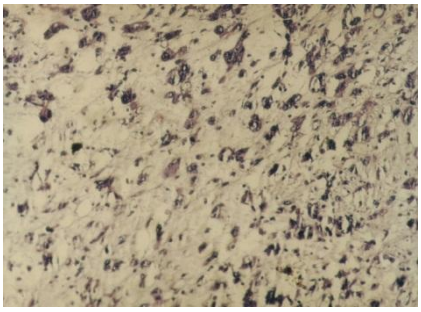
- ***histiocytic*** with or without hemosiderin inclusions; Touton cells; mononucleated histiocytes, oval or elongated, fusiform, with uniform nuclei; these cells are present in benign fibrous histiocytomas.

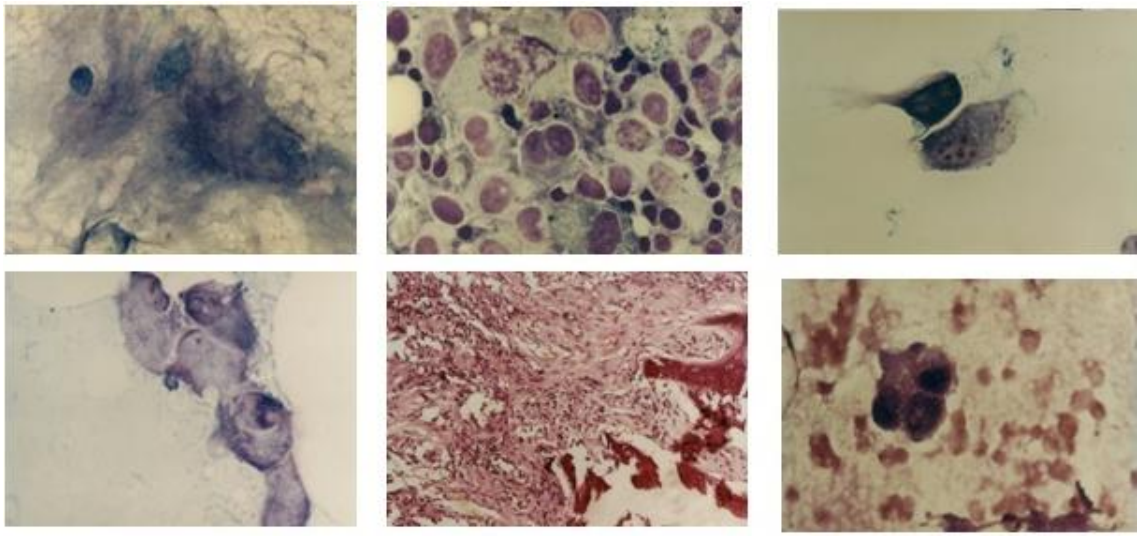
- ***non-histiocytic:*** mixed population of round cells of small dimensions; they are present in alveolar rhabdomyosarcomas.

b: **pleomorphic:- with histiocytic aspect**, with pale cytoplasm, intracytoplasmatic granulations, oval nuclei, some of them with elongated aspect, fusiform, nuclear atypia only in the tumoral forms of malignant fibrous histiocytoma of the III-rd and IV-th degree. If the myxoid matrix is present, this could suggest a fibromiosarcoma.

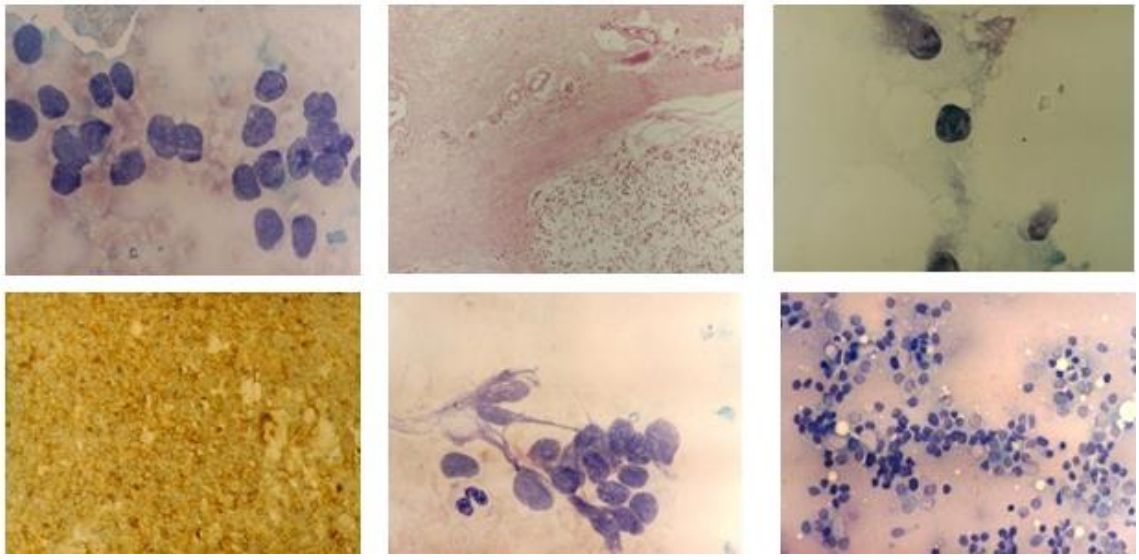


- gigantic cells with no histiocytic aspect: are seen in high malignancy sarcomas (liposarcomas, leiomyosarcomas, rhabdomyosarcomas). Sometimes the presence of this cells raises the problem of differential diagnosis with malignant melanoma.



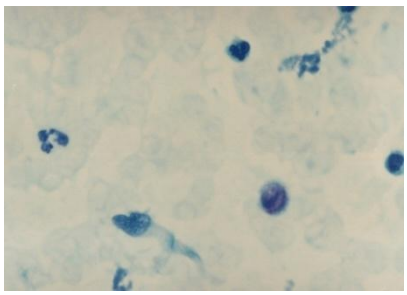
2. Small round cells:

- **with lymphogranular bodies**: - in lymphoid proliferations with rhabdomyoblasts (round cells with acidophilus cytoplasm and eccentric nuclei; irregular nuclei and dense chromatin); they are present in rhabdomyosarcomas.
- **Myxoid matrix**: - it is use for the differential diagnosis between myxoid extraskeletal condrosarcoma and botryoid rhabdomyosarcoma.
- **Pseudorossetes:** - used for the differential diagnosis between neuroblastoma and PNET.
- **Small, round, monomorphic cells**: - differential diagnosis between Ewing sarcoma, poorly differentiated rhabdomyosarcoma and neuroblastoma, and also the desmoplastic small round cell tumor.

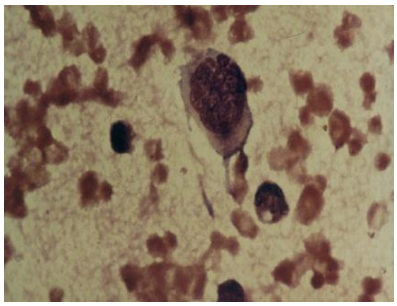
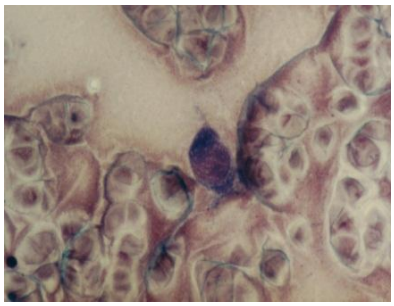


Celule fusiforme:

- Small round cell in groups or isolated – fibroblasts with matrix filaments, collagen, cellular detritus, small capillar fragments, atrophic rough muscle cells; they can be found in desmoid cells; in nodular fasciitis on the smear we can observe a fibrillar or mucoid matrix, containing cells resembling ganglionar cells, lymphocites, plasmocytes, macrophages charged with fat.



- **Fibroblast-like**, associated with histiocytes charged with fat or hemosiderin, they can be seen in the benign fibrous histiocytoma; when having a bipolar, monomorphic aspect, they suggest a protuberans dermatofibrosarcoma; they can also have a monomorphic bipolar aspect associated with mastocytes, calcifications and cords of `epithelial-like` cells in the synovial sarcoma; some poorly differentiated sarcomas have fibroblast like cells with polymorphic nuclei, imposing the differential diagnosis between pleomorphic fibrosarcoma, malignant schwannoma and leiomyosarcoma

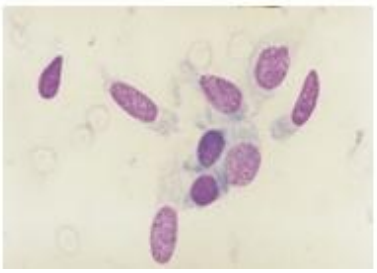
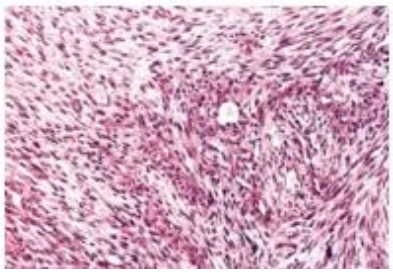
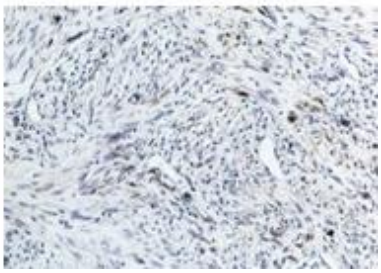



- **Non-fibroblastic cells**: they have a granular cytoplasm, smooth cell borders in rhabdomyoma and irregular margins in the granular cell tumors

3. Groups of fusiform cells

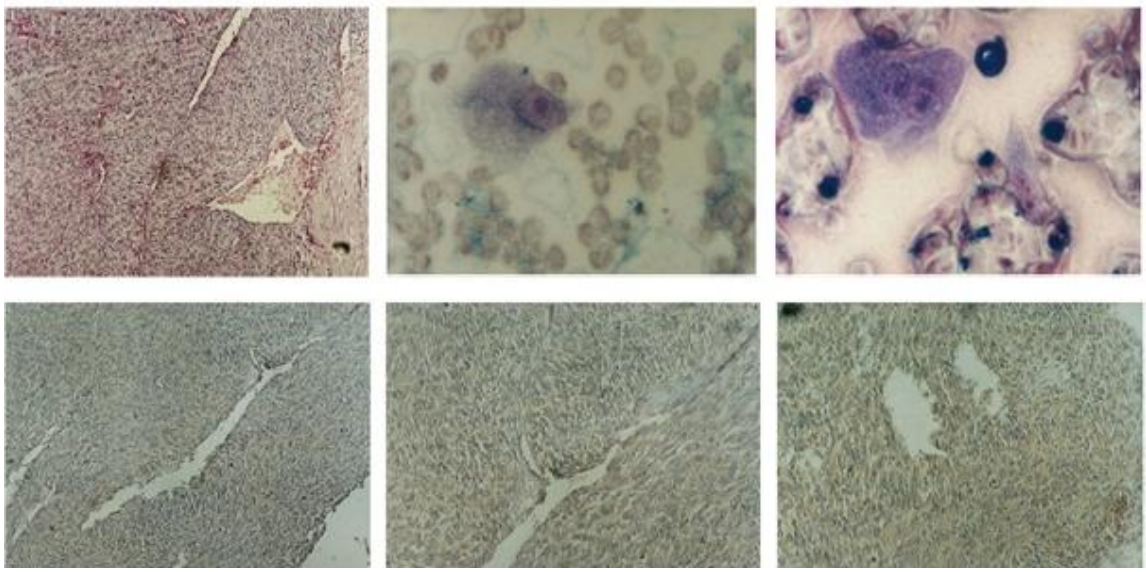
- **Ramified type**, syncytial-like with fibrillar margins, palisade nuclei and Verocay bodies, present in the benign sarcoma

-The type in groups, with precisely delimited margins, acidophilus cytoplasm, monomorphic nuclei, present in the leiomyosarcoma with low malignity degree

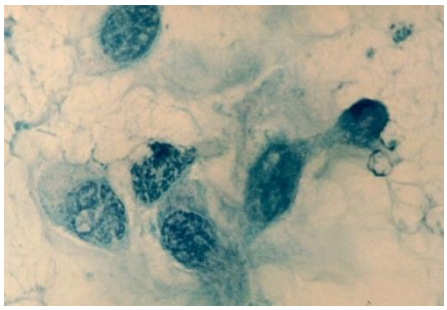
4. Epitelioid cell:

1. **Big cells with fine vacuoles**
2. **Medium size cells, homogenous**



The mixoid tumors have the following cytological characteristics:

- These do not include adipose cells, giant cells, small round cells or epithelial cells
- The matrix is myxoid, occasionally with macrophages (ganglion cyst)
- Rare stellar or fusiform cells, with uniform nuclei (intramuscular myxoma)
- Big fusiform cells



DISCUSSIONS

Fine-needle aspiration cytology (FNAC) is a reliable, affordable, easy, quick, alternative diagnostic method, which can, in some cases, eliminates the necessity for open biopsy with its unwanted surgical risks. The role of fine needle aspiration cytology/biopsy (FNAC/FNAB) in the diagnostic evaluation of neoplastic and non-neoplastic lesions has increased dramatically in many medical and surgical specialties.[1][2]

Although the method has been in existence for 150 years, being pioneered by Martin in the early 1930s for the head and neck region, its usefulness, safety, and diagnostic accuracy have been demonstrated repeatedly only during the last 20 years.[1]

FNAC technique can be used to diagnose a mass in the area that is palpable or visible by a radiological imaging method, to differentiate benign from malignant tumors, confirm a suspected malignancy, determine the extent of malignant disease, evaluate metastasis in suspected or enlarged lymph nodes, diagnose multiple tumors, verify recurrence of a previously treated neoplasm, document malignancy for patients with inoperable disease, identify microorganisms, and obtain material for culture from infectious masses and tumor-like conditions.[2]

This technique may also assist in establishing a specific diagnosis for radiolucent lesions of the jaw. The thinning or destruction of cortical bone permits the use of thin needles to aspirate such abnormalities.[1]

There are a lot of factors affecting the diagnostic accuracy of FNAC in this region. The most important of them are the experience of the clinician performing the procedure and the need for an expert cytopathologist, who is able to evaluate samples.

This technique allows a more rapid diagnosis, and if necessary, a re-aspiration can be done quickly at the time of initial testing.[3] The main cause for an erroneous diagnosis is the failure to obtain a representative sample because of the positioning of the needle outside of the target tissue or to central necrosis or cystic change in the tumor.[4] Diagnosis of aspirates from cystic lesions may be less specific than the solid lesions due to paucity of specific lesional cells in the former and also due to superimposed infection. [1]

Brennan et al [5] noted that repeat FNAC is useful in those patients whose initial aspirate does not provide enough information, or when a diagnosis cannot be made. He affirms that even when a cytological diagnosis is made, the distinction between malignant from benign disease should not rely upon FNAC completely, and should be combined with other investigations and clinical judgment for management of the tumor.

FNA and the information obtain through cytology are considered of great value today to delineate the lesional aspect in a sarcoma. Some authors appreciate the accuracy of FNAC diagnosis based on clinical and radiological data to be between 74-92%, while other studies report diagnosis accuracy which varies between 90-97% depending on the anatomical site of aspiration. [2]

The lesional screening through FNA and cytology had permitted in our study to determine the mesenchymal nature of a malignant tumor in 84% of cases. Subgrouping the sarcomatouse lesions can be very useful, because the cytological diagnosis can determine the early phases of the therapy and the prognosis (in high grade malignant sarcomas, the radical surgery is often combined with pre and postoperative complex radio and chemotherapy).

Varies studies support the use of FNAC in diagnosing lesions of oral and maxillofacial region based on accuracy and rarity of false positive results. The use of fine-needle aspiration cytology (FNAC) as the main initial diagnostic investigation for the tumors in head and neck region has many advantages, but still is not often used.[5] There is a relatively large volume of literature documenting the effectiveness of FNA for diagnosis of head and neck and salivary gland lesions. Few reports, however, explore the potential of FNA for the diagnosis of intraoral and lesions of maxillofacial region.[1]

Due to the anatomic complexity of the region, tumors affecting oral and perioral tissues often present a diagnostic challenge to the pathologist and the surgeon. Preoperative diagnosis is of utmost importance but the anatomy of the area, with a great variety of heterogeneous groups of benign and malignant tumors and tumor-like conditions, the absence of a specific architectural pattern makes this task difficult.[1][2][6]

CONCLUSIONS

Specific cytological diagnosis of the soft and skeletal tissue tumors is very difficult and an experienced cytologist is needed. Subgrouping the sarcomatouse lesions can be very useful, because the cytological diagnosis can determine the early phases of the therapy and the

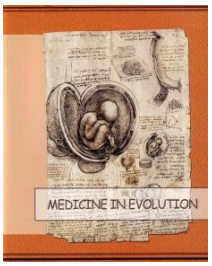
prognosis. The cooperation between the surgeon and the cytopatologist in obtaining and analyzing the sample in order to establish a precise diagnosis is important. When the cytological findings are correlated with treatment procedures planning, the results are satisfactory.

AKNOWLEDGEMENT: This paper is supported by the Sectorial Operational Programme Human Resources Development (SOP HRD) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/S/82839.

REFERENCES

1. Singh S, Garg N, Gupta S, Marwah N, Kalra R, Singh V, Sen R. Fine needle aspiration cytology in lesions of oral and maxillofacial region: Diagnostic pitfalls, J Cytol. 2011 Jul-Sep; 28(3): 93–97.
2. 2. Daskalopoulou, D., Rapidis, A. D., Maounis, N. and Markidou, S. (1997), Fine-needle aspiration cytology in tumors and tumor-like conditions of the oral and maxillofacial region. Cancer, 81: 238–252. doi: 10.1002/(SICI)1097-0142(19970825)81:4<238::AID-CNCR6>3.0.CO;2-L
3. 3. Scher RL, Oostingh PE, Levine PA, Cantrell RW, Feldman PS. Role of fine needle aspiration in the diagnosis of lesions of the oral cavity, oropharynx, and nasopharynx. Cancer. 1988;62:2602–6.
4. 4. Orell S, Sterrett G, Walters M, Whitaker D. The techniques of FNAC. In: Manual and atlas of fine needle aspiration cytology. 2nd edition. New York: Churchill Livingstone, 1992; 8-23.
5. 5. P.A. Brennan, B. Davies, D. Poller, Z. Mead, D. Bayne, R. Puxeddu et al. Fine needle aspiration cytology (FNAC) of salivary gland tumours: repeat aspiration provides further information in cases with an unclear initial cytological diagnosis, British Journal of Oral and Maxillofacial Surgery, 48 (2010), pp. 26–2
6. 6. Ostović KT, Luksić I, Virag M, Macan D, Müllers D, Manojlović S. The importance of team work of cytologist and surgeon in preoperative diagnosis of intraoral minor salivary gland tumours. Coll Antropol. 2012 Nov;36 Suppl 2:151-7.

CORRELATION BETWEEN ORAL HYGIENE INDEX AND LEVEL EDUCATION IN PRISON INMATES



ANDREEA VOICA[1], ALEXANDRU ANDREI ILIESCU[2], RAREŞ VOICA[3], ANDREI ILIESCU[4]

[1] Ploieşti Penitentiary, dentist, Phd U.M.F. Carol Davila, Bucharest
[2] Departament of oral rehabilitation, University of Medicine and Pharmacy, Craiova
[3] Pediatric Hospital Ploiesti, dentist
[4] Department of Endodontics, U.M.F. Carol Davila, Bucharest

ABSTRACT

Objective: to assess the oral hygiene in prison inmates and the importance of hygienic education as well, in order to improve the quality of life in detention setting.

Materials and methods: 694 inmates from Ploieşti Penitentiary of age between 18 and 75 years were included in this study. Clinical examination followed the WHO criteria. Age and initial index of oral hygiene were registered. A second evaluation of the oral hygiene index was done after performing the oral hygiene procedures.

Results: oral hygiene practices reduced with 10.54% the index of oral hygiene whose medium value was initially of 50.47%, respectively post-treatment, of 40.20%.

Conclusions: the status of oral hygiene is precarious in this population group but the educational measures leaded to a real improvement. Based on subjects feedback, starting appropriate projects of hygienic education the risk of oral diseases might be minimized.

Key words: *prison inmates, level education, oral hygiene index*

Correspondence to:

dr.Andreea Voica
Address: Ploiesti,Prahova, Str. Gheorghe Lazar nr 1
Phone: 00407450745815
E-mail address: avoica75@gmail.com

INTRODUCTION

It is well known gingival dental plaque role in triggering periodontal inflammation [1]as relevant as is the reversal of this process to varying degrees depending on the severity of illness as a result of plaque removal by known means cleaning oral [2]. Because of compliance lower educational level of oral hygiene measures and the socio-economic conditions prior to incarceration, prisoners are a high-risk population group on periodontal disease [3]. Many prisoners can not read about oral health information because the low levels of literacy, any material information relating to oral care should be designed methods according educational level.

OBJECTIVE.

Taking into consideration the level of schooling of inmates I have chosen to make a study on their oral hygiene, based on the hypothesis that education influences the level of hygiene. The level of dental hygiene was determined based on soft deposits or bacterial plaque and hard deposits.

The purpose of this study is to evaluate the state of oral hygiene on inmates with multiple educational and cognitive deficiencies, and developing projects and strategies in increasing the quality of life in a penitentiary preparing to social reintegration. Taking into consideration the level of schooling of inmates directs us to a study of their oral hygiene based on the hypothesis that education influences the level of hygiene. Was made to determine the level of oral hygiene by assessing soft deposits (plaque) and of hard (dental plaque) using some indicators literature on a sample of inmates in prison custody Ploiesti.

MATERIAL AND METHOD

The study was done on a social sample of 694 male inmates; the patients are serving their sentence Ploiesti in this institution. For this study there were not taken into consideration inmates that were passing through or those that did not want to participate.

After the number of years of schooling, the study group was divided into six groups of educational level, ranging from 0-17 grades, as follows: group I (unschooled), group II (first grade 1-4 classes), group III -a (second grade grades 4-8), Group IV (professional school), the group V(college) and Group VI (high school).

The medical history of the patients was recorded; a clinical examination was done according to WHO criteria. To assess oral hygiene status was determined index oral hygiene, resulting in summation the plaque index (soft deposits) and the tartar index (hard deposits), as indicated in the literature [1, 4]. IPT oral hygiene index (plaque index and tartar index) is obtained from the average of the two indices mentioned above.

As revealing plaque under the gum lining the Vaseline isolation was used Dentorama Blue Disclosing Pellets transitional PRO 155 which color red plate so recent (1-3 days) and old (more than 3 days).

Scores were noted with 0-3 plaque index values respectively of the tartar index, determined on six preselected surfaces (buccal surfaces of the molars of 6 years senior counterparts the inferior lingual, buccal of upper right central incisor, respectively incisor lower left), in accordance with accepted [1, 4].

Subjects were initially trained on daily brushing technique and frequency as well as additional resources oral hygiene, hygiene works after being subjected to surveillance, in which part of the study group (325 people) received complex procedures (scaling and local fluoridation). Finally IPT index was determined again, comparing to the initial values.

RESULTS

Analyzing the structure of the study group according to the educational level shows that graduates of second grade, ie a total of 4-8 years of schooling are nearly two times more numerous (33.71%) than in the group with first grade, or 1-4 years of schooling (16.28%) and about 4 times more than those unschooled. (9.94%) The lowest percentage is the high school (2.44%). (Table 1).

The oral hygiene is completely unsatisfactory, the mean oral hygiene index IPT reached 50.74% with a standard deviation of ± 30.06. (Table 2).

Supervised hygiene led to the improvement of oral health in all age groups, registering an average reduction of 10.54% with IPT index from the initial values. (Table 3).

Table 1. Structure lot depending on the level of years of schooling

Level of education	Real number	Procentaj
unschooled	69	9.94
First grade	113	16.28
Seconde grade	234	33.71
Professional school	123	17.72
College	138	19.88
High school	17	2.44
Media 7.40 clase	694	

Table 2. Changes in value of oral hygiene index (IPT)

Parametric	Valuate minim	Valuate maxim	Media	Deviation standard	Coefficient Of variation
Schooling level	0	17	7.40	3.84	0.52
Indice IPT (%)	0.16	100.00	50.74	30.06	903.54

Table 3. Evolution schooling level - IPT values

Age groups	IPT medium Initial (%)	IPT medium after treatment (%)
0 classes	50.74	40.20
0-4 classes	48.11	37.46
4-8 classes	52.16	41.27
8-10 classes	48.64	39.66
10-12 classes	50.84	39.55
12-17 classes	50.81	34.57
IPT global (%)	**50,74**	**40,20**

Although there is a positive feedback to all sample groups, there is a significant reduction in value was recorded in the sixth group (university graduates), followed by group V (10-12 classes). (Fig. 1)

It was also found that in the group of 694 subjects a majority (66.86%) responded positively

sanitation supervised brushing either professionally or individually, under strict supervision of medical staff. (Fig.2)

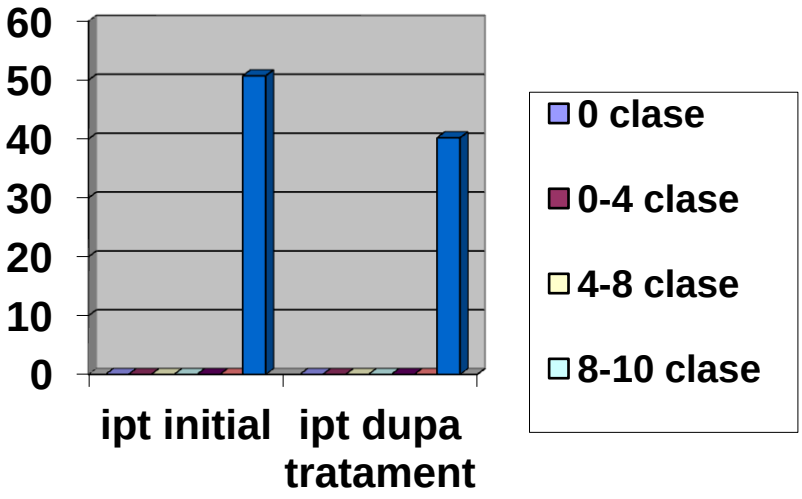


Figure 1: Evolution of the index after cleaning supervised IPT

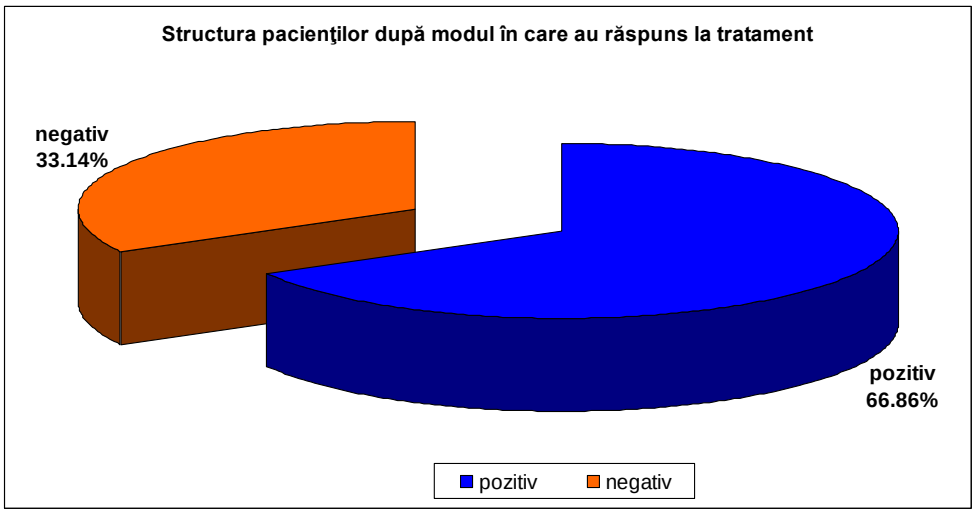


Figure 2: Structure of the lot by the way subjects responded to treatment

DISCUSSIONS

Although the authors of reference (Kinane and Lindhe, 2003) believes that age does not automatically bring increased susceptibility to inflammation of the gingival mucosa, while the cumulative effects of various risk factors contribute but certainly periodontal illness onset [5].

The accumulation of dental plaque and gingival inflammation, periodontal diseases are conditions with age and inversely proportional to the level of education, as noted, and Osborn and Butler in 2003. [6]

Maximum oral hygiene index IPT met the prisoners in Group III (4-8 classes), all this with a minimum feedback sanitation. Is response to treatment, caution in promoting oral health. the motivation for the acquisition of fair procedures and oral hygiene subjects involved was the result of persistent educational activities, repeated as ensuring long-term effectiveness of prevention measures can not only get a single briefing (Brand et al, 2013). [10]

Reduce our study to the average of 10.54% IPT Oral hygiene after brushing with fluoridated toothpaste daily confirms the importance of supragingival plaque removal in combating periodontal inflammation, as most handy cleaning process recommended in the literature. [7]

Encouraging that significant effects in improving oral health in people incarcerated have been achieved by using simple means of examination, diagnosis and prevention, which can be applied successfully in any business conditions, as quoted in other circumstances like. [8].

Prisoners, mostly coming from dysfunctional environments with chaotic lifestyles and little or possibilities maintenance dental care, abusing alcohol, tobacco or drugs is a highly exposed population group all diseases, including those the oral cavity [3].

As pointed out by D'Cruz and Aradhya (2013) in this context, as in any population group, a measure of oral hygiene education is a cardinal element. [9]. Besides this aspect met in our study, where 66.86% of the subjects gave positive feedback to supervised cleaning.

Oral health is a hub of health overall. Maintaining strict sense does not mean the absence of pathology in the oral cavity, involving the social or psychological issues including feeling good condition (Usha et al., 2013). [11]

Combination oral hygiene control psychological factor that gave us encouraging results as the proportion of positive feedback is a solid starting point for the design and implementation of preventive or curative treatment strategies specific features targeted population group (Dumitrescu et al., 2012)[12].Appropriate educational resources and establishing a supervised hygiene works.

CONCLUSIONS

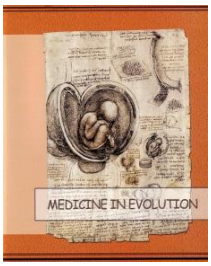
Oral hygiene status of the prison population is poor. Improving oral hygiene index after training recommended the establishment of effective preventive hygiene measures. The most important methods of education for maintaining oral health counseling inmates are training group and individual dental office of prison.

REFERENCES

1. **Dumitriu H.T., Dumitriu S., Dumitriu A.S.** Parodontologie ed. IV-a. Ed. Viața Medicală Românească, Bucureşti, 2006: 103-188
2. **Echeverria J.J., Sanz M.** Mechanical supragingival plaque control. In: Lindhe J, Karring T., Lang N.P., ed. *Clinical periodontology and implant* dentistry. 4-th ed. Oxford: Blackwell Munksgaard; 2003:449-463
3. **Cernat T., Comănescu M., Alexandru D., Cârlig V. –** Simultaneous occurence of other diseases among prison inmates with tuberculosis. *Current Health Sci J*, 2010;36(3):143-146
4. **Papapanou P.N., Lindhe J.** Epidemiology of periodontal diseases. In: Lindhe J, Karring T., Lang N.P., ed. *Clinical periodontology and implant* dentistry. 4-th ed. Oxford: Blackwell Munksgaard; 2003:50-80
5. **Kinane D.F., Lindhe J.** Chronic periodontitis. In: Lindhe J, Karring T., Lang N.P., ed. *Clinical periodontology and implant* dentistry. 4-th ed. Oxford: Blackwell Munksgaard; 2003:209-215
6. **Osborn, M., T. Butler, et al.** "Oral health status of prison inmates--New South Wales, Australia." Australian Dental Journal 48(1);2003: 34-8.
7. **Haps S., Slot D.E., Berchier C.E., Van der Weijden G.A. –** The effect of cetylpyridinium chloride-containing mouth rinses as adjuncts to

toothbrushing on plaque and parameters of gingival inflammation: a systematic review. *Int J Dent Hygiene*, 2008;6:290-303

8. **da Silva R.P., Pereira A.C., de Castro Meneghim M., Mialhe F.L.** – Development of an auxiliary resource for diagnosis of dental caries in epidemiological surveys. *Int J Dent Hygiene*, 2011;9(4):250-253
9. **D'Cruz A.M., Aradhya S.** – Impact of oral health education on oral hygiene knowledge, practices, plaque control and gingival health of 13- to 15-year-old school children in Bangalore city. *Int J Dent Hygiene*, 2013;11(2):126-133
10. **Brand V.S., Bray K.K., MacNeill S., et al.** – Impact of single-session motivational interviewing on clinical outcomes following periodontal maintenance therapy. *Int J Dent Hygiene*, 2013;11(2):134-141
11. **Usha G.V., Thippeswamy H.M., Nagesh L.** – Comparative assessment of validity and reliability of the oral impacts on daily performance (OIDP) frequency scale: a cross-sectional survey among adolescents in Davanagere city, Karnataka, India. *Int J Dent Hygiene*, 2013;11(1):28-34
12. **Dumitrescu A.L., Zetu L., Teslaru S.** – Instability of self-esteem, self-confidence, self-liking, self-control, self-competence and perfectionism: associations with oral health status and health-related behaviours. *Int J Dent Hygiene*, 2012;10(1):22-29



MECHANICAL-CHEMICAL TREATMENT OF THE CAVITY: ELECTION METHOD FOR THE PATIENTS WITH MIXED DENTITION

DANIELA JUMANCA[1], ATENA GALUSCAN[1], ANGELA PODARIU[1], ROXANA OANCEA[1], RAMONA POPOVICI[1], RUXANDRA SAVA-ROSIANU[1]

[1]Department of Preventive, Community Dentistry and Oral Health, Faculty of Dentistry, University Of Medicine And Pharmacy "Victor Babes" Timisoara

ABSTRACT

Introduction: Dental caries continues to represent a major problem which affects all groups of age. This is why it must be insisted upon the primary prevention and upon the secondary prevention und specific measurements must be applied to each individual depending on the found caries risk. The disconfort of the the use of the rotary instruments can be removed easily by using the chemo-mechanical method.

Aim: The aim of this study was to evaluate the use of Carisolv, a simple minimal invasive treatment. We followed the quality of the obtained obturation, the effects upon the patients, the necessary time for this type of treatment.

Material and method: We performed a study in vivo on a group of 47 childrens with the age between 6 and 12 years, the study had a length of 1 year and 6 months. In parallel we performed a study in vitro which has aimed the comparation of the dentinal surface resulted from after the removal of the infected dentine by using the classical rotary method and by the mechanical-chemical method using the Carisolv system.

Results: After a period of 6 months the patients were called to a first evaluation of the results of the treatment with Carisolv. It was observed that there were no painful reactions, meaning that the pulp organ of the treated teeth was not affected. Also there were no secondary caries or relapses of caries. As a result of the analyses of the treated surfaces by using the 2 methods, we noted that the aspect of the dentinal tubes is similar in the case of the 2 types of preparation.

Conclusions: the patients accepted easily this type of treatment because it is more comfortable, it gives less pain and this why they were more relaxed during the treatment related to the treatment of the caries realized by classical methods

Key words: *minimal invasive, chemo-mecanical method, Carisolv*

Correspondence to:

Dr. Atena Galuscan
Address: Department of Preventive, Community Dentistry and Oral Health, Faculty of Dentistry, University Of Medicine And Pharmacy "Victor Babes" Timisoara, Spl. Tudor Vladimirescu nr. 14A
Phone: 0256-204950
E-mail address: proiectetm@yahoo.com

INTRODUCTION

The prevalence of the dental caries has known an important decline in the last years including in our country, but still, this affection continues to represent a major problem which affects all groups of age. This is why it must be insisted upon the primary prevention and upon the secondary prevention und specific measurements must be applied to each individual depending on the found caries risk.

The minimal invasive treatment in the preparation of the dental surfaces includes: mechanical techniques (rotary technique with high and low speed; atraumatic restorative technique: the use of the Black spoons and of the sonic oscillations produced by the sonic apparatus for scaling); mechanical-chemical techniques: (Caridex, Carisolvit) and kinetic techniques: the of the abrasive powders on the basis of the aluminum oxide, the ozone and the laser therapy.

From all the methods, the most used one is the preparing of the cavities with the help of the rotary instruments. This is the classical treatment and has over 100 years of age. Although it has also inconveniences: the removal of the decrepit dentine removal with the rotary instrument leads also to loses of the healthy dental tissue determining the necessity of the realization of an more larger and more unstable obturation. At the same time the sound produced by the rotary instrument is perceived as not pleasant, especially among the young patients who become very rapidly anxious. The atraumatic modern restoration techniques like the laser and the abrasive powders need a much expensive equipment, a supplementary preparation and at the same time it does not fully eliminate the fear of the patients of the dental instruments.

The disconfort of the the use of the rotary instruments can be removed easily by using the chemo-mechanical method. The first used product on a large scale was the Caridex which had in it's composition a single aminoacide. In 1980 were initiated chemo-mechanical studies of the removal of the caries tissue by the Swedish researchers from the Univeristy of Malmo Huddinge and Goteborg and as well Chalmers Technical University of Goteborg. By the sustained efforts by Christer Hedward, Lars Strid, Dan Ericson and Rolf Bornstein from Malmo namely form Huddinge, was obtained the Carisolve, a new chemo-mechanical system of the removal of the caries tissue which was approved for the clinical use in the dental practice by the Swedish Corporation US FDA.

AIM

The purpose of the realization of this paper was to evaluate this simple minimal invasive treatment. We followed the quality of the obtained obturation, the effects upon the patients, the necessary time for this type of treatment.

We selected a group of children with the age between 6 and 12 years, whom we treated by using the mechanical-chemical method and whom we followed for a period from 1 year and 6 months. We chose this method because the classical treatment (with rotary instrument) is not pleasant among the patients of this age. The children, generally, do not like the dental maneuvers which imply the use of the syringe for the anesthesia but also not a rotary instrument which causes pain and noise. We tried the little use of the rotary instrument (for the realization of the access to the caries lesions) in favour of the specific hand instrument used in the treatment with Carisolv.

We evaluated: the necessity of the use of the rotary instruments in different types of lesions (initial, medium and profund), the necessity of

the local anesthesia, the number of applications of necessary gel, the medium necessary time for the cleaning of the cavity but the answer of the patient to this type of treatment.

We tried that by the reduction of the patients' stress during the treatment, to change their attitude towards the attendance at the dentist and to educate them to present themselves regularly at the praxis, by realizing the dental profilaxy.

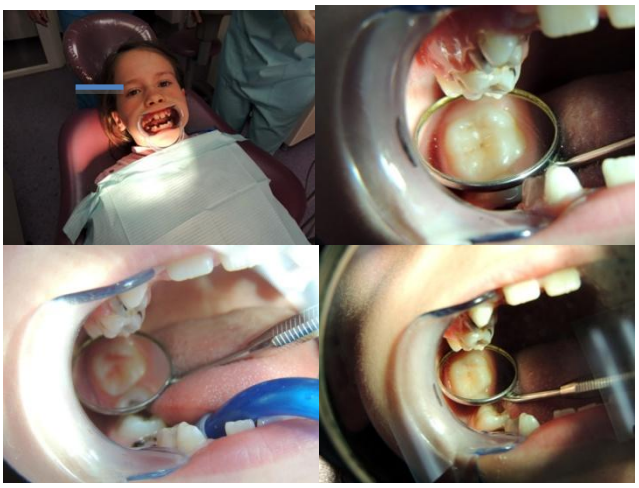
MATERIAL AND METHOD

We performed in parallel 2 studies : a study « in vivo » and one « in vitro ».

We performed a study in vivo on a group of 47 childrens with the age between 6 and 12 years, the study had a length of 1 year and 6 months. We chose this age group because the teeth are then in change, at 12 years the permanent dentition must be complete and the confidence with which the children very important when they come to the next check up. The patients have presented a number of 26 initial lesions (on which we performed the opening with the turbine), 6 lesions of medium depth with an already existent opening, all situated on the occlusal surface.

We used the Carisolv kit which contains a syringe with gel and 5 hand instruments. Before the treatment the patients was given a sanitary education lesson regarding the dental hygiene. Then a professional sanitation was performed (scaling, brushing and sealings).

The treatment with Carisolv was realized in the following stages: the isolation of the operator field with cotton rolls and saliva cleaner; after the isolation the mixture fo the gel was realized and its application in the cavity for 30 seconds; the excision of the decrepit dentition with the hand instrument and then the check up of the cavity.. if it is necessary, there can be realized repeated applications of the gel until the total removal of the decrepit dentition.



1. Patient 9 years
2. Initial lesion 1.6.
3. Applied gel
4. Aspect of the final cavity

In parallel we performed a study in vitro which has aimed the comparation of the dentinal surface resulted from after the removal of the infected dentine by using the classical rotary method and by the chemo-mechanical method using the Carisolv system. Within this study we used 10 extracted teeth for the orthodontic purpose, teeth which presented occlusal or cervical cavity caries lesions.

After the extraction we extracted the teeth in a saline solution at a temperature of 4°C until the moment at which we realized the study. We divided the teeth into 2 groups of each 5 teeth of which: la 5 of these with the infected dentinal cavities were prepared by using iron ball millings adapted to the size of the caries process at the elbow part (with water cooling), and at the rest of 5 teeth, removal of the infected dentine was realized by using the Carisolv system.

The control of the removal of the infected dentine was realized by using an excavator with which we checked the consistence of the rest dentine. From a clinical point of view, we considered that the hard dentine at palpation presents the guarantee of the total removal of the infected dentine coating. Then we rechecked the accuracy of the total removal of the infected dentine with the help of the dentine dye. On 2 of the 10 examined teeth, the surface of the dentine presented a light pink dye after the removal of the dye agent and we continued the manual removal of the dentine until the complete disappearance of the color.

Later we selected the perpendicular mesial-distal treated teeth and then horizontal at the level of the prepared quantity and we examined it with the help SEM (Scanning Eletronic Microscopy).

As a result of the analyses of the treated surfaces by using the 2 methods, we noted that the aspect of the dentinal tubes is similar in the case of the 2 types of preparation. This fact suggests the absence of the dentine demineralization processes in the case of the treatments with Carisolv, which means that the contained substances in the Carisolv concoction does not realize the dental irritation.

RESULTS

After a period of 6 months the patients were called to a first evaluation of the results of the treatment with Carisolv. It was observed that there were no painful reactions, meaning that the pulp organ of the treated teeth was not affected. Also there were no secondary caries or relapses of caries. Because of this type of treatment, less traumatic for the patient (the lack of anesthesia in the most cases, by minimal use of the rotary instrument) these came back more relaxed at the clinic, requesting this type of treatment and later interventions.

Although in our country there are few doctors who use this method, it is used on a large scale in other countries in Europe. The resulted surface after the removal of the dentine in the case of use of the Carisolv concoction it is not more fractioned than in the cases of the preparation with milling at the elbow piece. In the case of the Carisol, the prepared cavity is much smaller but with irregularities depending on the manner in which the dental caries progressed.

In the following table are presented depending on the gravity of the lesions:: the necessity of the anesthesia, the necessity of applying a new gel coating and the medium necessary time for the realization of the cavity preparation:

Total Nr of the lesures: 27	Total Nr of necessary anesthesia: 4	Nr of roots on which a second application of the gel is needed	The medium necessary time for the caries preparation (min)
Initiated lesions : 26	0	0	5,53
Medium lesions: 6	1	2	7,63
Profound lesions: 5	3	4	11,02

DISCUSSIONS

At the majority of the caries lesions was necessary the use of the rotary instrument in order to create the access for the application of the Carisolv gel, but the use of the gel was not necessary anymore for the removal of the decrepit dentine, using the hand tools specific to this minimal invasive technique. Also we tried by reducing the stress of the patients during the treatment to change their attitude atitudinea towards the dentist and to educate them to come regularly at the clinic, for the realization of the dental prophylaxis. Because of the lack of pain during the Carisolv treatment the patients requested especially that the other cavities to be prepared in that manner. The lack of pain and the necessity of the syringe and needle, meaning anesthesia, led to the reduction of the patients' stress during the visits at the dentist. Althoug the necessary time for the removal of the infected dentine by using Carisolv system is much bigger than in the cases of the use of millings, but this fact was considered by the patients unimportant in the absence of pain. The absence of pain, of the noises, of the smell and of the unpleasant taste motivated the patients who were initially anxious and frightened to become calm and relaxed.

Considering that the experience of the pain is subjective, the use of the chemo-mechanical method of removal of the caries dentine and all the clinical circumstances which come along with the procedure, it is very useful particularly in the situation of the treatment of the very profound lesions at the anxious patients.

CONCLUSIONS

The main conclusions we put across as a result of these studies are:

- the patients accepted easily this type of treatment because it is more comfortable, it gives less pain and this why they were more relaxed during the treatment related to the treatment of the caries realized by classical methods;
- The realized studies in vitro with the help of SEM showed that the prepared dentine surface was clean and there were no areas of decrepit dentine which was not totally removed;
- By the check ups from 6 to 6 months we observed that there were no cases with painful reactions, meaning the pulp organ of the treated teeth was not affected;
- There were no secondary caries or relapses of caries which means that the caries process was fully removed;
- Taking into consideration the age of the patients, we didn't use diga only the classical isolation with cotton rolls but the quality of the preparation and of the blocking was not affected;
- Absolutely all the patients came back with much more confidence to the clinic for the next check up.

REFERENCES

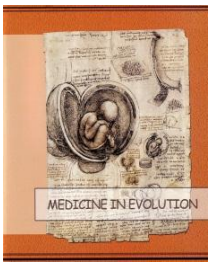
1. Ayad, MF, Rosentiel, SF., Hassan, MM. Surface roughness of dentin aftertooth preparation with different rotatory instrumentation. J Prosthet Dent. 75:122-128, 1996.
2. Banerjee A, Kidd EAM, Watson T F. Scanning electron microscopic observations of human dentine after mechanical caries excavation. Journal of Dentistry 2000;28:179-186.
3. Irena Balčiuniene, Ruţa Sabalaite, Inga Juškiene. Chemomechanical Caries Removal for Children. Stomatologija, Baltic Dental and Maxillofacial Journal,

7:40-4, 2005

4. M.P. Teodorovici, A.V.Sandu, Galina Pancu, Simona Stoleriu3, S.Andrian. A Comparative Study On The Topography Of The Dentinary Surface Resulting After The Removal Of Pathological Tissues By Various Techniques. Odontology volume 14 • issue 4 October / December 2010 • pp 278-282
5. Bergmann J, Leitão J, Kultje C, Bergmann D, Clode MJ. Removing dentine caries in deciduous teeth with Carisolv: a randomised, controlled, prospective study with six-month follow-up, comparing chemomechanical treatment with drilling. Oral Health Prev Dent. 2005;3(2):105-11.
6. Bahr Aloloumi Z., Dasdar M., Falahzadeh H. Clinical evaluation of caries in primary molars using Carisolv and rotary instruments. Majallah-I-Dandanpizishki Fall 2006; 18(3 (60)):18-14
7. J A Beeley, H K Yip & A G Stevenson. Conservative dentistry: Chemochemical caries removal: a review of the techniques and latest developments. British Dental Journal 188, 427 - 430 (2000) Published online: 22 April 2000 | doi: 10.1038/sj.bdj.4800501
8. Fure S, Lingström P, Birkhed D. Evaluation of Carisolv for the chemo-mechanical removal of primary root caries in vivo. Caries Res. 2000 May-Jun;34(3):275-80.

Solveig Fure, P. Lingström. Evaluation of the chemomechanical removal of dentine caries in vivo with a new modified Carisolv gel. Clinical Oral Investigations. September 2004, Volume 8, Issue 3, pp 139-144

WHAT DO OUR PATIENTS WANT? A STUDY REGARDING THE QUALITY OF THE DENTAL MEDICAL SERVICES



CRISTINA PÎRVU[1], ION PĂTRAŞCU[2], DANIELA PÎRVU[3], ANDREEA DIDILESCU[4], ANCA AXANTE[5]

[1]Department of Oro-Dental Diagnosis, Ergonomics and Research Methodology, University of Medicine and Pharmacy "Carol Davila", Bucharest
[2]Department of Dentures Technology and Dental Materials, University of Medicine and Pharmacy "Carol Davila", Bucharest ;
[3]Department of Embryology, University of Medicine and Pharmacy "Carol Davila", Bucharest ;
[4]Department of Dentures Technology and Dental Materials,University of Medicine and Pharmacy ,"Carol Davila", Bucharest ;
[5]Department of Oro-Dental Diagnosis Ergonomics and Research Methodology University of Medicine and Pharmacy "Carol Davila", Bucharest

ABSTRACT

Aim and objectives: the present study develops an analysis of the quality of the dental medical services, in an attempt of contouring the demands and expectations of the patients when addressing practitioners and their private practices.

Material and methods.The study involved two stages. In the first stage an interview chart was used which was presented to a group of doctors and patients, demanding them to mention 5 important aspects of the dental practice which they consider of outmost interest when choosing the doctor or the practice (the doctors were asked to make remarks from their patients perspective). In the second stage a 16 aspects chart was administered to the patients (the aspects derived from the first interview) and they were asked to grade them in accordance with how important they see them.

Results.The main results are represented on a scale of the importance they have in the mentalis of the 16 patients. The data was analyzed and compared regarding sex and age groups.

Conclusions: „What do our patients want?": reliability regarding hygiene and infection control, deep human concern manifested through empaty towards their suffering, responsability and proffesionalism, respect towards their time and their money and lots of others.

Key words: *dental medical services, quality, management*

Correspondence to:

Cristina Pîrvu
University of Medicine and Pharmacy,,Carol Davila", Bucharest
Phone: 0721278028
E-mail address: crstnprv@yahoo.com

INTRODUCTION

Nowadays one can no longer neglect the fact that medical dental practice - which is mainly private - must be regarded as a business and treated likewise. Therefore the dentist, manager of its practice in most of the cases, must develop managing abilities next to his medical ones. In his managerial activity he must confront the demand of ensuring patients-customers who are the main activity of his business [1].

Ensuring the desired quality in the health department requests a certain atitude towards work, an ensemble of practical activities, a scientific approach and attention towards patients' needs and demands. It also needs constant adaptation to the evolution of these demands, flexibility, inventively and creativity [2].

Regardless of how the pactitioners percieve the quality they offer their patients they should actually consider the evaluation and apreciation of their patients. The patients constantly evaluate us- as a team and as a practice- to see and understand weather they feel confortable with us and weather they can trust us. They develop such judgements every time they meet us and develop their appreciation abillities in time [3]. They cannot objectivly appreciate the doctor and his treatment and therefore tend to judge the superficial aspects (not the proffesional, technical ones) of the medical care and the interraction with the members of the team. They use substitute appretiation factors- instead of technical ones, such as: comfort (do they feel like everything is being done to ensure them with maximum confort?), cost (the quality of the health care is in accordance with the price they pay? Have all the costs been explained to them?), punctuality and treatment duration (are they required to wait? Is the team operational?). In such a manner it is possible for a patient to end up trusting a doctor without knowing its professional skills, simply because he feels that the doctor does the best that he can in the interest of the patient. On the other hand problems can appear when the team members do not satisfy the patient's non-technical demands, such as: they do not communicate in an understandable manner and they show disrespect and lack of consideration to the patient. Not respecting the values and the expectations of the patient has direct consequences on the addressability, even when the professional skills are special [4].

Aim(s)

In the present study we have planned an analysis of the quality of the dental medical services, in an attempt of contouring as detailed as possible the demands and expectations of the patients when addressing dental professionals and their practices. A comparative appreciation of the perception of the quality of services in dental medicine has been made, looked upon from two perspectives- of the doctors – services providers and of the patients as beneficiary clients. The necessity of such a comparison and ranking the aspects in correlation to the importance they have in the patients' mind appeared with the question: to what extent do the professionals in dental medicine domain and the dental clinics managers know the demands and expectations of the patients. We predict that a correct perception of these expectations and demands of the patients/clients is of great usefulness to the development of the practice in a professional medical manner and a profitable one.

In order to achieve this goal we have defined clear work objectives and stages. One of the first questions asked is: „what do doctors think is important to their patients?" and „what do patients declare is important when choosing the doctor and the practice?. The second and more important stage

answers to another question: „how important are the aspects we have proposed our patients to appreciate?" or shortly „what do our patients want?".

MATERIAL AND METHOD

In order to elaborate this study we have conceived two study charts, in accordance with different stages: an interview chart (one for the doctors and one for the patient) destined to the first stage of the research and a questionnaire chart (addressed to the patient) used in the second stage. Study design was transversal survey.

In the first stage 36 doctors, fellow practitioners, were asked to appreciate which they believe are the most important 5 factors that give attractiveness and quality to the services they offer in dental medicine and that determine the patients to choose a certain doctor or a certain practice. It's worth mentioning that the doctors were asked to try to think as patients. Also, 60 patients (authors' patients and other colleagues' patients) were asked to mention 5 factors they consider important to them, that are determinant in choosing a certain practice or a certain doctor, regarding their experience as patients in different practices and with different doctors.

These demands had a double goal: one of them was obtaining from doctors and from patients lists containing elements of appreciation of services, which are to be ordered in accordance with their frequency, and the second goal was to obtain a common list – which is to be used in the second part of the study.

In the second stage, data from the anterior part were used in order to conceive a questionnaire containing 16 aspects regarding the quality of the dental services. These aspects were obtained from the data gathered in the first stage- both from the doctors and from the patients. They were presented to the patients included in the screening (patients who were addressing the authors and other colleagues for treatment) asking them to appreciate these aspects in accordance with the importance they have to them when choosing the dentist or the practice, and to grade them from very important to unimportant. There were no inclusion-exclusion criteria for the participants in the study.

In order to determine them to make comparative choices the participants were asked to choose 5 very important aspects, 5 important aspects and 6 less important ones. Their choices will be useful in obtaining after the statistical analysis, a scale of their importance from the viewpoint of the patients, which is important in order to have a good practical orientation.

The questionnaire was distributed to a number of more than 200 patients, out of witch 215 were correctly filled in and used in the study. We have collected important data, that are to be statistically analised. Data distributions were expressed as means, standard deviations (SD), ranges, and percentages, as appropriate. Associations were tested using the Pearson Chi-squared test.We used Stata 11IC (StataCorp LP, Texas, USA, version 2009) in the data analyses. A p-value < 0.05 was considered statistically significant.

RESULTS

The result of the first stage is represented by a series of aspects, specific for dental practice, presented by doctors ad by patients on the charts filled in. The second stage is the one offering the most interesting and valuable results.The 16 aspects in the questionnaire chart were the following:

A. The doctor's skills, who shows a lot of concern while working and the lack of pain.

B. Respecting appointments, punctuality and reduced waiting time.

C. Location of the office- close to work or household, so that it is easily accessed.

D. The ambiance of the practice and the welcoming attitude.

E. Special offers, free services and advertising.

F. Good doctor-patient communication and treatment explaining.

G. Doctor's and personnel pleasantness; doctor's availability and patience for listening patients demands. The ability of the personnel in calming fearfull patients.

H. Doctor's professionalism, expertise and responsibility; trustfulness in the doctor and in the solutions suggested.

I. The quality of the medical services, satisfaction with prior treatments and with the warranties accorded

J. Prompt scheduling, by request and prolonged working hours.

K. Modern equipment and high quality materials used by the dentist.

L. Recommended doctor and/or with good reputation.

N. Acceptable prices and flexibility in payment.

O. Nonsmoking doctor with nice, healthy teeth.

P. Practice hygiene and instrument sterilization.

In order to better understand patients perception and the character of their requests I have grouped the aspects in the questionnaire chart in threee groups:

1. Organizational aspects(Org.): B,C,D,E,J,N.
2. Technical aspects (Tech.): K,M,P.
3. Human aspects (Hu.):A,F,G,H,I,L,O.

After data analysis the results are: 215 participants, 81 male, 134 female, aged between 18-80 (average age 37,2). For each of the aspects in the questionnaire a total score was calculated resulted from the appreciations of each of the study participants. The score was assessed as follows: Total number of "important" answers + (total number of "very important" answers x 2) = the value attributed by the patients.

According to the score obtained by each of the 16 aspects we obtained their order- in accordance with their importance for the patient. From the most important to the least important the order is:

1. Practice hygiene and instrument sterilization (P).
2. The quality of the medical services, satisfaction with prior treatments and with the warranties accorded (I).
3. Doctor's professionalism, expertise and responsibility; trustfulness in the doctor and in the solutions suggested (H).
4. Good doctor-patient communication and treatment explaining (F).
5. The doctor's skills, who shows a lot of concern while working and the lack of pain(A).
6. Respecting appointments, punctuality and reduced waiting time (B).
7. Modern equipment and high quality materials used by the dentist (K).
8. Doctor's and personnel pleasantness; doctor's availability and patience for listening patient's

demands. The ability of the personnel in calming fearful patients (G).

9. Recommended doctor and/or with good reputation (L).

10. Acceptable prices and flexibility in payment(N)

11. Prompt scheduling, by request and prolonged working hours.

12. Access to different specialists at doctor recommendation, and diverse services offered (orthodontics, surgery, implantology) (M).

13.The ambiance of the practice and the welcoming attitude (D).

14. Location of the office- close to work or household, so that it is easily accessed(C).

15. Special offers, free services and advertising (E).

16. Nonsmoking doctor with nice, healthy teeth (O).

The numbers we have obtained offer us an image of the appreciation degree of each aspect, as presented in Figure 1.

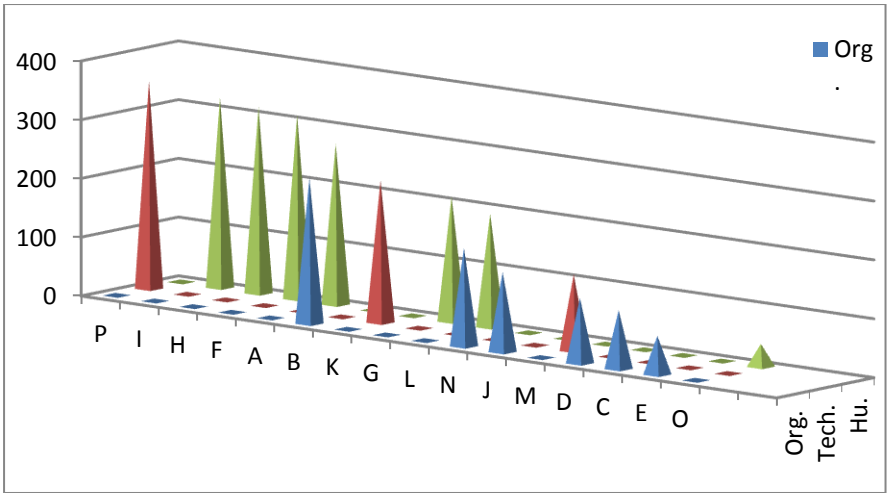


Figure 1: Ranking quality aspects in accordance with the scoring obtained

I have calculated the total scoring for each aspect gender related- for male –female respectively and in accordance with the age group (18-39, 40-59, 60-80 years).

The results as presented in figure 2 show no significant difference between male and female appreciation. In accordance with this observation there is no statistically significant association between gender and answer for either one of the questions (Pearson Chi-squared test, $p>0.05$).

Following the results for the three age groups (figure 3) one can notice no significant difference - age group related in the appreciation of the 16 elements.

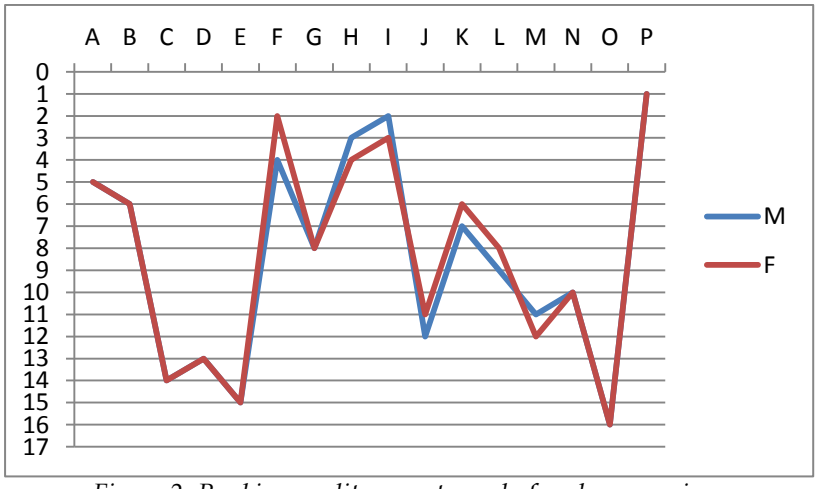


Figure 2: Ranking quality aspects, male-female comparison

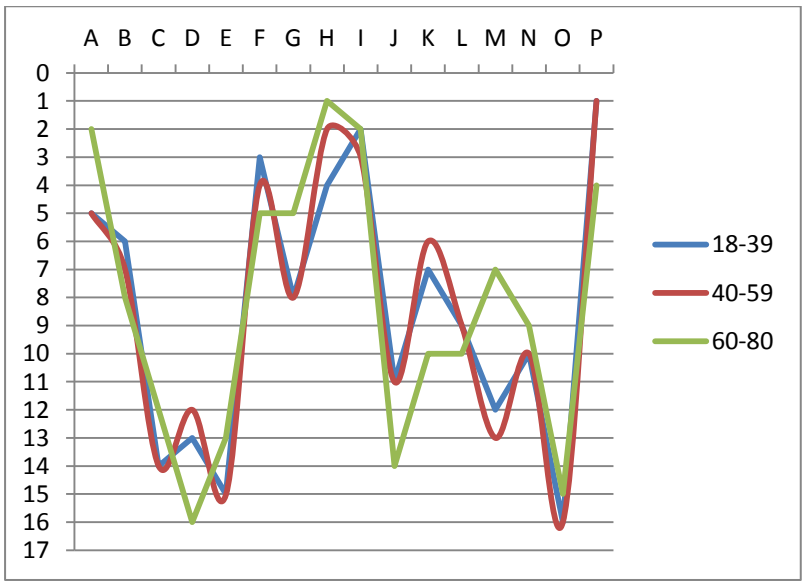


Figure 3 Ranking quality aspects age related:

DISCUSSIONS

From the study of the scale obtained and from figure 1 we obtain a distribution of the interest of the patient for different types of aspects. We noticed that most of the human aspects are at high level of appreciation from the patient, being therefore grouped at top of the scale, whereas most organizational aspects are less appreciated. The technical aspects are to be discussed separately. Anyhow, choosing the doctor and the practice is the result of a sum of appreciations, which are generally subjective.

These results show a technical aspect which holds the highest rank in patient's requests, P aspect: practice hygiene and instruments sterilization. Might this be determined by the real problems perceived by the patients in the dental practices they have addressed to and by a form of 'phobia' of transmitted infections? We believe that, regardless of the cause, this result must lead to a major motivation in ensuring hygiene, aseptically and antiseptically working conditions in the dental practices.

This aspect is followed by a series of human aspects, those related to personnel implication, weather it means ability to relate or professional skills: I,H,F,A. Other two important human aspects are well placed in patient's apreciation: G and L. The positioning of these two aspects reflects patient's needs to be treated with maximum care, of receving maximum attention for their requests and wishes and their need for security, considering the fact that they are trusting someone else with their health.

The reputation of the doctor and of the practice and it being recommended by someone familiar are strong values and motivations which reflect in addressability.

The ranking places in the middle part both an organizational aspect and a technical one. Respecting appointments, punctuality and reduced waiting time (B), organizational aspect, fairly appreciated by the patient should get more attention from the managers and the doctors. Regarding the dynamics of the social life where time is of great importance, respect towards the time and programmer of the patient is translated into respect towards the patient. Appreciating technical aspects like modern devices and materials (K) shows that patients understand the way using advanced working technologies and material quality

reflect in the final quality of the product and of the service.

At the bottom of the ranking we find organizational aspects mainly, J, D, C, E. The appreciation of these aspects and their weight is reduced only in comparison to the other aspects we have discussed.

Somehow surprisingly is the position that the price holds in our ranking. Too many times, even us as practitioners we tend to overvalue this aspect. Results of the study show that many other aspects are by far more important for the patient than the price. Special offers, free services and advertising don't seem to influence drastically patients' choices.

The position of the prompt scheduling suggests the availability of the patient to adapt to the possibilities offered by our programmer, considering the fact that their choice is based on multiple aspects.

The design of the practice and welcoming atmosphere, together with the location of the practice in relation to the household or working place are organizational aspects that concern the manager in the initial phases- when starting the business. Their positioning in the ranking shows that patients don't necessary expects a "luxurious" aspect, and that they are willing to travel longer distances in order to address the practitioner or the office they desire.

Access to different specialists, at the recommendation of the general practitioners, and the diversity of the services offered (M) is a technical aspect that once submitted to their attention has received some interest, though it is remotely placed compared to the top of the list. This leads us to the conclusion that patients are still strongly 'bonded' to the general practitioner but they are beginning to understand the necessity of collaborating with other specialists from the field.

Doctor's image- nonsmoking doctor, with nice healthy teeth (O) – fades in importance when compared to other aspects analyzed. We are yet to ask ourselves weather in a society in which aspect holds an increasing role shouldn't we be more aware of the image of the professions- which should in it reflect health.

Aspects related to the quality of the medical services are of little interest in the scientific literature. In a similar study published in 1996 [5] the results showed that the three most important criteria chosen by the patients in appreciating the quality of the dental medical services were: explaining the medical procedures, hygiene and infection control, and doctor's practical skills, the last three were: extremely up to date equipment, nice environment, a good image of the office.

CONCLUSIONS

We consider that the present study has achieved its goal, offering us important data regarding factors related to patient's expectations and demands, which are often perceived as being subjective and discussable by the doctors and managers. The increased number of factors and their organizing in accordance to the importance the patients think they have can be of great help we carefully analyzing the elements that provide quality to the dental medical practice. In this manner we can better orient the offers in this domain to patients' expectations.

"What do our patients want?": safety regarding hygiene and infection control, deep human concern and empathy towards their suffering, high levels of professionalism and professional responsibility, respect for their time and money and lots of others.

A correct orientation of the dental medical practice, as a business to the patient's service, cannot be realized

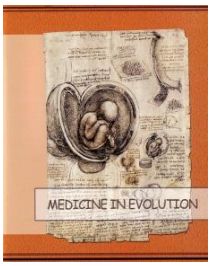
unless we place the desire to satisfy the expectations and demands of our patients among our major goals. The final appreciation of the medical services remains the patient's task, whereas resolving specific problems remains the professional's responsibility. In fact, the patient and his medical problems, extremely complex represents the motivation for us existing as a profession and as a business.

For elaborating this study I have benefited from the help of my fellow practitioners in Bucharest, and implicitly the availability of their patients, and for this we thank them all.

REFERENCES

1. Mc.Guigan P.J., Eisner A.B., *Marketing the dental practice- Eight steps toward success,* JADA 2006;137: 1426-1433.
2. Opincaru C., Gălățescu E-M, Imbri E., *Managementul calității serviciilor în unitățile sanitare*, Bucureşti, Editura Coresi,2004
3. Kevin R., *The Dissidentist...Your patients will love you ,Business leadership for dentistry* www.kevinrose.co
4. Newsome P., Wolfe I.S., *Value gaps in dental Practice- Understanding how differences in core values can adversely affect the practice,* JADA 2003;134:1500-1504.
5. Burke L, Croucher R. *Criteria of good dental practice generated by general dental practitioners and patients*. Int Dent J 1996;46:3-9

PERIODONTAL DISEASE AND CVD. CONDITIONAL OR COINCIDENTAL ASSOCIATION?



PAULA DERBAN[1], CAROLINE KRALEV[1], ANDREEA POGAN [1], DAN ONISEI[1], DOINA ONISEI[1]

[1]University of Medicine and Pharmacy „Victor Babes" Timisoara, Department of Periodontology

ABSTRACT

Recent studies deepen our understanding of the mechanisms involved in the pathogenesis of CardioVascularDisease and Periodontal Disease. A causative relation seems to emerge from the findings of the late 20 years which could propose PD as a risk factor for CVD.The link is not completely elucidated, but physiological mechanisms following the pathways of systemic inflammation seem to creat a logical cascade that runs along with the effect of acute –phase proteins and systemic inflammation markers to the formation and progression of atherosclerotic plaques and consequent onset and progression of CVD.

On the other hand periodontal treatment seems to lower the levels of plasmatic CRP and fibrinogen along with other acute-phase proteins relieving the circulatory system of the inflammatory burden.

Key words: *periododontal disease (PD), cardiovascular disease (CVD), systemic inflammation, C-reactive protein (CRP), fibrinogen*

Correspondence to:

Prof.Dr.Doina Onisei
"Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, Department of Periodontology, Faculty of Dental Medicine
Phone: 0722942607
E-mail address: donisei@umft.ro

INTRODUCTION

Periodontal (PD) and cardiovascular disease(CVD) are very common aflictions of modern society. Over the last century physicians suspected a connection between oral infections and systemic disease. Starting with Mattila`s study in 1989 (8), several inquiries were conducted on the relationship of oral and systemic health. A link between the two was often proposed, even if the nature and degree of their association has been never fully elucidated.

PD

Severe periodontal disease affects 15–20% of middle-aged adults.

Worldwide, about 30% of people aged 65–74 have no natural teeth.

Inflammation of gingival tissues due to the accumulation of dental plaque results in the onset of periodontal disease. As the condition progresses, subsequent inflammatory distruction of the supporting tissue occurs, leading from gingivitis to periodontitis.

Initially, glicoproteins derived from salivary components adhere to the surface of newly cleaned teeth and form the pellicle. The pellicle is further rapidly inhabited by microorganisms of salivary origin and constitutes itself into a biofilm, a bacterial ecosystem in a polymeric matrix that covers the surface of teeth. The supragingival areas are bathed by saliva and the subgingival ones by the transudative fluid .The microbial species differ in the supra- and subgingival areas.

Streptococcus sanguis, Streptococcus oralis, Streptococcus mutans, Actinomyces naeslundii, and Actinomyces odontolyticus have a special affinity for constituents of the pellicle, and are therefore its initial colonizers.Fusobacterium nucleatum is one of the secondary colonizers, which are later followed by other specific bacteria.

As gingivitis occurs, subgingival microflora changes and progressivly shifts to species typical for periodontitis,namely, from gram-positive to gram-negative anaerobic bacteria: Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Selenomonas noxia, Campylobacter rectus, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, and spirochetes.

As shown above, the primary etiology of periodontal disease is represented by bacteria, situated in the biofilm.Although the main role in periodontal infections is accredited to such bacteria, the initiation of the disease depends widely on the host response. Bacterial products determine at first a local inflammatory response activating the innate immune system through toll-like receptors expressed by leucocytes and resident cells.

So, from the initial stage of gingivitis, which is a limited local inflammatory process, periodontal disease evolves to periodontitis, a condition which implies loss of periodontal tissue and a progressive distructive course.

Epidemiological studies usually summarize parameters such as: bleeding on probing(BOP) – indicator of inflammation in the gingival tissue and affection/alteration of the sulcular epithelium; probing pocket depth (PPD) -measured from the gingival margin to the epithelial attachment, clinical attachment level CAL), – which measures apical migration of the periodontal tissue and the degree of tissue loss.

With dental plaque as the leading etiological factor of periodontal infection, we still must acknowledge the importance of the host response in the progression and stabilization of periodontal disease. (7)

CVD

Globally, CVD tends to be the leading cause of premature death, causing 42% of deaths before 75 years of age in women and 38% in men.

Arteriosclerotic vascular diseases (ASVD) affect the heart and the blood vessels. Their major components, defined as diseases of the circulatory system by the International Classification of Diseases, 9th Revision, are as follows:

1) Ischemic heart disease,

2) Cerebrovascular diseases, and

3) Diseases of arteries, arterioles, and capillaries (also known as peripheral vascular disease)

ASVD is a chronic progressive process which can cause acute clinical events, including acute coronary syndromes, myocardial infarction, and stroke.

Major independent risk factors are:

- Advancing age
- Cigarette smoking
- Diabetes
- Elevated blood pressure
- Elevated serum total (and LDL) cholesterol
- Low serum HDL cholesterol

Predisposing risk factors

- Abdominal obesity
- Ethnic characteristics
- Family history of premature coronary heart disease
- Obesity
- Physical inactivity
- Psychosocial risk factors

Conditional risk factors

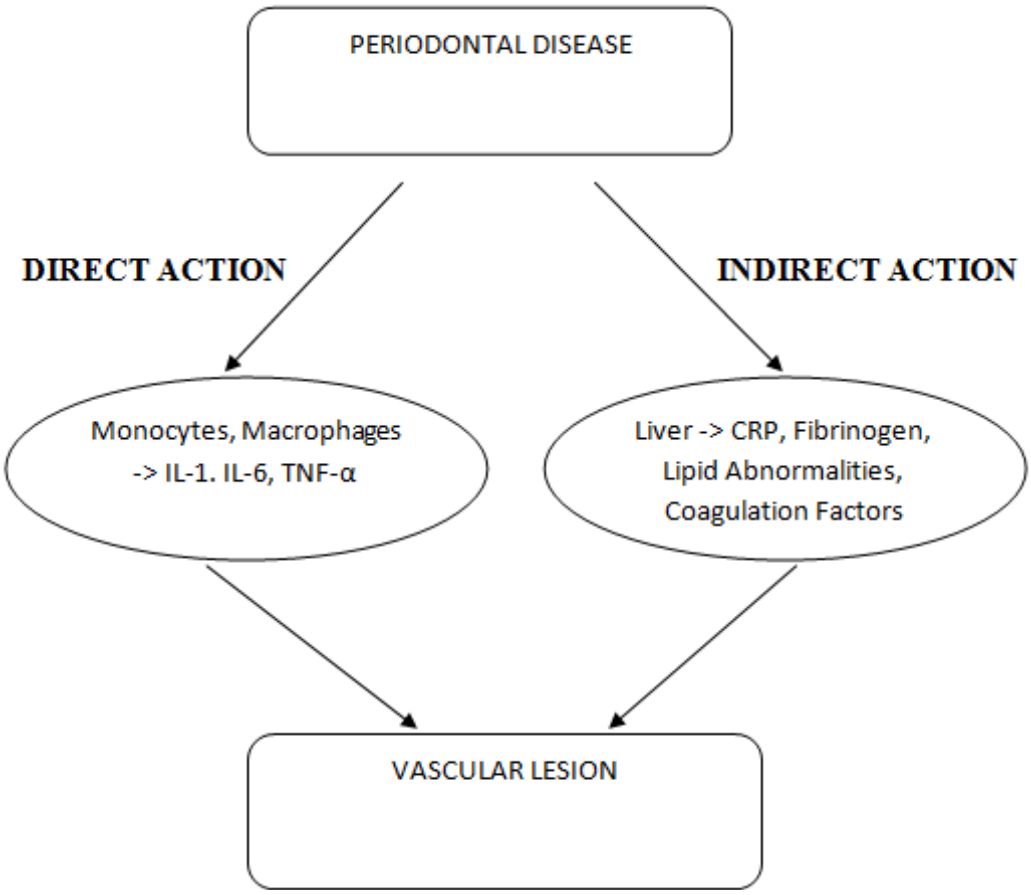
- Elevated serum homocysteine
- Elevated serum lipoprotein
- Elevated serum triglycerides
- Inflammatory markers (e.g.C-reactive protein)
- Prothrombotic factors (e.g.fibrinogen)
- Small LDL particles (12)

The question is if the available data allows us to support a conditional relation between periodontal disease and CVD and even to acknowledge the role of PD as a risk correlate for CVD.

SYSTEMIC COMPLICATIONS OF PERIODONTAL INFLAMMATION

Over the last two decades considerable progress has been made in finding a relationship between PD and CVD. The liaison between ischemic heart disease, cerebrovascular diseases,and peripheral vascular disease is atherosclerosis, which seems to be significantly influenced by systemic inflammation.

Periodontitis contributes to the state of systemic inflammation acting directly on the vascular walls and also indirectly through acute phase proteins produced in the liver. Bacteria from periodontal pockets, such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans, were found to be capable of migrating and living in the vascular system in atherosclerotic plaques. Also acute-phase proteins (CRP, fibrinogen, Il-1, IL-6, IL-8 and TNF- α) were reported to be elevated in patients with myocardial infarction (MI) and periodontal disease, which indicates a systemic inflammatory state.



Consequently, the presence of periodontal bacteria in the vasculature induces an exagerated inflammatory response and the release of acute-phase proteins which determine a systemic inflammatory state.

On the other hand, periodontal treatment seems to lower inflammatory markers such as CRP and IL-6 and improve vascular function.(11)

CRP

C-reactive protein is an acute-phase protein synthesized in the liver, and a member of the pentraxin family of proteins. Its plasmatic concentration rises in inflammatory states and is therefore of clinical relevance in determining the presence and degree of systemic inflammation. CRP binds to specific molecules on the surface of dying (or dead) cells and bacteria determining the recognition and phagocytotic immunologic response.(3)

Recent studies associate even slightly elevated CRP levels with subsequent major cardiac events.(1)

It is a strong and independent risk factor for MI or sudden death, conditions associated with coronary artery atherosclerosis.

Compared to other serum biomarkers (IL-6, homocystein,serum amyloid A and standard lipid measures) CRP was proven to be the strongest predictor of cardiovascular risk.

By induction of protrombotic factors and interfering with endothelial nitric oxide synthase, CRP is directly involved in augmenting the innate inflammatory response.(4)

CRP levels can be raised by non-specific infections, such as periodontal disease, wich determine an acute phase reaction and a systemic inflammatory state.(10) CRP was also proven to be produced by the gingiva(5). Thus periodontitis may induce an inflammatory response increasing CRP values and presenting itself as a risk factor for CVD.

PD was reported to be common in patients with acute myocardial

infarction (AMI) and is associated with higher CRP levels as part of a systemic inflammatory response.The reported correlation seems to be independent of other contributing factors.(2)

FIBRINOGEN

Fibrinogen is a plasmaglycoprotein synthezised in the liver, which is converted by thrombin into fibrin during blood clot formation.

Increased levels of fibrinogen are clearly associated with the risk of cardiovascular events. A strong and independent association of higher plasma fibrinogen levels and the onset and progression of ischaemic heart disease, was confirmed in a large number of studies starting with the Northwick Park Heart Study in 1986.(9).

CONCLUSIONS

Several studies of the last 2 decades related cardio-vascular events to the state of oral health, especially to periodontitis – it being a chronic stabilized infection, which allows and determines long term local and systemic inflammation.

Early studies such as Lowe et al (6), associate the number of missing teeth directly to subsequent cardio-vascular events in healthy subjects.

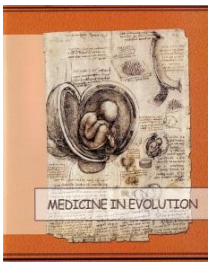
The correlation to periodontitis is further elaborated by investigating the paths through which it can influence the onset and progression of CVD. In the causal chain periodontal bacteria, the innate immune system, its mediators and acute phase protein such as CRP, fibrinogen, IL-1, IL-6 and TNF-α find their definite places and contribute to the damaging relation that is to be established on local and systemic level. On the other hand, studies exist that prove the oportunity and benefit of periodontal treatment on the systemic inflammatory status.

REFERENCES

1. Black S., Kushner I, Samols D, C-reactive Protein, J Biol Chemistry Vol. 279, No. 47, Issue of November 19, 2004, pp. 48487–48490,
2. Deliargyris EN et al, Periodontal disease in patients with acute myocardial infarction: prevalence and contribution to elevated C-reactive protein levels. Am Heart J. 2004 Jun; 147(6):1005-9.)
3. Du Clos TW, Function of C-reactive protein, Ann Med.2000 May;32(4):274-8.
4. Genco RJ, Williams RC, Periodontal Disease and Overall Health: A Clinicians Guide, Ed. Professional Audience Communications, 2010
5. Lu Q, Jin L, Human gingiva is another site of C-reactive protein formation. J Clin Periodontol 2010, 37:789–796,
6. Lowe.G, Woodward M, Rumleya A., Morrisonc C, Tunstall-Pedoed H, Stephene K, Total tooth loss and prevalent cardiovascular disease in men and women: Possible roles of citrus fruit consumption, vitamin C, and inflammatory and thrombotic variables, J Clin Epidemiol. 2003 Jul; 56(7):694-700.
7. Mani Ameet M.,Tejnani Avneesh H.,Pawar Babita R., Marawar Pramod , The Relationship Between Periodontitis and Systemic Diseases – Hype or Hope?, J Clin Diagn Res 2013 Apr;7(4):758-62.
8. Mattila K J, Nieminen M S, Valtonen V V, Rasi V P, Kesäniemi Y A, S. Syrjälä S L, Jungell P S, Isoluoma M, Hietaniemi K, and Jokinen M J. Association between dental health and acute myocardial infarction, BMJ. 1989 March 25; 298(6676): 779–781.
9. Meade TW, Mellows S, Brozovic M, Miller GJ, Chakrabarti RR, North WR, Haines AP, Stirling Y, Imeson JD, Thompson SG., Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study., Lancet. 1986 Sep 6;2(8506):533-7.
10. Pejcic A,Kesic L J and Milasin J, C-reactive protein as a systemic marker

of inflammation in periodontitis, Eur J Clin Microbiol Infect Dis. 2011 Mar;30(3):407-14. doi: 10.1007/s10096-010-1101-1. Epub 2010 Nov 6.
11. Shanies S, Hein C, The Significance of Periodontal Infection in Cardiology, Grand Rounds, May 2006, Vol. 1, No. 2.
The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts), European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

THE GOLDEN PROPORTION IN THE ANTERIOR MAXILLARY REGION



CAIUS CRISTESCU[1], HORATIU URECHESCU[2], ANGELA CODRUTA PODARIU[3]

[1] PhD student at the University of Medicine and Pharmacy „Victor Babes" Timisoara
[2] Department of Maxilo-facial and Oral Surgery, University of Medicine and Pharmacy „Victor Babes" Timisoara
[3] Head of Department 1, University of Medicine and Pharmacy „Victor Babes" Timisoara

ABSTRACT

This study was conducted on a group of 69 patients, dentists and dental students of the University of Medicine and Pharmacy „Victor Babes" Timisoara (40 female and 29 male), with ages between 18 and 33 years old. The participants were selected using the following criteria:

- *Above average oral hygiene*
- *No prosthetic restorations in the maxillary anterior region*
- *No fillings in the maxillary anterior region*
- *No malpositions in the maxillary anterior region*

The purpose of this study was to assess the golden proportion in the maxillary anterior region on a group of young people with above average oral hygiene.

Key words: *golden proportion, golden ratio, Fibonacci, maxillary anterior region*

Correspondence to:

Caius Cristescu
Phone: +40722534320
E-mail address: caius.cristescu@yahoo.com

INTRODUCTION

The first correlations between the golden proportion and dentistry were made in 1978 and have as a guideline the Fibonacci sequence and "Phi" (1,618/0,618). The Fibonacci sequence starts with the numbers 0 and 1 and after that, each number is represented by the sum of the two previous numbers: 0,1,1,2,3,5,8,13,21,34,55……

Mathematically, Fibonacci numbers are number is defined by the sum of the previous two:

$F_0 = 0$

$F_1 = 1$

$F_x = F_{x-1} + F_{x-2}$ for $x \geq 2$

0,1,1,2,3,5,8,13,21,34,55……

The golden ratio is the ratio between any two successive numbers in the sequence. To be noted that for the numbers at the beginning of the sequence, the ratio slightly differs from 1,618034…, but the bigger the pair of numbers, the closer the approximation (table 1).

Theories in dental esthetics say that the ratio between the central incisor and the lateral incisor, the one between the lateral incisor and the canine, as well as the one between the canine and the first premolar is Phi. Also, the ratio between the width of the central incisors and their height is also Phi (Fig 1)

Table 1.

A	B	A/B
2	3	1,5
3	5	1,6666
5	8	1,6
8	13	1,625
…..	…..	…..
144	233	1,618055
233	377	1,618025
…..	…..	…..

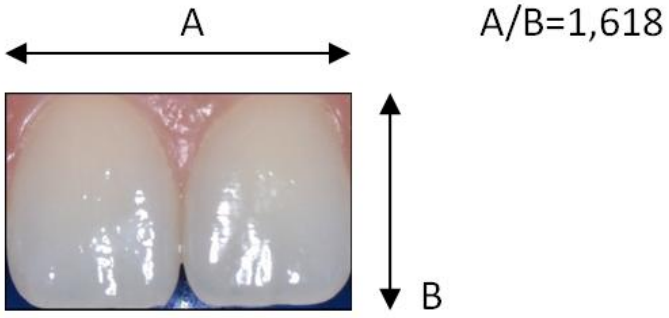


Figure 1

AIM AND OBJECTIVES

The main objective of this study was to assess the golden proportions in the maxillary anterior region (1.4-2.4). Therefore, the aim was to establish the ratio between the widths of the teeth in the maxillary anterior region: 1.2/1.1, 1.3/1.2, 1.4/1.3, 2.2/2.1, 2.3/2.2, 2.4/2.3. Also, the ratio between the width of the central incisors and their height was calculated. As a secondary objective, if the rule of the golden proportion proved true, it would be eligible to be applied in esthetic dentistry with the help of the "digital smile design" concept.

MATERIAL AND METHOD

The study was conducted on a group of 69 patients, dentists and dental students of the University of Medicine and Pharmacy „Victor Babes" Timisoara, with ages between 18 and 33 years old, from which 40 of them were female and 29 male. The average age was 22,14 years (female: 22,025; male:22,31). These 69 participants were selected by the following criteria:

- Above average oral hygiene
- No prosthetic restorations in the maxillary anterior region
- No fillings in the maxillary anterior region
- No malpositions in the maxillary anterior region

For each participant in the study, photographs were taken from frontal view, using retractors. A tripod was also used and the patient positioned on a chair so that the photographic plane would be parallel to the vestibular plane of the central incisors. The images were made with a DSLR camera (NIKON D3100), equipped with a 90mm f/2.8 MACRO lens (Tamron SP AF 90mm F/2.8) and ring-flash (Sunblitz RL716 Macro RingLite LED). To standardize the photos, the protocol for photographic presentation of the American Academy of Cosmetic Dentistry (AACD) was used as a guide. The following camera settings were used: 1/250 shutter speed, f/22 aperture and ISO 100 sensitivity.

The photos were analyzed digitally using dedicated software (Adobe Photoshop CS5; Adobe Systems Inc., San Jose, California). The widths of the teeth in the maxillary anterior region were determined in pixels, as measured between parallels through the contact point of the two central superior incisors and the most distal point of each distal proximal face of 1.4, 1.3, 1.2, , 1.1, 2.1, 2.2 , 2.3 and 2.4 (fig. 2). The width of the two central incisors was calculated as the sum of the widths of 1.1 and 2.1, and their height was determined as being the distance (in pixels) between two parallels, one through the most incisal point of the incisal edges of the two central incisors and a second one through the highest point of the gingival level (fig. 3).

Figure 2

Figure 3

Once the measurements were made and the dimensions (in pixels) were recorded, the following formulas were used to determine the ratios:

$1.2 = \frac{1.2 \times 100}{1.1} =$ ..... % din 1.1

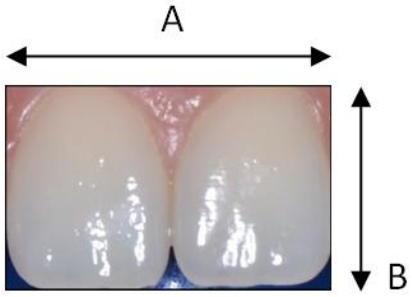
$2..2 = \frac{2.2 \times 100}{2.1} =$ ..... % din 2.1

$1.3 = \frac{1.3 \times 100}{1.2} =$ ..... % din 1.2

$2.3 = \frac{2.3 \times 100}{2.2} =$ ..... % din 2.2

$1.4 = \frac{1.4 \times 100}{1.3} =$ ..... % din 1.3

$2.4 = \frac{2.4 \times 100}{2.3} =$ ..... % din 2.3



$$B = \frac{B \times 100}{A} = \ldots\ldots\ldots\ldots \% \text{ din A}$$

It is important to mention that the dimensions we calculated are not real ones, but projected ones, as well as the ratios, due to the fact that the measurements were made on photographs, which are projected images of the 3D reality in a bi-dimensional plane. However, the golden proportions and the digital smile design concept recognize this kind of measurements in 2D, use them and then translate them (using different methods) in 3D.

RESULTS

To establish the ratio between the lateral incisors and the central incisors, measurements were made on both sides (left and right), and so 138 measurements were made. The ratio obtained was 67,71 %. For the female participants, the ratio was 67,64 %, and for the male participants 67,82 %. Statistics were also made for both female and male participants on each side (right and left). So, the ratio for female participants was 68,3 % on the right side and 66,98 % on the left side. The ratio for male participants was 68,85 % on the right side and 66,79 % on the left side. The ratio for each side (male + female) was 68,53 % on the right side and 66,9 % on the left side (Table 2).

To establish the ratio between the canine and the lateral incisor, measurements were made on both sides (left and right). Extreme values bigger than 95 % were eliminated, and so 120 measurements were taken into consideration. The ratio obtained was 79,72 %. For the female participants, the ratio was 80,84 %, and for the male participants 78,4 %. Statistics were also made for both female and male participants on each side (right and left). So, the ratio for female participants was 79,68 % on the right side and 81,92 % on the left side. The ratio for male participants was 75,43 % on the right side and 80,77 % on the left side. The ratio for each side (male + female) was 79,29 % on the right side and 81,42 % on the left side (Table 2).

To establish the ratio between the first premolar and the canine, measurements were made on both sides (left and right). Extreme values under 40 % were eliminated, as well as first premolar malpositions, and so 123 measurements were taken into consideration. The ratio obtained was 60,51 %. For the female participants, the ratio was 59,93 %, and for the male participants 60,98 %. Statistics were also made for both female and male participants on each side (right and left). So, the ratio for female participants was 60,71 % on the right side and 59,23 % on the left side. The ratio for male participants was 62,92 % on the right side and 59,6 % on the left side. The ratio for each side (male + female) was 61,66 % on the right side and 59,39 % on the left side (Table 2).

To establish the ratio between the width of the central incisors and their height, 13 participants were eliminated due to the fact that they presented

complete incisal abrasion on both central incisors, and therefore the measurements wouldn't have been conclusive. The ratio obtained was 60,79 %. For the female participants, the ratio was 60,02 % and for the male participants, the ratio was 61,79 % (Table 2).

Table 2.

	P1/C	C/IL	IL/IC	A/B(fig.1)
Raport mediu	60,51%	79,72%	67,71%	60,79%
Rapot mediu F	59,93%	80,84%	67,64%	60,02%
Raport mediu B	60,98%	78,4%	67,82%	61,79%
Femei cadran I	60,71%	79,68%	68,3%	
Femei cadran II	59,23%	81,92%	66,98%	
Barbati cadran I	62,92%	75,43%	68,85%	
Barbati cadran II	59,6%	80,77%	66,79%	
Total (F+B) cadran I	61,66%	79,29%	68,53%	
Total (F+B) cadran II	59,39%	81,42%	66,9%	
Phi	61,8%	61,8%	61,8%	61,8%

CONCLUSIONS

1. Due to the obtained results, at least for the group of population the study was conducted on, the golden proportion was not valid, and therefore, is not recommended to be used in cosmetic dentistry.

2. Regarding the ratio between the width of the central incisors and their height, the golden proportion is considered to be valid. The 1,01 % difference between the golden ratio (61,8 %) and the obtained result (60,79) is considered to be insignificant; also, the ratio for the male participants was 61,79 %. Therefore, in this case, we can consider the golden proportion valid.

3. Further research is necessary to be able to completely disapprove or approve the use of the golden proportion in cosmetic dentistry.

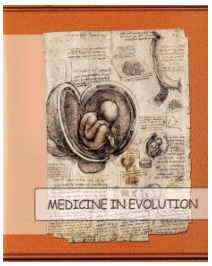
4. No significant sex-dependent and side-dependent variations between the ratios were found.

REFERENCES

1. A Dürer (1528). Vier Bucher von menschlicher Proportion.
2. A Koestler (1962). The Perfect Solids in The Watershed, Heinemann.
3. Benyafield and Adams (1976). The Golden Section Hypothesis. Brit J Psychol 67: 11-15.
4. Boyd JG. AACD accreditation process. Tex Dent J. 2005;122: 976-9
5. DW Thompson (1952). Growth and Form. Cambridge University Press, Oxford
6. E Lendvai (1971). Béla Bartók An Analysis of his Music. Kahn & Averill, London.
7. HSM Coxeter (1961). Introduction to Geometry. John Wiley & Sons Ltd, London
8. HE Huntley (1970). The Divine Proportion. Dover Publications, New York.
9. J Hambidge (1921). Dynamic symmetry. Scientific American 4:23.
10. Le Corbusier (1961). The Modulor. Faber and Faber, London.
11. L Paccioli (1896). Divina Proportione. C Winterberg, Wien Graser.
12. M Borissavlievitch (1958). The Golden Number. Alec Tiranti, London.

13. M Ghyka (1964). Goemetrical Composition and Design. Alec Tiranti, London.
14. M Gardner (1966). More Mathematical Puzzles and Diversions. Penguin Books, London.
15. R Lawlor (1982). Sacred Geometry Philosophy and Practice. Thames and Hudson Ltd, London.
16. RM Ricketts (1981). The Golden Divider. J Clin Orthodon vol XV, No 11:752-759.

PERMANENT TEETH EMERGENCE IN CHILDREN RELATED TO CARIES EXPERIENCE AND MALIGNANCIES



CRISTINA BICĂ[1], ANCA DRAŞOVEANU[1], CHINCEŞAN MIHAELA[2], DANIELA EŞIAN[1]

[1]Paediatric Dentistry Department, University of Medicine and Pharmacy of Târgu Mures
[2]Paediatric Haematology-Oncology Department, University of Medicine and Pharmacy of Târgu Mures

ABSTRACT

Purpose: To assess the incidence of carious lesions of primary teeth and the emergence patterns of permanent teeth in children with malignant conditions; to establish if malignancy influences emergence patterns of permanent teeth.

Materials and methods: We included two groups of study made of children aged 8-11 with mixed dentition and no dental agenesis. We determined the caries intensity with the help of dmft individual indices and the emergence sequence of permanent teeth through periodical clinical and radiologic examinations.

Results: The value of dmft was ≥5 in nearly 47% of healthy children and in approximately 64% of children with malignancies. We noticed optimal emergence sequences of permanent teeth in the maxilla in a ratio of 38% in healthy children and 25% in diseased children. In the mandible the favorable sequences occurred in 41% of healthy children and in 31% of diseased children.

Conclusions: The damage caused by caries of primary teeth in the second phase of mixed dentition is quite high in both groups studied. The untreated dental caries and their complications modify the emergence sequences of permanent teeth and favor the appearance of dental anomalies.

Key words: *children malignancies, teeth emergence, dental caries*

Correspondence to:

Dr. Cristina Bică
Address: Paediatric Dentistry Department, University of Medicine and Pharmacy, 38, Gh. Marinescu Str, 540000 Târgu Mures, Romania
Phone: +40 723 180 682
E-mail address: cristina.ioana.bica@gmail.com,cristina.bica@umftgm.ro

INTRODUCTION

The emergence of permanent teeth is a complex phenomenon employed in the processes of growth and development of the child, and it is influenced by general factors (systemic diseases, specific treatment, sex, race, socioeconomic factors, climate, geographical region) and local factors represented by untreated tooth decay of temporary teeth, periapical complications and their premature extraction [10].

Damage done to deciduous teeth by temporary tooth decay in children has increased sensibly in the last decades: institutionalized children and also children with special needs in all indices showed tooth decay with high intensity [1, 4]. Evaluation of the oral-dental status in children with malignant affections has also indicated growing frequency of untreated simple and complicated carious lesions at the level of primary teeth [12, 13, 16].

The compromising of primary teeth through caries leads to problems with the emergence of the permanent teeth [8, 14] and a lack of space for the last replacement teeth, usually the superior canines and inferior second premolars, with the subsequent occurrence of dental anomalies.

The research's premise started from the following issues: the complicated caries of the deciduous teeth modify the processes of dental permutation; data from the specialty literature indicates an increased risk in the occurrence of caries in children with malignant affections after chemotherapy and/or radiotherapy [3, 5, 6, 15]; however, there are no studies referring to the teeth emergence patterns of the permanent teeth in these children.

This study aimed to evaluate the incidence of the carious lesions of the primary teeth and the emergence patterns of permanent teeth in a group of children with malignant affections compared to a group of healthy children and also to assess whether the malignant condition affects the emergence pattern of the permanent teeth in lateral sectors of the arches.

MATERIAL AND METHOD

This study included children with mixed dentition between the ages of 8-11, grouped as follows:

- *The group of children with malignant affections*

The children invited to take part in this study were in the remission stages of malignant affections who followed chemotherapy and/or radiotherapy according to specific protocols. Eligibility criteria for this study were the installation of the second phase of mixed dentition (8-11 years) and lacking any type of dental agenesis of permanent teeth. Thus 36 children were selected (22 with leukemia, 14 with solid tumors) that formed the group of children with malignancies.

- *The group of healthy children*

Included in this group were 58 healthy children who have had dental injuries treated or under treatment at the Dental Center, University of Medicine and Pharmacy of Targu Mures. These children also met the study eligibility criteria: aged 8-11 years, the installation of the second phase of mixed dentition and lacking any type of dental agenesis of permanent teeth.

For each subject included in the study, the caries' intensity were determined with the help of dmft (decay-missing-filling-teeth) individual indices and the emergence sequences of the permanent teeth (3-canine, 4-first premolar, 5-second premolar) in the 4 quadrants of the oral cavity. The

assessment of tooth emergence patterns was conducted through periodic clinical and radiologic examinations, with the help of the orthopantomograms.

Statistical analysis: with the help of the methods of statistic calculation (Fisher exact test, significance level $p<0.05$) we established the frequency of each emergence pattern in the healthy and sick children as well as the association between that respective pattern and the oncological condition.

RESULTS

•Caries experience

46.55% of healthy children and 63.88% of children with malignant affections presented values of the dmft index ≥5. We noticed dmft ranging from 1-4 in 39.65% of the healthy children and 30.55% of children with malignancies. Of the total of 94 children examined, only 10 (8 healthy, 2 sick) did not develop any carious lesions and were classified as dmft=0 (Table 1 - Caries intensity in the second phase of mixed dentition).

•Patterns of permanent teeth emergence

We assessed the sequence of emergence of permanent teeth in 376 maxillary and mandibular quadrants of the 94 children included in the study and we found a number of 5 patterns of emergence, 2 favourable and 3 unfavourable, separately for the upper arch and lower arch (Table 2 - Emergence patterns of permanent teeth in the maxilla, Table 3 - Emergence patterns of permanent teeth in the mandible).

In the maxilla, the favourable replacement sequences (4-5-3 and 4-3-5) represented 38% of the total of tooth emergence patterns in the healthy children and 25% in the children with oncological conditions without spotting an association from a statistical point of view between the oncological disease and the tooth emergence pattern (Table 2). We showed the unfavourable emergence sequences of type 5-4-3, 3-4-5 and 5-3-4 in proportion of 23% in the healthy children and 14% in the children with malignant affections.

In the mandible, the optimal replacement order of type 3-4-5 and 4-3-5 occurred in 77 quadrants (41%) in healthy children and in 58 quadrants in children with malignant affections (31%). We noticed statistically significant negative association between the malignant condition and the tooth emergence sequence (Table 3). The unfavourable patterns 3-5-4, 5-3-4 and 4-5-3 represented a share of 21% of the total of tooth emergence sequences in the mandible in healthy children towards 7% in children with malignant conditions.

DISCUSSIONS

The process of dental replacement is conditioned by the size differences between the deciduous teeth and the permanent ones. The primary molars present greater mezio-dystal diameters than the replacement premolars' with approximately 1.5 mm at the maxilla and 2.5 mm at the mandible. This extra space, also called lee-way-space, allows the harmonious replacement with permanent teeth, thus, the integrity of canines and primary molars until the replacement physiological age is especially important [2].

In the second phase of mixed dentition, the change of tooth emergence patterns is due especially to complicated caries of the primary teeth that can lead to periapical osteitis,

accelerating the emergence of under adjacent teeth. Thus, the periapical infectious complications of the primary molar determines the emergence of the secondary premolar before the first premolar and the canine (patterns 5-4-3 and 5-3-4), this disturbance of the tooth emergence sequence favoring the loss of the lee-way-space through the mesialisation of the first permanent molar, affecting then the canine framing.

In our study, the sharing of the unfavourable sequences with the emergence of the secondary premolar before the first premolar and the canine was more important in the maxilla than in the mandible, both in healthy children and in children with oncological conditions. 29.79% of the total of teeth emergence patterns in the maxilla, corresponding to a number of 32 healthy children and 22 children with malignancies, is characterized by the initial emergence of the secondary premolar. In the mandible, the unfavourable sequences 5-3-4 have a much more reduced incidence than in the maxilla, representing 15.41% of the total of the emergence patterns assessed in 19 healthy children and 10 sick children.

The small number of patients with malignancies and healthy children group composition (with dental injuries that cause changes in patterns of eruption of permanent teeth, therefore not representative of the entire population) could be the causes of statistical results, hence the need for future study including a larger sample of subjects.

Leroy [11] assessed the relation between the incidence of the optimal emergence sequences and the health status of the primary teeth on an extended group of children and over a period of six years. In the case of children with the lack of caries on the primary molars, the replacement order was predominantly favourable. On the contrary, in the situations when both deciduous molars were affected by caries, the unfavourable sequences predominated in the maxilla and mandible, both in boys and girls. In our study, children examined presented intensity indices with high values and the share of optimal sequence in the maxilla was of 38% in the healthy children and 25% in the children with malignancies. In the mandible, the favourable sequences were met in 41% of the total or emergence patterns in healthy children and in 31% in the case of children with oncological conditions.

The process of dental emergence was also monitored on a group of 270 children aged between 6-14 years diagnosed with diabetes mellitus [9] comparatively with a group of 320 healthy children and the same age category. The authors noticed delays regarding the teeth emergence age and unfavourable replacement sequences of the primary teeth with the permanent teeth that are mostly produced in the second phase of the mixed dentition, both in the maxilla and the mandible. In the study conducted by us on children with malignancies also in the second phase of mixed dentition, we emphasized precocious emergencies of the permanent teeth and unfavourable replacement patterns in higher proportions in the maxilla than in the mandible.

Other authors [7] investigated the age and emergence sequences of the permanent teeth in children with Down syndrome comparatively to the same parameters in healthy children without genetic or systemic conditions. Children with Down syndrome presented delayed emergences and asymmetries in the emergence of permanent teeth, especially the canines and premolars. Regarding the symmetry of the replacement process, the clinical and radiological examinations within this present study emphasized the fact that replacement patterns are mostly symmetric in the right and left quadrants in the maxilla and the mandible, both in children with oncological conditions and in

healthy children: in the group of healthy children we noticed a number of 4 asymmetries regarding the emergence sequences in the mandible, and in the group of diseased children we emphasized 9 asymmetries of which 4 in the maxilla and 5 in the mandible.

CONCLUSIONS

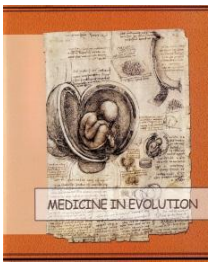
Damage caused by caries of primary teeth in the second phase of mixed dentition is quite high in children with malignant affections as well as in healthy children. The untreated dental caries and their complications modify the emergence sequences of the permanent replacement teeth and favor the appearance of dental anomalies. A future study including a larger sample of subjects could provide more relevant statistical data.

REFERENCES

1. Bissar AR, Kaschke I, Schulte AG. Oral health in 12- to 17-year-old athletes participating in the German Special Olympics. International J Paediatric Dentistry 2010; 20:451-457
2. Christensen JR, Fields HW. Treatment Planning and Management of Orthodontic Problems. In: Pinkham JR (ed) Pediatric Dentistry. Infancy through Adolescence, 4rd edn. Elsevier Saunders, St. Louis 2005; 608-649
3. Da Fonseca MA. Oral and Dental Care of Local and Systemic Diseases. In: Pinkham JR (ed) Pediatric Dentistry. Infancy through Adolescence, 4rd edn. Elsevier Saunders, St. Louis, 2005; 74-89
4. Du RY, McGrath C, Yiu CKY, King NM. Health- and oral-health-related quality of life among preschool children with cerebral palsy. Quality Life Research 2010; 1367-1371
5. Hong CHL, Napeñas JJ, Hodgson BD et al. A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer 2010; 18:1007-1021
6. Hutton A, Bradwell M, English M, Chapple I. The oral health needs of children after treatment for a solid tumour or lymphoma. International J Paediatric Dentistry 2010; 20:15-23
7. Jara L, Ondarza A, Blanco R, Valenzuela C. The sequence of eruption of the permanent dentition in a Chilean sample with Down's syndrome. Archives Oral Biology 1993; 38:85-89
8. Kochhar R, Richardson A. The chronology and sequence of eruption of human permanent teeth in Northern Ireland. International J Paediatric Dentistry 1998; 8:243-252
9. Lal S, Cheng B, Kaplan S, Softness B, Greenberg E, Goland RS et al. Accelerated Tooth Eruption in Children with Diabetes Mellitus. Pediatrics 2008; 121:e1139-e1143
10. Leroy R, Cecere S, Lesaffre E, Declerck D. Variability in permanent tooth emergence sequences in Flemish children. European J Oral Science 2008; 116:11-17
11. Leroy R, Cecere S, Lesaffre E, Declerck D. Caries experience in primary molars and its impact on the variability in permanent tooth emergence sequence. J of Dentistry 2009; 37:865-871
12. Majorana A, Schubert MM, Porta E et al. Oral complications of pediatric hematopoietic cell transplantation: diagnosis and management. Support Care Cancer 2000; 8:353-365
13. Márta A, Kovalecz G, Nemes J et al. Oral health of long-term childhood cancer survivors. Pediatr Blood Cancer 2004; 43:88-90
14. Posen AL. The effect of premature loss of deciduous molars on premolar eruption. Angle Orthodontist 1965; 35:249-252
15. Wogelius P, Dahllöf G, Gorst-Rasmussen A et al. A population-based observational study of dental caries among survivors of childhood cancer. Pediatr Blood Cancer 2008; 50:1221-1226

16. Wogelius P, Rosthoj S, Dahllöf G, Poulsen S. Oral health-related quality of life among survivors of childhood cancer. International J Paediatric Dentistry 2011; 21:465-467

PERIODONTAL MAINTENANCE THERAPY



DOINA ONISEI[1], DAN ONISEI[1], CAROLINE KRALEV[1], ANDREEA POGAN[1]

[1]University of Medicine and Pharmacy „Victor Babes" Timisoara, Department of Periodontology, School of Dentistry

ABSTRACT

Maintenance therapy (MT) or supportive therapy is essential to the long-term stability of patients with periodontitis. The clinical strategy for MT is often determined according to "clinical needs" of the patient and is thus determined by clinical observation and individual decision-making, rather than being based on the best available evidence. There is growing evidence of the fundamental role of personal oral hygiene in supportive periodontal care. In patients with rapid and severe periodontal destruction, especially where local and/or systemic risk factors are present, personal oral hygiene becomes a key factor in the long-term preservation of periodontal tissues.

Key words: *Periodontitis, maintenance therapy, oral hygiene, risk factors*

Correspondence to:

Onisei Doina
Address: "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, Faculty of Dentistry,
Phone: 0722942607
E-mail address: donisei@umft.ro

INTRODUCTION

Periodontal diseases are infections with a high potential for recurrence, progressive loss of attachment and represent the major cause of tooth loss. Current therapies for periodontal diseases are highly predictable in arresting disease activity 1.

Concept of modern periodontics is a triangle based on prophylaxy, active therapy and maintenance therapy. Supportive periodontal care has been shown to be very effective in maintaining support when adapted to each particular case.The primary goal of periodontal therapy is elimination of gingival inflammation and correction of the conditions that cause and perpetuate it 2. No treatment should be started until the treatment plan has been established.

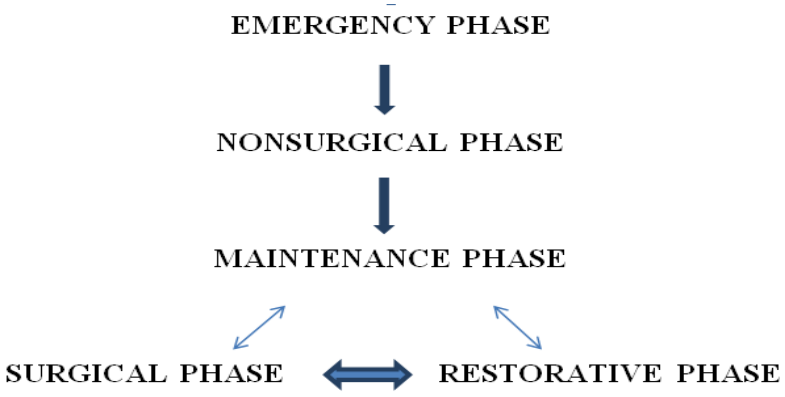
Characteristics of the master plan for periodontal treatment :

1. Coordination of all procedures to create a well-functioning dentition in a healthy periodontal environment;
2. Encompasses different areas of therapeutic objectives for each patient, according to his/her needs;
3. Based on the diagnosis, disease severity and other factors;
4. Includes a reasoned decision on the therapeutic endpoints and the techniques used to reach these objectives.

The treatment plan represents a blueprint for Case Management. It consists of :

- Extraction of hopeless teeth
- Pocket therapy techniques, surgical or nonsurgical
- Occlusal corrections, implant therapy and restorative procedures
- Orthodontic and endodontic procedures
- Esthetic considerations

Preferred sequence of periodontal therapy is illustrated in Tab.1



Tab.1 – Preferred sequence of periodontal therapy

The maintenance phase starts immediately after the completion of nonsurgical phase and the necessary surgical and restorative procedures are performed during it. This ensures that all areas of the mouth retain the good degree of health obtained after first phase 3.

Transfer of the patient from active therapy to maintenance therapy is an important step, maintenance therapy representing an individualized long-term treatment, for prevention of recurrence of periodontal disease. Maintenance therapy constitutes the key of positive long-term clinical results and preservation of the teeth for a long period of time. 4

OBJECTIVES

Maintenance therapy has to promote the following objectives :

- Stable alveolar support;

- Stable attachment level (CAL);
- Control of inflammation;
- Reevalution of personal hygiene;
- Maintenance of a healthy and functional oral environment.

Recurrence of periodontal disease occurs by incomplet biofilm removal, recolonization of bacteria, transmision of bacteria and reduction of pacients motivation. Clinical signs of recurrence are loss of clinical attachment level (CAL) and the presence of active sites.5

MAINTENANCE PROGRAM

Periodic recall visits are the foundation of a long-term maintenance program. Initially, the interval between visits is scheduled at 3 month, but the interval could be changed, according to the patient's needs.

Each recall visit comprises 3 parts:

1. Updated medical and dental history. Periodontal examination and evaluation.
2. Treatment
3. Final recommendations

Updated medical and dental history

Updating the medical and dental history is very important especially in cases of perio-systemic links. Diabetes, cardiovascular diseases, genetic diseases, pregnancy, are risk factors for recurrence of periodontal disease. 6

Examination and evaluation

Updating of changes are important parts of the recall visit, including presence of plaque/calculus, caries, restorations, endodontic lesions, prostheses, occlusion, tooth mobility, gingival status, probing depths, bleeding on probing (BOP), presence of gingival suppuration, clinical attachment level (CAL), furcation, progressive/stable gingival recession.7

Plaque control must be reviewed and correct until the patient has a good proficiency, the amount of supragingival plaque affecting the number of subgingival anaerobic bacteria. Checking of plaque control is established by plaque/gingival index and PCR (Microbiological exam). 4

Radiographic examination should be performed every year. The radiographic findings at the recall visit should be compared with the findings on previous radiographs, checking the bone high, osseous defects, signs of periodontal trauma and endoperio lesions. Radiographs should be always correlated with clinical data.

Treatment

Disruption of the subgingival biofilm remains the cornerstone of the periodontal therapy. This is achieved by minutios oral prophylaxis and scaling and rootplaning (SRP). Sometimes, depending on the patient's needs, it provides antibioterapy and periodontal surgery.

Irrigations with antimicrobial agents should be performed, sometimes placement of site-specific antimicrobial devices (Periochip) are used in patients with remaining pockets.

Final recommendations

Final recommendations are personalized for each patient, according to patient's needs. It comprises the frequency of future recall and referral to other specialists.

The recall evaluation is important because of achieving the success in preventing further loss of attachment and the possible alternatives to currently accepted protocols. It is a long-term reevaluation including changes of CAL, Rx interproximal alveolar bone height, presence of gingival inflammation, BOP, presence of gingival exudate, subgingival presence of biofilm/calculus and other changes of periodontal tissues.8,9

BOP and the presence of deep periodontal pockets are considered to be the best site-specific indicators for periodontal disease progression during

the maintenance phase of periodontal therapy. 10.

The time schedule in the maintenance phase is related to the followings :

- Clinical needs of the patient
- Disease's severity
- Oral hygiene efficiency
- Age
- Control of inflammation
- Risk profile.

RISK DIAGRAM

The risk diagram evaluate the risk of further progression of periodontal disease.11 It has been imagined by an Excel Microsoft Software (EXCEL XP for PC, Redmont, WA).

The multilevel risk assessment comprises 6 vectors :

- BOP;
- Number of sites with PD >5mm;
- Rx values ≥ 4mm between CEJ and bone;
- Age/ distruction
- Systemic/genetic factors;
- Smoking (environmental factors).

The correlation between the value and the score of the vectors are illustrated in Tab. 2

The risk diagram is a radar type diagrame, including the 6 vectors of risk (Fig. 1, 2, 3, 4)

The larger the shaded area, the higher is the periodontal risk .12.

Score	%BOP	Residual pockets>5mm	Nr. tooth loss	% bone loss/age	Environmental/ smoking
0	0-4%	0-1	0	0-9%	0
1	5-9%	2-3	1-2	10-19%	1-39
2	10-6%	4-5	3-4	20-29%	40-89
3	17- 5%	6-7	5-6	30-39%	90-189
4	25-5%	8-9	7-8	40-49%	180-364
5	36% +	10+	9+	50%+	365 +

* + systemic/genetic

Tab. 2 – Correlation score/value of vectors

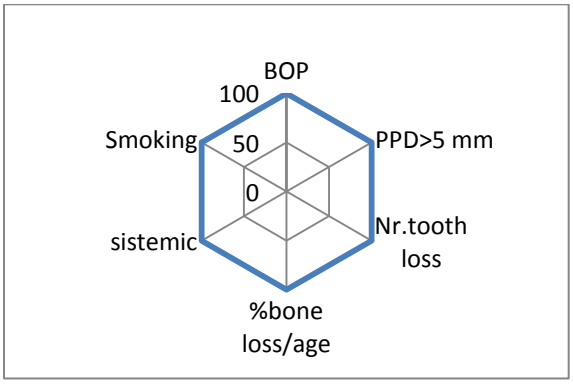


Figure 1: Risk diagram

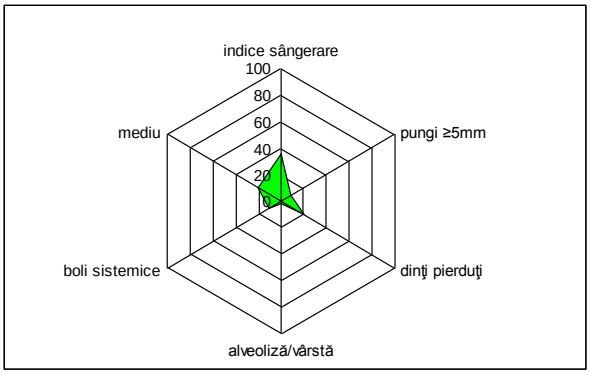


Figure 2 Low risk diagram:

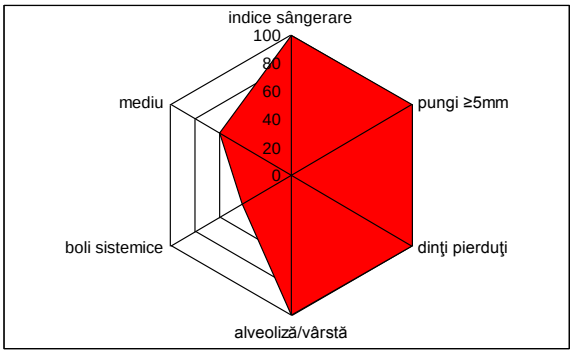


Figure 3: Medium risk diagram

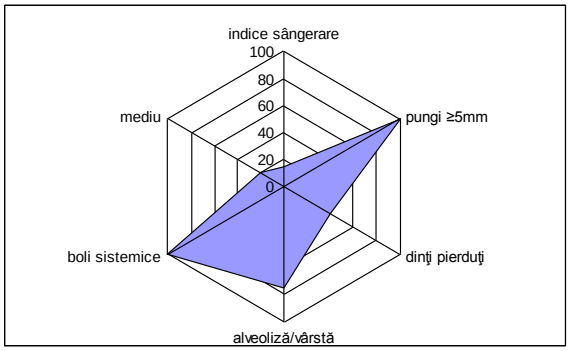


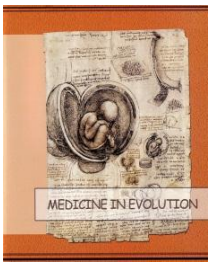
Figure 4 Low risk diagram:

CONCLUSIONS

1. Maintenance therapy should be initiated after nonsurgical therapy or pre/post surgical
2. The maintenance regimen is scheduled at 3 month
3. If oral hygiene is inadequate, maintenance interval should be shortened
4. Medical, dental history, radiographs should be updated and comprehensive periodontal examination should be performed
5. If active disease persists, retreatment should occur, options include nonsurgical, surgical or chemotherapeutical agents
6. It is the dentist's responsibility to advise the patient of the importance of periodontal treatment
7. Individuals who are not particularly perturbed by the thought of loosing their teeth are generally not good candidates for periodontal treatment

REFERENCES

1. Chapple ILC : Periodontal diagnosis and treatment – where does the future lie? Periodontology 2000 October 2009 Volume 51, Issue 1: 9–24
2. Genco RJ., Williams RC : Periodontal Disease and Overall Health: A Clinician's Guide, Professional Audience Comm. Yardley/USA/ 2010
3. Newman, Takei, Klokkevold, Carranza – Carranza's Clinical Periodontology, 11-th Ed. W. B. Saunders Company 2012
4. Onisei D, Onisei D : Parodontologie clinică, Ed.Mirton Timişoara 2011.
5. AAP (Position paper) Parameter on Periodontal Maintenance J Periodontol May 2000 (Suppl); Vol 71, nr.5:849-851
6. AAP (Position paper) Periodontal Maintenance J Periodontol 2003;74:1395-1401.
7. AAP (Position paper) Parameter on Comprehensive Periodontal Examination J Periodontol May 2000 (Suppl); Vol 71, nr.5:847-848
8. Lang NP, Tonetti MS : Periodontal Risk Assessment (PRA) for Patients in Supportive. Periodontal Therapy (SPT) Oral Health & Preventive Dentisty 1/2003, S. 7-16
9. Leung WK., Ng DKC., Jin L, Corbet EF : Tooth loss in treated periodontitis patients1responsible for their supportive care arrangements Journal of Clinical Periodontology April 2006 Volume33, Issue 4: 265–275,
10. Lorentz TCM, Miranda Cota LO, Cortelli JR, Vargas AMD, Costa FO : Prospective study of complier individuals under periodontal maintenance therapy: analysis of clinical periodontal parameters, risk predictors and the progression of periodontitis Journal of Clinical Periodontology January 2009 Volume 36, Issue 1: 58–67
11. Garcia RI., Nunn ME, Dietrich T : Risk calculation and periodontal outcomes Periodontology 2000 June 2009 Volume 50, Issue 1: 65-77,
12. Onisei D, Oprescu I , Onisei D : The assessment of periodontal patient's risk factors. Medicina Stomatologica, 2006,nr.1, vol.10:61-65



IMMUNOLOGICAL STUDY REGARDING THE ROLE OF CA(OH)2 PASTE ON THE MMP8 EXPRESSION FOR TEETH WITH CHRONIC PERIAPICAL LESIONS

MIHAELA SALCEANU[1], ANCA MELIAN[2], T. HAMBURDA[1], LIANA AMINOV[1], MARIA VATAMAN[3], FLORIN ZUGUN[4], UNGUREANU DIDONA[5]

[1]Assistent, Discipline of Endodontics, Faculty of Dental Medicine, U.M.F."Gr.T.Popa" Iasi
[2]Lecturer, Discipline of Endodontics, Faculty of Dental Medicine, U.M.F."Gr.T.Popa" Iasi
[3]Professor, Discipline of Endodontics, Faculty of Dental Medicine, U.M.F."Gr.T.Popa" Iasi
[4]Lecturer, Discipline of Immunology, Faculty of General Medicine, U.M.F."Gr.T.Popa" Iasi
[5]Associate Prof., Discipline of Biochemistry, Faculty of General Medicine, U.M.F."Gr.T.Popa" Iasi

ABSTRACT

Introduction. MMP8 are secreted as inactive proproteins, stored in secondary granules within neutrophils and are activated by autolytic cleavage. The function of MMP8 is degradation of type I, II and III collagens. In this context, the concentration of MMP8 can be related to the intensity of inflammatory processes associated with chronic periapical lesions.

Objectives. The aim of our study was to measure changes of MMP8 within the periapical secretion of teeth affected by periapical lesions and treated with antibacterial medication, using immunological tests.

Methods. Study group included 22 patients with age 22-64 years. A number of 30 teeth with periapical lesions (periapical granuloma and diffuse periapical osteitis) were submitted to endodontic treatment and filled with Ca(OH)2 paste. The periapical secretion was collected with paper points at baseline, after 14 days and after 28 days. The concentration of MMP8 was assessed using ELISA test Quantikinine (Human MMP-8 Immunoassay,R&D System,USA) based on quantitative sandwich enzyme immunoassay.

Results and discussions. At baseline the mean concentration of MMP8 was 31,3 ng/mL. The concentrations of MMP8 were closely related to the type of periapical lesion: 12,5 ng/mL for incipient periapical lesions, 18,1 ng/mL for small periapical granuloma and 91,6 ng/mL for extended periapical granuloma. The levels of MMP8 decreased gradually after 2 weeks and 4 weeks comparing with baseline.

Conclusion. Metaloproteinases (MMP8) could be used as biochemical markers of the periapical status of inflammatory procesess in course of initial stage of endodontic therapy.

Key words: *chronic periapical lesions, calcium hydroxide, metalloproteinases, MMP8*

Correspondence to:

Mihaela Salceanu
Assistant Professor, PhD, Discipline of Endodontics, Faculty of Dental Medicine
Address: University of Medicine and Pharmacy "Grigore T. Popa" - Iasi, Romania, 16, Universitatii Street, 700115
Phone: +40 744588269
E-mail address: salceanu.mihaela@yahoo.com

INTRODUCTION

The periapical reaction related to endodontic infection consists of a mixed inflammatory cell infiltrate, including large numbers of T cells, B cells, neutrophils, macrophages and plasma cells. The principal role of the proper endodontic treatment of the chronic periapical lesions is represented by the elimination of bacteria and endodotoxins associated with inflammatory reactions. Finally, it reduces latent and active forms of enzymes related to the destruction processes. Matrix metalloproteinases (MMPs) are an important family of metal-dependent endopeptidases that represent the major class of enzymes responsible for degradation of extracellular matrix (ECM) components. MMP8 are secreted as inactive proproteins, stored in secondary granules within neutrophils and are activated by autolytic cleavage. The function of MMP8 is degradation of type I, II and III collagens. MMP8 are secreted by PMN, monocites, macrofages, fibroblasts. In this context, the concentration of MMP8 can be related to the intensity of inflammatory processes associated with chronic periapical lesions. In this regard, clinical experience and radiographic exam must be completed with immunological tests that can confirm the initiation of healing processess.

Aim and objectives

The aim of our study was to measure, using immunological tests, the changing values of MMP8 within the periapical secretion of teeth affected by periapical lesions and treated with antibacterial medication based on Ca(OH)2.

MATERIAL AND METHOD

The study group included 22 patients with age between 22-64 years. The patients were informed about study goals and gave written consent. A number of 30 teeth with periapical lesions were submitted to classical endodontic treatment. The chronic periapical lesions were divided in three categories: incipient periapical lesions (8 teeth), periapical granuloma under 0,5cm (16 teeth), severe periapical lesions (6 teeth). The excluding criteria were as follows: teeth with acute periapical reactions, radicular cysts, severe coronal destructions, endoperiodontal lesions. The stages of endodontic treatment were as follows: mechanical and chemical disinfection (EDTA 17%, NaOCl 3%), root canal medication (Ca(OH)2 pastes) for 28 days, root canal filling using gutta-percha points and sealer (Endoflas, Sanlor, Florida) with lateral condensation technique. The stage of root canal medication consisted of two appointments with calcium hydroxide pastes, changed at 14 days intervals. The periapical exudate was collected with paper points at baseline, after 14 days and after 28 days. The paper points were introduced in 50 µL sterile distilled water, in 1,5mL Eppendorf tubes, stored at -800C until immunochemical tests were performed. The concentration of MMP8 was assessed using ELISA test performed with Quantikinine kit (Human MMP-8 Immunoassay,R&D System,USA). This test is based on quantitative sandwich enzyme immunoassay. The evolution of periapical inflammatory reactions was also evaluated using clinical and radiographic examination, with radiographs taken at baseline and after 28 days.

RESULTS

For each category of above mentioned lesions we present a relevant image (Fig.1,2,3).

The values of MMP8 at baseline, 14 days, 28 days are presented in table I and fig.3. Related to the extension of chronic periapical lesions, minimal and maximum values of MMP8 were as follows: 0 ng/mL- 20 ng/mL (incipient), 5 ng/mL- 15 ng/mL (periapical granuloma with diameter under 0,5 cm), 5 ng/mL- 15ng/mL (periapical lesions with diameter over 0,5 cm). The mean values of MMP8 levels are presented in table 1: 12,5 ng/mL for incipient periapical lesions, 18,1 ng/mL for small periapical granuloma and 91,6 ng/mL for extended periapical lesions.

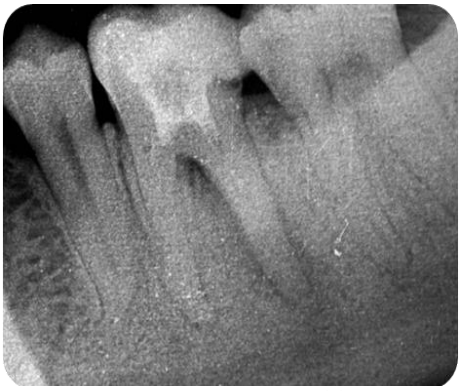


Figure 1: Incipient periapical lesion

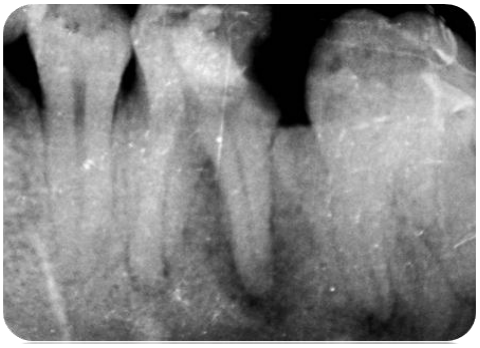


Figure 2: Periapical granuloma (Ø < 0,5 cm)

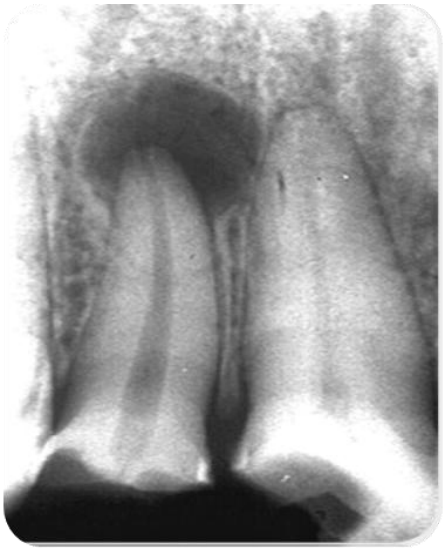


Figure 3: Extended periapical granuloma (Ø > 0,5 cm)

Table I. MMP8 levels related to the type of periapical lesion

Incipient periapical lesion	Small periapical lesion	Extended periapical lesions
12,5 ng/mL	18,1 ng/mL	91,6 ng/mL

The progressing decrease of MMP8 levels is presented in graph 1. The mean value at baseline was 35ng/mL. After 2 weeks, 26 cases had a positive evolution associated with the absence of acute periapical reactions. For these cases values of MMP8 after 2 weeks ranged between 5 ng/mL-125 ng/mL. After 4 weeks, these 26 cases maintained their positive evolution and values of MMP8 after ranged between 0 ng/mL-15 ng/mL.

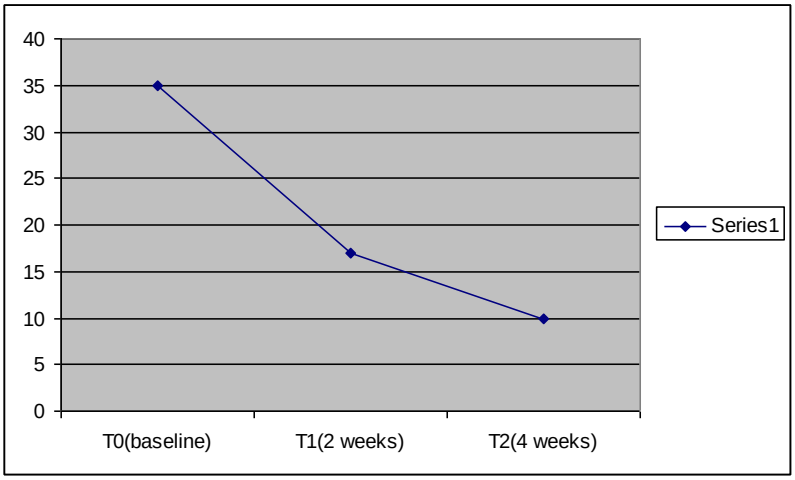


Figure 4: The mean values o MMP8 at baseline (T0), 2 weeks (T1), 4 weeks (T2)

Statistical test Wilcoxon was used to determine the existence of statistical differences between MMP8 levels at baseline, 14 days, 28 days. (tables II-IV).

Table II. a-b.The Wilcoxon test for M1 (baseline) and M2 (2 weeks)

Ranks

		N	Mean Rank	Sum of Ranks
M2 - M1	Negative Ranks	18[a]	9,50	171,00
	Positive Ranks	0[b]	,00	,00
	Ties	8[c]		
	Total	26		

a. M2 < M1

b. M2 > M1

c. M2 = M1

Test Statistics[b]

	M2 - M1
Z	-3,800[a]
Asymp. Sig. (2-tailed)	,000

a. Based on positive ranks.

b. Wilcoxon Signed Ranks Test

The decreasing of MMP8 after 2 weeks of root canal medication with calcium hydroxide is statistically significant (tables II.a,b)

Table III. a-b. Test Wilcoxon for M2 (2 weeks) and M3 (4 weeks)

Ranks

		N	Mean Rank	Sum of Ranks
M2 - M3	Negative Ranks	8[a]	6,00	48,00
	Positive Ranks	6[b]	9,50	57,00
	Ties	12[c]		
	Total	26		

a. M2 < M3

b. M2 > M3

c. M2 = M3

Test Statistics[b]

	M2 - M3
Z	-,289[a]
Asymp. Sig. (2-tailed)	,772

a. Based on negative ranks.

b. Wilcoxon Signed Ranks Test

The decreasing of MMP8 between day 14 and day 28 is not statistically significant comparing with the changing of MMP8 values between baseline and day 14 (tables III.a,b)

Table IV. a-b. Test Wilcoxon for M1(baseline) and M3 (4 weeks)

Ranks

		N	Mean Rank	Sum of Ranks
M1 - M3	Negative Ranks	4[a]	6,50	26,00
	Positive Ranks	16[b]	11,50	184,00
	Ties	6[c]		
	Total	26		

a. M1 < M3

b. M1 > M3

c. M1 = M3

Test Statistics[b]

	M1 - M3
Z	-3,027[a]
Asymp. Sig. (2-tailed)	,002

a. Based on negative ranks.

b. Wilcoxon Signed Ranks Test

DISCUSSIONS

The decreasing of MMP8 between baseline and day 28 is statistically significant comparing, following antibacterial and antiinflammatory effects of hydroxil ions released from calcium hydroxide paste (tables IV.a,b)

The reduction of MMP-8 after 2 weeks and 4 weeks can be correlated with the absence of acute periapical reactions, blocking of destruction processess of organic matrix and osteoclastic processess at the level of mineral tissues.

Our results sustain literature data related to connection between changing of MMP-8 level accordingly to severity and therapeutical stage of chronic periapical lesions. Andronovska B.&col. (2008) correlated the levels of colagenases (including

MMP8) with severity of chronic periapical lesions, having similar results with our study (1). Ma Z.&col.(2011) demonstrated the role of PMN on the secretion of metalloproteinases (including MMP8) after the interaction with E.faecalis (4). Francisco WG&col.(2010) prove that teeth with apical periodontitis submitted to root canal treatment using calcium hydroxide presented a lower inflammatory cell infiltrate with a moderately organized connective tissue, a lower prevalence of bacteria, and a lower number of MMP-positive cells, similar to healthy teeth submitted to treatment (2). Gendron&col. (1999) observe the inhibition of metalloproteinases secretion after repeated cleanings of root canals using chlorhexidine (3). Wahlgren&col.(2002) show that the absence of MMP8 decreasing after two appointments of intracanal medication with calcium hydroxide pastes can be considered failure of endodontic treatment(8). Metzger (2000), Takahashi (1998) and Tjaderhane (2001) recommend the introduction in dental practice of chair-side tests for the assessment of periapical lesions activity(5,6,7).

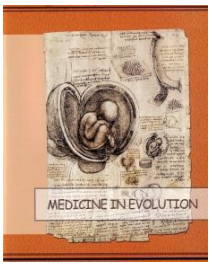
CONCLUSIONS

- The decrease of MMP8 concentration in periapical exudates following intracanal medication with calcium hydroxide proves its role in the initiation of healing periapical processes;
- The changing of MMP8 concentration, during initial stages of endodontic treatment, can indicate the success or potential failure of clasical endodontic therapy of the extensive chronical periapical lesions;
- Metalloproteinases MMP8 could be used as biochemical markers to assess the activity of periapical inflammatory processes and the efficacy of the endodontic therapy.

REFERENCES

1. **1.Andonovska B**, **Dimova C**, **Panov S**. Matrix metalloproteinases (MMP-1, -8, -13) in chronic periapical lesions. Vojnosanit Pregl., 2008; 65(12): 882-886.
2. **2.Francisco WG, Léa AB, Yvonne LK.** Matrix Metalloproteinase Expression in Teeth with Apical Periodontitis Is Differentially Modulated by the Modality of Root Canal Treatment. J Endod., 2010; 36(2): 231
3. **3.Gendron R, Grenier D, Sorsa T, Mayrand D.**. Inhibition of the activities of matrix metalloproteinases-2, -8, and -9 bychlorhexidine. Clinical and Diagnostic Laboratory Immunology, 1999, 6: 437-439.
4. **4.Ma Z**, **Wang Y**, **Zhu X**, **Zhang C**, **Li S**, **Jin L**, **Shen Y**, **Haapasalo M**.Role of polymorphonuclear neutrophils in the clearance of Enterococcus faecalis derived from saliva and infected root canals. J Endod., 2011; 37(3): 346-352.
5. **5.Metzger Z.**. Macrophages in periapical lesions. Endodontics and Dental Traumatology, 2000, 16: 1-8.
6. **6.Takahashi K**. Microbiological, pathological, inflammatory, immunological and molecular biological aspects of periradicular disease. International Endodontic Journal, 1998, 31:311-25.
7. **7.Tjaderhane L, Palosaari H,Wahlgren J, Larmas M, Sorsa T, Salo T.**. Human odontoblast culture method: the expressionof collagen and matrix metalloproteinases (MMPs). Advancesin Dental Research, 2001, 15: 55-58.
8. 8.Wahlgren J, Salo T, Teronen O, Luoto H, Sorsa T,Tjaderhane. **Matrix metalloproteinase-8 (MMP-8) in pulpal and periapical inflammation and periapical root-canal exudates. International Endodontic Journal, 2002; 35: 897-904**

TONGUE ABSCESS, A RARE CLINICAL ENTITY – CASES PRESENTATION AND A REVIEW OF THE LITERATURE



M. PRICOP[1], H. URECHESCU[1]

[1] Oro-maxillo-facial Departament, Faculty of Dentistry, University of Medicine and Pharmacy „Victor Babes" Timisoara

ABSTRACT

The tongue abscess is a very rare condition that occurs in immunocompromised patients or in healthy persons with local etiological factors. In some text books of maxillo-facial surgery, there are no mentions about this disease. Over the last 30 years, only 69 cases of tongue abscess have been reported in the English literature. In our article, we try to compare literature data with those obtained from our cases studies.

Key words: *tongue, abscess*

Correspondence to:

Assoc. prof. dr. M. Pricop
Address: Oro-maxillo-facial Departament, Faculty of Dentistry, University of Medicine and Pharmacy "V. Babes" Timisoara, Bv. Take Ionescu, nr. 5
Phone: 0256433352
E-mail address: pricopmarius@yahoo.com

INTRODUCTION

The tongue abscess is a rare clinical entity since the discovery of antibiotics, despite the relatively frequent exposure of the tongue to bite trauma during mastication and seizures. Some of the reasons for this tongue relatively infection immunity are:

- the tongue's constant mobility, which helps the saliva to produce a cleansing effect
- the thick covering keratinized mucosa, which is not easily penetrated by microorganisms
- the rich muscle tissue, with its rich vascular supply and lymphatic drainage
- the immunologic properties of saliva (4)

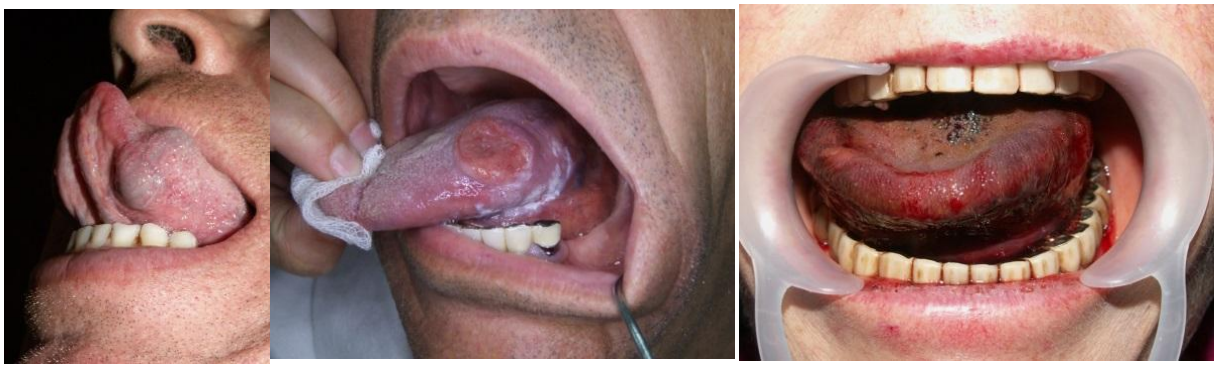
The tongue abscess is considered an emergency, because aero-digestive upper airway obstruction, as well as dissemination of abscess in surrounding lodges. It is also considered a life-threatening abscess. Any acute tongue swellings, especially when host defenses are severely impaired, can be considered a tongue abscess.

There are some etiologic factors of the tongue abscess: puncture wound, foreign bodies, lingual piercing, trauma by dental caries, periapical dental processes of lower premolars and molars, acute glossitis, lingual hematoma overinfected, spread from neighboring spaces (especially sublingual space), unspecified.

Tongue abscess frequently presents as painful swelling, with congested mucous membrane covering. Sometimes, the dorsal tongue is completely covered with yellow deposits. Protrusion of the tongue, dysphagia, odynophagia, and difficulty with speech are others symptoms commonly encountered. The submandibular, submental and cervical nodes can be palpable and tender. Agitation, fever, dehydration, and biological parameters of infection are usually found. Abscesses located in the anterior two thirds of the tongue are easy to diagnose on the basis of physical findings, while those situated in the posterior third may be difficult to diagnose (1,2,3).

Clinical examination, puncture aspiration, and imagistic (radiography, ultrasound, CT, MRI) establish the diagnosis (5). For the abscesses located in the anterior two third of the tongue, the diagnostic is main clinic. When the abscess is located in the posterior third of the tongue or when the cause of acute tongue swelling is unknown, diagnostic imaging techniques can differentiate lingual abscess from other lesions. Plain radiograph and CT image are useful for evaluation of fish bone and dental etiology. However, dental amalgam artifacts may obscure the CT findings (2). MRI may reveal a posterior abscess of the tongue in patients who presented with acute tongue swelling, fever, and upper airway involvement, and in whom the lesion missed at physical examination (4).

The differential diagnosis of tongue abscess includes: tumor (malignant, cyst), edema, hematoma, metabolic macroglossia (in hyperpituitarism or hypothyroidism), developmental macroglossia (lingual thyroid or ectopic lymphoid tissue) (6,7).



Tongue angioma, tongue carcinoma and tongue hematoma

Treatment should be done by surgical incision and drainage. Antibiotics, anti-inflammatories, analgesics are medications of choice.

MATERIAL AND METHOD

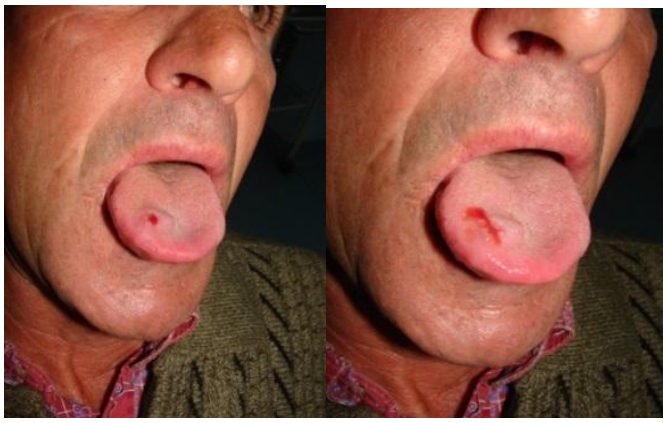
We present 3 cases of tongue abscess and the surgical treatment approaches for managing them. All the cases in this series were males between the age group 32-58 years.

Case 1

Patient, 50 years, male, with no systemic diseases was consulted in ambulatory with a small collection in the anterior third of the tongue. The patient was not exposed to trauma recently, and he could not identify an etiologic factor.

On physical examination, a 2 cm diameter spherical collection (painful and fluctuant) was found at the right side of the tongue. No perimandibular nodes were palpable and tender. The hematological investigations were normal.

The case was diagnosed as tongue abscess, and managed successfully with local incision and drainage (the pus was evacuated), followed by antibiotic and analgesic medication. The patient had a favorable local and general evolution at 24 hours, after which the patient never present to control.



Case 1. Anterior abscess of the tongue (pre- and postincision)

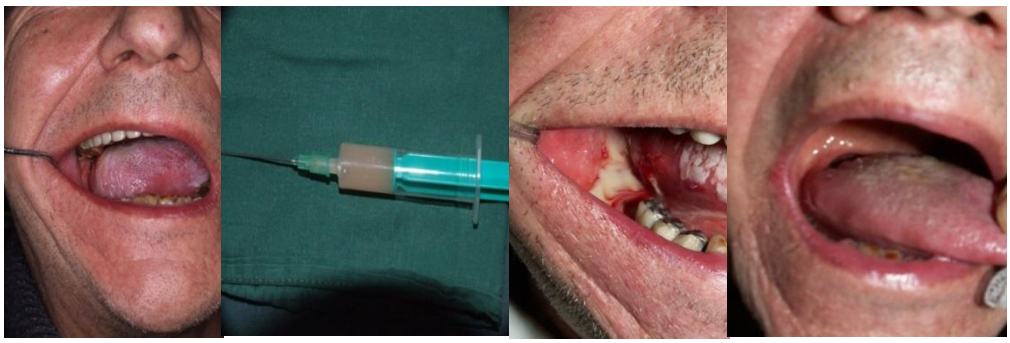
Case 2

A 58-year-old man with no systemic diseases was admitted with a painful mass on the tongue. The patient was not exposed to trauma recently, and I could not identify an etiologic factor.

On admission, the patient was agitated, with breathing and swallowing dificulties. On physical examination, a diffuse collection was

found at the body and right side of the tongue. The mass was painful and fluctuant. The right submandibular nodes were palpable and tender. All hematological investigations were normal.

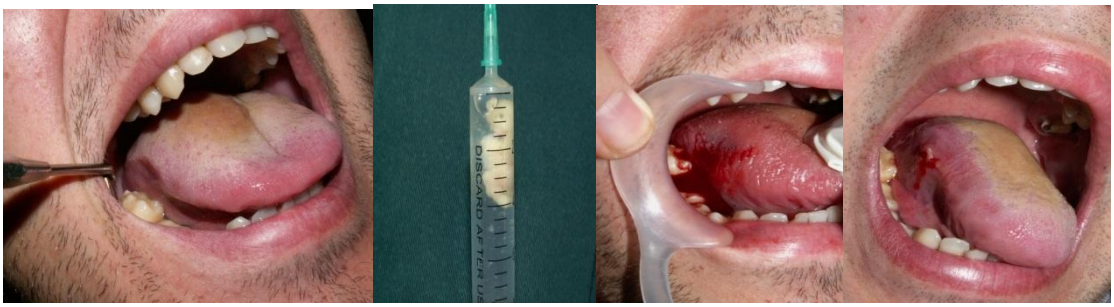
Aspiration puncture of the lesion was positive. The case was diagnosed as tongue abscess, and managed successfully with immediately local incision and drainage, followed by antibiotic and analgesic medication. There was no recurrence on the subsequent review visits.



Case 2. Clinical symptoms, positive aspiration puncture, pus from the incision, the final aspect

Case 3

A 32 year man, healthy, with no systemic disease, complained a painful swelling in the body and right side of the tongue (3 day duration). The swelling increased progressively, determining severe functional disorders of swallowing and phonation. On admission, the patient was agitated, with breathing, swallowing and speaking disorders. On physical examination, the tongue was swollen in block, with overlying mucosa red, and covered with white deposits. On the edges of the tongue were observed adjacent teeth prints. A diffuse collection was palpable in the body and right side of the tongue. There was no regional lymphadenopathy. All hematological investigations were normal. Aspiration puncture of the lesion was positive. The patient had no symptoms after surgery (local incison and drainage) and antibiotic treatment. Later, the patient was followed for 1 months without any recurrence. I could not identify an etiologic factor of the abscess.



Case 3. Clinical symptoms, positive aspiration puncture, incision, the final aspect

RESULTS

The three cases had a favorable outcome and were cured without general or local complication. The lingual superficial abscess (case 1) was incised ambulatory, had a favorable local and general evolution at 24 hours,

after which the patient never present to control. The second patient was treated in hospital seven days (incision made immediately after admission). The third patient was treated in hospital nine days (incision made immediately after admission), because the lingual edema slowly withdrew. The costs of the treatment were high for the cases 2 and 3. No recurrences of abscesses were observed in none of the patients.

CONCLUSIONS

The tongue abscess is a rare, but life-threatening abscess.

For the abscesses located in the anterior two third of the tongue, the diagnosis and treatment is easier, and the evolution and prognosis are favorable. For the abscesses located in the posterior two third of the tongue, the diagnosis is difficult, and the treatment must be done urgently to avoid major complications occur.

We experienced 3 cases of tongue abscess without a clear etiological factor. We don't find lingual abscess due to fish bone impaction in our experience, that confirm literature data that lingual abscess due to fish bone impaction is rare.

The use of CT and MRI in the diagnostic of the tongue abscess can be very useful, but require technical conditions, qualified personnel, and is more expensive. A puncture aspiration well directed, can be done immediately, with good results. If the puncture aspiration is not well directed, there is a risk for the abscess to be not diagnosed.

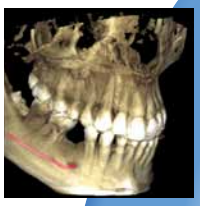
In the presence of pus collection, a rapid incision and drainage is mandatory. Few authors describe good result with the repeated aspiration puncture, but we consider the method to be insufficient and risky.

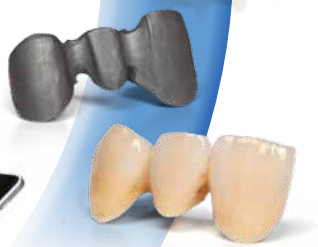
REFERENCES

1. D. G. Balatsouras, P. N. Eilopoulos, and A. C. Kaberos, Lingual abscess: diagnosis and treatment, Head and Neck 2004, 26: 550–554.
2. H. J. Kim, B. J. Lee, S. J. Kim, W. Y. Shim, S. K. Baik, and M. Sunwoo, Tongue abscess mimicking neoplasia, American Journal of Neuroradiology 2006, 27: 2202–2203.
3. Hehar SS, Johnson IJM, Jones NS. Glossal abscess presenting as unilateral tongue swelling. J Laryngol Otol 1996;110:389–390 5.
4. Munoz A., Ballesteros Ana Isabel, Brandariz Castelo A. Primary Lingual Abscess Presenting as Acute Swelling of the Tongue Obstructing the Upper Airway: Diagnosis with MR. AJNR Am J Neuroradiol March 1998; 19:496 –498.
5. Osammor JY, Cherry JR, Dalziel M. Lingual abscess: the value of ultrasound in diagnosis. J Laryngol Otol 1989;103:950–951.
6. Pal J, Prakash J. Lingual abscess. J Indian Med Assoc 1976; 66:57–60 4.
7. Renehan A, Morton M. Acute enlargement of the tongue. Br J Oral Maxillofac Surg 1993; 31:321–324.

ProMax 3D • PlanScan • ProFace

Unique 3D combination for open CAD/CAM





Digital perfection

Planmeca sets new standards with world's first dental unit integrated intraoral scanner for open connectivity to various CAD/CAM systems.

We would like to invite you to explore the dentistry in new dimensions – see the perfect combination of digital intraoral scan, CBVT and 3D facial photo datasets in one 3D image. This digital perfection enables you to study patient's complete anatomy in detail, plan and utilise open interface with modern CAD/CAM systems according to your needs. Now you can be one of the pioneering specialists, whether you are an implantologist, endodontist, periodontist, orthodontist or maxillofacial surgeon. The new era of dentistry is reality. It's your decision.

Planmeca Oy, Asentajankatu 6, 00880 Helsinki, Finland
tel. +358 20 7795 500, fax +358 20 7795 555, sales@planmeca.com, www.planmeca.com

PLANMECA

1971 - 2011

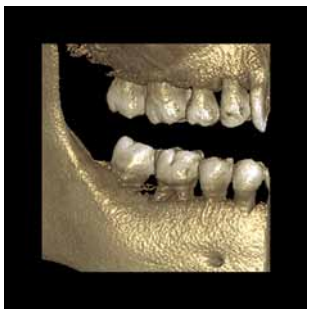
Planmeca ProMax 3D

All volume sizes

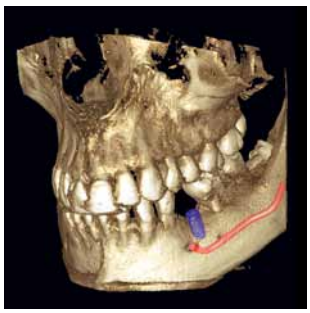
The Planmeca ProMax concept offers a full range of imaging volumes providing detailed information on patient anatomy. The comprehensive Planmeca ProMax platform complies with every need in dental radiology, offering digital panoramic, cephalometric, and 3D imaging as well as 3D face photo together with advanced imaging software.

At the heart of the concept is the robotic SCARA technology: the unique robotic arm enables any movement pattern required by existing or future program, eliminating all imaging restrictions. With the Planmeca ProMax concept superior maxillofacial radiography can be performed with a single platform, today and in the decades to come.

All volume sizes

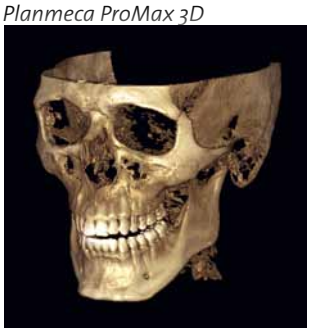


Planmeca ProMax 3D s
Ø42 x 42 mm–90 x 60 x 130 mm



Ø34 x 42 mm–140 x 105 x 130 mm

Planmeca ProMax 3D



Planmeca ProMax 3D Mid
Ø34 x 42 mm–Ø160 x 160 mm

Planmeca ProMax 3D Max
Ø42 x 50 mm–Ø230 x 260 mm

Planmeca Oy, Asentajankatu 6, 00880 Helsinki, Finland
tel. +358 20 7795 500, fax +358 20 7795 555
sales@planmeca.com, www.planmeca.com

PLANMECA

Planmeca Romexis

Software refined

Available on the App Store

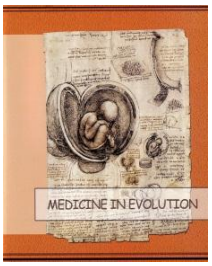
Planmeca Romexis is the software of choice for all dental imaging purposes. All patient's digital images – intraoral and extraoral X-ray images, 3D volumes, and photographs – are processed and stored in one easy-to-use system. Planmeca Romexis offers a complete set of tools for image viewing, enhancement, measurement, and implant planning, and fully integrates digital imaging with the patient's other clinical data.

Thanks to its powerful printing features, stunning printouts can be produced. Planmeca Romexis provides direct image capture from Planmeca X-ray units, interfaces with 3rd party devices via TWAIN, and is fully DICOM-compatible. Planmeca Romexis is a JAVA software that runs on Windows, Mac OS, and Linux operating systems, and embraces modern IT standards.

Planmeca Oy, Asentajankatu 6, 00880 Helsinki, Finland
tel. +358 20 7795 500, fax +358 20 7795 555
sales@planmeca.com, www.planmeca.com

PLANMECA

1971 - 2011



RESEARCHES REGARDING OBTAINING SELECTIVE EXTRACTS WITH HYPOGLYCEMIANT PROPERTIES FROM VEGETAL INDIGENOUS PRODUCTS (CICHORII HERBA AND FRAXINI FOLIUM) NOTE IV. THE DYNAMICS OF ACCUMULATION OF PHENOLIC COMPOUNDS FROM CICHORII HERBA

TITINA ALINA IORDACHE[1], LAURIAN VLASE[2], VIORICA ISTUDOR[1]

[1] University of Medicine and Pharmacy „Carol Davila", Faculty of Pharmacy, Department of Pharmacognosy, Phytochemistry, Phytotherapy 6 Traian Vuia, 020956, Bucharest
[2] University of Medicine and Pharmacy "Iuliu Hatieganu", Faculty of Pharmacy, Department of Pharmaceutical Technology and Biopharmaceutics 13, Emil Isac, Cluj-Napoca, Cluj 400023

ABSTRACT

The aim of this study is to establish the dynamics of accumulation of polyphenolic compounds (phenolcarboxylic acids, flavones and tannin) from Cichorii herba harvested at different stages of development compared to those from SC. Phytotherapy Bucharest S.A and to verify their presence by high performance liquid chromatography coupled with mass specum and UV (HPLC/MS/UV). The sample harvested in August has the highest content in polyphenolic derivatives. By HPLC/MS and HPLC/UV were identified quercitrin (quercetin 3-O--rhamnoside), isoquercitrin (quercetin 3-O-glucoside), acids caftaric and gentisic not mentioned in the literature consulted.

Key words: *Cichorii herba, HPLC/MS/UV, quercitrin*

Correspondence to:

Laurian Vlase
Address: MSc, PhD, Pharm. Chem., Associated Professor Dept. of Pharmaceutical Technology and Biopharmaceutics Faculty of Pharmacy, University of Medicine and Pharmacy "Iuliu Hatieganu" 13, Emil Isac, Cluj-Napoca, Cluj 400023, Romania
Phone: 0732069892
Fax: +40 264 595 770
E-mail address: laurian.vlase@yahoo.com, laurian.vlase@umfcluj.ro

INTRODUCTION

Cichorii herba is used to treat digestive disorders (anorexia

gallbladder disease, bloating, flatulence, slow digestion), adjuvant in slimming belts and diabetic nutrition [1, 2, 9, 10]. Cichorii herba does not have a monograph in any of the pharmacopoeias (Romanian Pharmacopoeia 10-th edition, European Pharmacopoeia 7-th edition, United State Pharmacopoeia 31-th) and it is not mentioned in the literature for hypoglycemic activity. Previous phytochemical investigations revealed the presence of phenolic acids (cichoric acid = dicafeoil tartaric acid, chlorogenic acid, isochlorogenic acid), flavones (hiperoside, quercetin-3O-galactoside, isorhamnetine, apigenin-7-O-L-arabinoside, luteolin-7-O – glucuronide, quercetin -3-O – glucuronide, campheroil -3-O-glucoside), flavonols (luteolin and apigenin), sesquiterpenid lactones (lactucin, lactucopicrin, 8-desoxylactucin), guaianolid glycosides (cichoroisides B and C, sonchuside C C), hydroxycoumarins (umbelliferone, esculin, cichorine) and polyynes [9, 10]. Some of these constituents are mentioned in the literature for their inhibitory effect on the aldose-reductase (ARI), on 11-β-hydroxy steroid dehydrogenase 1 (11- β HSD1) and AGE compounds (which are involved in the pathogenesis of diabetes and aging processes) [3]. Also it is known that polyphenolic compounds present antioxidant action and could be involved in regulating glucose metabolism and vascular disorders induced by hiperglicemia. Therefore we focused to researches the dynamics of accumulation of polyphenolic compounds (phenolcarboxylic acids, flavones, polyphenols, tannins) in order to choose properly growth stage of a high content of phenolic compounds, namely a material of the highest quality, subsequently used to obtain a pharmacologically active extract, standardized to polyphenols.

MATERIAL AND METHOD

The study material was supplied by Phytotherapy Bucharest (batch CF) and was spontaneous harvested from Piatra-Olt (Olt county) in 2011, in different periods of vegetation (July – batch C1, and August – batch C2). I followed their quality through quantitative measurements (spectrophotometric) and high performance liquid chromatography coupled to mass spectrum and ultraviolet (HPLC / MS and HPLC / UV).

In order to verify the quality, the following active principles were assayed, using specific methods:

■flavones using spectrophotometric method based on the reaction with AlCl3/CH3COONa, according to Romanian Pharmacopoeia 10th edition, Cynarae folium monograph, rutin standard calibration curve, λ = 427 nm, spectrophotometer UV-VIS Cecil 2000) [4, 11];

■phenolcarboxilic acids (using Arnow's method, caffeic acid standard calibration curve, λ = 510 nm, spectrophotometer UV-VIS Cecil 2000) [4, 11] and after the European Pharmacopoeia 6thedition, the monograph Fraxini folium (λ = 525 nm spectrophotometer Jasco V-530) [12].

■polyphenols using spectrophotometric method based on the reaction with Folin-Ciocâlteu reagent according to the method reported by Singleton et al (1999) with some modification (gallic acid standard calibration curve, calculated by the formula: Y = A + B * Conc, where A = -

0.0094, B = 0.1382; allure linear in the concentration range from 1.08 to 7.56 mg / mL, r = 0.999370, λ = 765 nm, spectrophotometer Jasco V-530) [7, 8].

All determinations were performed in triplicate, the mass of product close. Results are the mean and standard error.

Research HPLC/MS and HPLC/UV

The HPLC experiment for flavonoids and phenolcarboxilic acids were carried out using an Agilent HPLC Series system (Agilent U.S.A.) equipped with degasser, binary pump, column thermostat, autosempler and UV detector. The HPLC system was integrated with Agilent 1100 mass spectrometer (LC/MSD Ion Trap VL). For the separation, a reverse-phase analytical column was used (Zorbax SB-C18 100 x 3.0 mm i.d., 3.5 µm particle); the working temperature was 48°C. The mobile phase was a binary gradient prepared from methanol and a solution of acetic acid 0.1% (v/v). The elution started with a linear gradient, beginning with 5% methanol and ending at 42% methanol, for 35 minutes; isocratic elution followed for the next 3 minutes with 42 %. The flow rate was 1 mL min -1 and the injection volume was 5µL. The detection of the compounds was performed on both UV and MS mode. The UV detector was set at 330 nm for the first 17.5 min., then at 370 nm. The MS system operated using an electrospray ion source in negative mode. The chromatographic data were processed using ChemStation and DataAnalysis software from Agilent USA . The following standards were used: caftaric acid, gentisic acid, caffeic acid, chlorogenic acid, p-cumaric acid, ferulic acid, sinapic acid, hyperoside, isoquercitrin, rutin, miricetin, fisetin, quercitrin, quercetin, patuletine, luteolin, kaempferol and apigenin (fig. 1). Calibration curves in the 0.5-50 µg mL-1 range had a good linearity (r2= 0.999, n = 5) [5, 6].

Sample preparation. For extraction of polyphenolic compounds, 1 g powedered sample (batch C2) was refluxed with 100 mL of 50% methanol for 30 minutes. Extraction solution was filtered into a 100 mL volumetric flask and fill to the mark (SE-1). For extraction of free aglycons, 50 mL of SE-1 is hydrolysed with 50 mL of 2 N HCl trough the water bath maintained at 80°C for 60 minutes (SE-2).

RESULTS AND DISCUSSION

The spectrophotometric results (Table I) showed the highest content of active principles in the sample of bach C2 (harvested in August). So, the sample C2 was further selected for HPLC analysis.

Table 1. Results of spectrophotometric determination

Batch	flavones (g% rutin) ± STD	phenolcarboxilic acids (g% caffeic acid)± STD	phenolcarboxilic acids (g% chlorogenic acid) ± STD	polyphenols (g% gallic acid) ± STD	tannin (g% gallic acid) ± STD
C1	0,1307±0,014	2,7173±0,202	1,8105±0,030	2,3731±0,560	0,7660±0,069
C2	0,1632±0,013	3,3109±0,189	2,7010±0,099	2,7156±0,309	0,9181±0,079
CF	0,1451±0,023	2,4660±0,450	2,1965±0,171	2,5238±0,232	0,5258±0,247

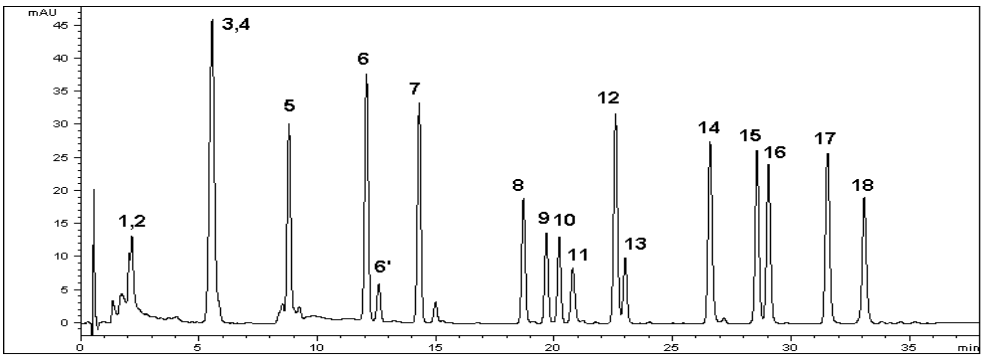


Figure 1: The standards cromatogram, UV detection at λ=330 and 370 nm: caftaric acid (1), gentisic acid (2), caffeic acid (3), chlorogenic acid (4), p-cumaric acid (5), ferulic acid (6), sinapicacid (7), hyperoside (8), isoquercitrin (9), rutin (10), miricetin (11), fisetin (12), quercitrin(13), quercetin (14), patuletine (15), luteolin (16), kaempferol (17) and apigenin (18).

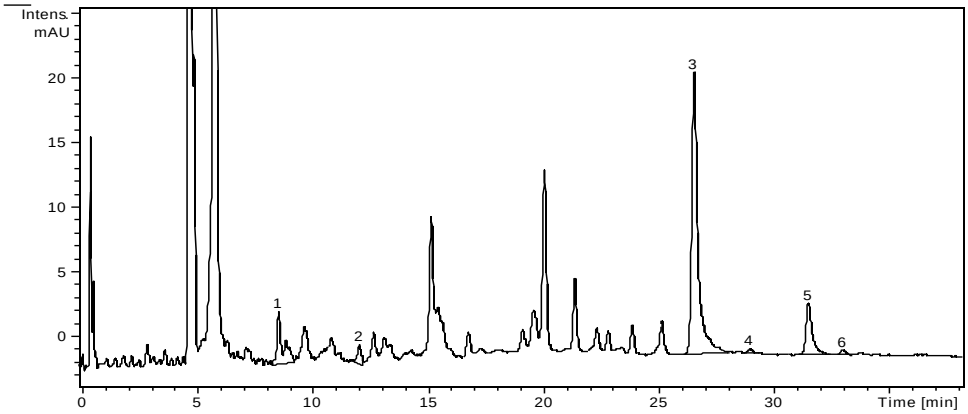


Figure 2: The chromatogram of the unhydrolyzed solution SE-1

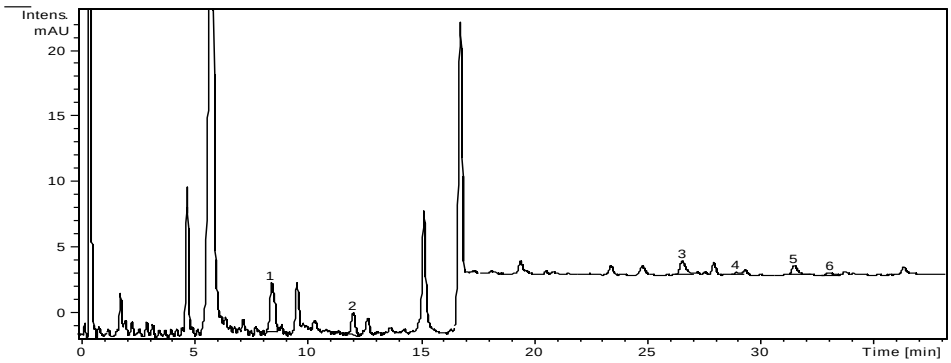


Figure 3: The chromatogram of hydrolyzed solution SE-2

Research HPLC / MS on SE-1 (non-hydrolyzed solution)showed the presence of phenolic acids (caftaric, caffeic, chlorogenic, ferulic) and flavones (rutin, quercitrin, isoquercitrin)(Fig.2) and in SE-2 (hidrolyzed solution) the presence of phenolic acids (caftaric, caffeic, chlorogenic, ferulic, p-coumaric and gentisic) and flavonoid aglycone (apigenin, luteolin, kaempferol and quercetin) (Fig. 3). Four polyphenols (caffeic acid, caftaric acid, gentisic acid and chlorogenic acid) cannot be quantified in the current chromatographic conditions due to overlapping (Table II). Ferulic acid is in free form and heterosides, which shows its solubility in this solvent. From Table II, we find increasing the amount of ferulic acid by hydrolysis, which suggests the existence of a derivative glycosides or esters.

Table 2. Quantification of polyphenols by HPLC/UV/MS (mg/100g pv)

Compound	HPLC/MS		HPLC/UV	
	SE-1	SE-2	SE-1	SE-2
Caftaric acid	+	+	-	-
Caffeic acid	+	+	-	-
Chlorogenic acid	+	+	-	-
Ferulic acid	0,6079	1,0618	+	+
Gentisic acid	-	+	-	-
p-coumaric acid	-	3,2094	-	+
Isoquercitrin	22,2724	-	+	-
Rutin	0,8238	-	+	-
Quercitrin	4,0953	-	+	-
Quercetin	-	1,0538	-	+
Luteolin	-	02599	-	+
Kaempferol	-	0,8798	-	+
Apigenin	-	0,3839	-	+

Legend: + positiv, -negative

Flavonoid aglycones resulting by hydrolysis are: quercetin (of rutin and isoquercitrin), kaempferol (probably of astragalină = kaempferol 3-O-glucoside, unread of scientific literature or kaempferol-3-O-glucuronide, cited above), apigenin and luteolin. Due to the lack of reference substances, their glycosylated compounds have not been identified by this method in the species studied by us. Scientific literature does not mention the presence of luteolin (5,7,3',4'-tetrahidroxyflavone) and gentisic acid in the composition of chicory, therefore those compounds are mentioned here for the first time.

CONCLUSIONS

Cichori herba (bach C2 harvested in August) has the highest content in polyphenolic derivatives. So it will be used in the process to obtain the dry extract, standardized (in flavones, polyphenols and tannins). Because the phenolic compounds (flavones, tannins and polyphenols) are cited in the literature as aldose -reductase inhibitor (ARI), 11-β-hydroxy-steroid dehydrogenase-1 (11-β-HSD1) and AGE compounds involved in the pathogenesis of diabetes mellitus II and aging processes, we consider that through these compounds Cichorii herba could intervene in regulating glucose metabolism and vascular disorders induced by hiperglicemia. Therefore we oriented achieving pharmacologically active extracts, standardized flavones, tannins and phenolic acids, which are further processed into a pharmaceutical product.

Identification by HPLC method quercitrin, isoquercitrin, luteolin and gentisic acid is a modest contribution to the knowledge of the chemical composition of indigenous product (compounds are not quoted in its chemical composition).

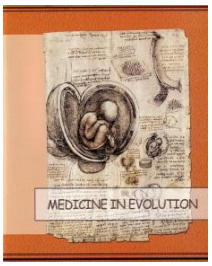
Acknowledgement

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/6/1.5/S/17..

REFERENCES

1. Istudor V., Farmacognozie, Fitochimie, Fitoterapie, vol. II, Ed. Medicală, Bucureşti, 2001, p. 303-304
2. Gîrd C.E., Curs de farmacognozie, fitochimie, fitoterapie, vol. 2, Ed.Curtea Veche, Bucureşti, 2010, p. 217-219.
3. Istudor V. şi colab., Fitoterapia bolilor metabolice, Editura Tehnoplast Company, 2008, pag. 22, 24, 36, 38.
4. Gîrd C.E., Duțu L.E., Popescu M.L., Pavel M., Iordache T. A., Experimental research regarding the active extracts, polyphenols-standardized. Note I. Hyperici herba, pharmacognostic analysis of the raw material, Farmacia, 2009, 57 (1), 35-42.
5. Khalaf I., Vlase L., Lazăr D., Corcioavă A., Ivănescu B., Lazăr M.I., HPLC-UV-MS Study of Polyphenols from *Glycyrrhiza Glabra*, Farmacia,2010, 58(4), 416-420.
6. Nencu I., Vlase L., Istudor V., Duțu L.E., Gîrd C.E., Preliminary research regarding the therapeutic uses of *Urtica Dioica* L., Note I The polyphenols evaluation, Farmacia, 2012, 60(4), 493-500.
7. SingletonV.L., Orthofer R, Lamuela-Raventos R. M, Analysis of total phenols and other oxidation substrates and antioxidants by means of the Folin–Ciocalteu reagent Methods in Enzymology, 299 (1999), 152–178.
8. 8.Singleton V.L., Rossi J.A., Colorimetry of total phenolics with phosphomolybdic-phosphotungstic acid reagents, Am.J.Enol.Vitic, 1965,16(3), 144-158.
9. xxx - PDR for Herbal Medicines, Ed. Thomson, 2005, third edition, p. 51-52, 191-192.
10. xxx - Assessment report on *Cichorium intybus* L., radix EMA/HMPC/113041/2010
11. xxx - Farmacopeea Română, ed. a X-a, Ed. Medicală, Bucureşti, 1993, p. 334-335, 1016, 1057-1058.
12. xxx - European Pharmacopoeia, 5 th edition, Council of Europe, Strassbourg, 2006, 1027.

NEW ASPECTS ON THE CIGARETTE SMOKE TOXICITY



CONSTANTIN PETRARU[1], DAN BĂLĂLĂU[2], MIHAELA ILIE[3]

[1]Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Toxicology Dept., Chemist, PhD student
[2]Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Toxicology Dept., Professor, PhD
[3]Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Toxicology Dept., Senior Scientific Researcher, PhD

ABSTRACT

Cigarette smoking is primarily a manifestation of nicotine addiction. Nevertheless, social, economic, and personal influences play an important part in determining patterns of smoking prevalence and cessation. Cigarette smoke is a complex mixture that contains more than 4000 chemical components including oxidants, free radicals, and carcinogens. Taken alone, part of these substances were tested for their risk for health, but the attempt of evaluating the health risk of synergistically acting compounds of cigarette smoke is too difficult to be investigated. Meanwhile, numerous studies indicate that pathogenesis of most of the cigarette smoke-induced diseases is associated with oxidative stress.

The paper is a review of recent findings on mechanisms that underlie the toxic response of organisms under the effect of cigarette smoke, focusing on cancer, chronic pulmonary obstruction disease and cardiovascular diseases.

Key words: *cigarette smoke; mainstream smoke; sidestream smoke; toxicity*

Correspondence to:

Mihaela Ilie
Address: Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Toxicology Dept., 6 Traian Vuia St., 020956 Bucharest, Romania
Phone: 0213111152
E-mail address: mihaela.ilie@umf.ro, m16ilie@yahoo.com

INTRODUCTION

Cigarette smoke (CS) is a complex mixture of more than 4000 compounds, including free radicals and long-lived radicals, generated by combustion, pyrolysis and pyrosynthesis upon burning of the ingredients of tobacco. While smoking a cigarette, the emergent smoke can be divided into two main categories: the mainstream smoke (MS), which is inhaled by the smoker, being a mixture of gas and aerosol with particles as large as 0.1-0.8 μm, and sidestream smoke (SSM), which is dispersed in the environment (Figure 1). The gas (vapor) phase contains large amounts of carbon monoxide, carbon dioxide, and nitrogen dioxide, while nicotine, phenols, polyaromatic hydrocarbons, and certain tobacco-specific nitrosamines are contained in the particulate phase, which may also enter the bloodstream. The particulate phase of CS contains >1017 free radicals per g, and the gas phase contains >1015 free radicals per puff [1]. The radicals contained in the tar phase are long-lived (hours to months), whereas those associated with the gas phase have a shorter life span (seconds) [1]. Nicotine, carbon monoxide, reactive oxygen species (ROS), and acrolein are CS toxins with significant inflammatory and immunomodulatory potential. In a burning cigarette, one can distinguish different zones, in which different kind of toxic substances can be generated (Figure 1).

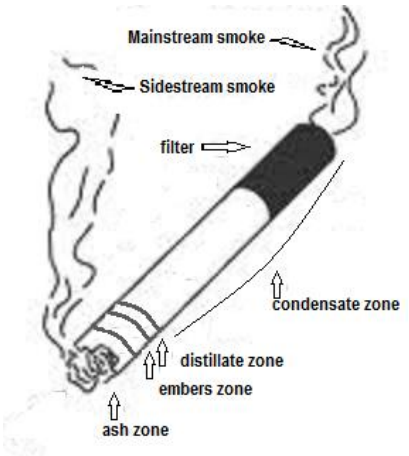


Figure 1. Burning cigarette

For non-smokers, a third category of smoke is taken into consideration: the second hand smoke (SHS), which consists in a mixture of exhaled MS and SSM. While all forms of environmental tobacco smoke exposure have been shown to cause genetic damage, the detriments of SHS to a person vary, based on proximity to source of smoke, time, and environment. MS is generated at high temperatures in the presence of oxygen, resulting in larger particles than SSM. SSM is generated at lower temperatures in an oxygen-poor environment, therefore presents higher concentrations of ammonia, nitric oxides, and other carcinogens [2].

The paper aims to present recent results of studies performed to investigate the effects of tobacco smoke on three major diseases: cancer, chronic obstructive pulmonary disease and cardiovascular diseases.

CIGARETTE SMOKE AND CANCER

Approximately 250 carcinogenic and noxious chemicals have been measured in both SSM and MS [3]. To date, however, there is no generally accepted laboratory animal bioassay for LC (lung cancer) induced by chronic cigarette MS inhalation. Some chronic MS inhalation studies with mice or rats that followed specific design considerations were positive in demonstrating lung tumor formation [4].

The most promising rodent strain studied so far for investigating smoke-induced LC seems to be the A/J mouse because of its high susceptibility to

spontaneous and chemically induced LC development and its reproducible positive LC response to inhalation of a mixture of cigarette sidestream and MS used as an environmental tobacco smoke surrogate [5].

In a recent study, Guo et al. [6] tested smoke condensate from 11 different cigarette brands and found that they all demonstrated dose-dependent mutagenic effects. Moreover, the tobacco-specific N-nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) induces lung tumors in several species regardless of the route of administration.

Tobacco smoke-induced methylation and resulting loss of gene expression has been detected in cell lines derived from cigarette smoke- or tobacco carcinogen induced mouse lung tumors. Hypermethylated promoters have been also observed in clinically cancer-free and cancer-bearing smokers. This frequent hypermethylation in smoker tissues has been explained by the high levels of DNA methyltransferase 1 (DNMT1) that correlated with smoking status in lung tumor samples [7]. In vitro and murine in vivo experiments have further shown that NNK acts through Akt signaling and inhibits DNMT1 protein degradation. Subsequently, DNMT1 protein accumulation leads to increased tumor suppressor gene hypermethylation. The aberrant methylation was detected at very early time points, before any obvious lung histopathology. Based on their results, Phillips and Goodman [8] suggested that regions of altered DNA methylation could serve as both biomarkers of exposure and effect.

Inflammation has been considered to be involved in tumorigenesis although the causal role of specific inflammatory processes in the various steps of tumorigenesis remains to be elucidated. The enhanced inflammatory environment of the lung can also promote tumor initiation and progression of malignant cells through the activation of transcription factors that promote cell proliferation and inhibit apoptosis [2]. A mechanistic link between chronic obstructive pulmonar disease (COPD) and LC via such inflammatory processes has been recently hypothesized by Adcock et al. [9]. Because chronic airway inflammation is a risk factor for COPD and is related to the increase of human cancers, it is hypothesized that COPD and lung cancer may share chronic inflammation as a common pathogenic mechanism [10].

CIGARETTE SMOKE AND CHRONIC OBSTRUCTIVE PULMONAR DISEASE (COPD)

CS is the principal cause of COPD, a disorder characterized by airway inflammation. Nadigel et al. compared the intracellular response of normal human bronchial/tracheal epithelial cells (NHBE) and COPD-diseased human bronchial/tracheal epithelial cells (DHBE) to cigarette smoke condensate (CSC) for 24 h using the level of IL-8 production and toll-like receptor 4 (TLR4) expression [11]. They found that NHBE cells increased IL-8 production in a dose-dependent manner, while DHBE cells had a much lower production of IL-8 in response to CSC compared to NHBE cells, whilst no change in TLR4 expression with CSC exposure could be noticed, thus showing that indicating that COPD is associated with a reduced capacity of airway epithelial cells to respond to xenobiotics.

COPD is believed to be an independent risk factor for lung cancer. Prevalence of COPD in lung cancer cases is six-fold higher than in smokers without lung cancer [10].

CS has considerable oxidative stress potential, leading to impaired histone acetylation and further to enhanced expression of inflammatory mediators, which in turn leads to

amplified pulmonary inflammation. SHS exposure is as well detrimental to the lung either by direct effect of the toxic substances included and by inhibiting the repair mechanisms of the lung cells. Continued SHS exposure can also lead to the development of inflammation, which worsens COPD, due to the abnormal polarization of T– and B– cell differentiation [2].

The pro inflammatory activity of CS at the endothelial level further extends to the expression of several vascular adhesion molecules by endothelial cells that promote the adherence of circulating inflammatory cells to the luminal endothelial surface followed by their migration and the resultant vascular inflammatory response [12]. Pulmonary emphysema, a characteristic feature of COPD, has been described in several laboratories for mice after approximately 6 months of MS inhalation [13]. Inflammatory, emphysematous, and tumorigenic effects were observed in A/J mice exposed to MS for 18 months or combinations of shorter term chronic inhalation and postinhalation periods [4].

CS-induced endothelial dysfunction seems to be primarily caused by accelerated inactivation of NO (an important vasodilator substance critical to the normal homeostasis of the endothelium) due to increased production of ROS. The mechanism appears to involve several key enzyme systems, including NADH/NADPH oxidase and xanthine oxidase, both of which significantly contribute to ROS formation [14].

In humans, smoking-induced COPD is considered to be irreversible, and smoking cessation may only interrupt the progression of the disease [15].

To et al. showed that oxidative stress, directly or indirectly via histone deacetylase reduction, plays a role in plasminogen activator inhibitor-1 (PAI-1) expression in COPD via activation of NF-κB [16], as the mean PAI-1 level in COPD sputum was higher than that of both age-matched smokers without COPD and healthy non-smokers; furthermore, histone deacetylase 2 enhanced TNF-α-induced PAI-1 induction concomitant with enhancement of NF-κB p65 acetylation and NF-κB DNA-binding activity.

CIGARETTE SMOKE AND CARDIOVASCULAR DISEASES (CVD)

Epidemiologic studies have established that cigarette smoking is a strong risk factor of cardiovascular disease (CVD), but the molecular mechanisms and temporal progression of CS-induced pathophysiological disorders are still not clear.

It has been indicated that free radical-mediated oxidative stress might play a role in causing myocardial injury and damage of vascular endothelium that leads to the genesis of pathological cardiovascular events. Das et al. [17] showed that p-benzoquinone, derived from p-benzosemiquinone is a major risk factor responsible for causing CS-induced oxidative damage, which is followed by inflammation and apoptosis, ultimately leading to myocardial injury. The injury is accompanied by vascular thrombosis, collagen deposition in the left ventricular part of the heart and release of Troponin T and I in the serum.

Lung inflammation, the major driver of both lung cancer and COPD, has also been linked to CVD. It is believed that when lung inflammation, or even acute lung injury, turns systemic, it further stimulates events that lead to the activation of the vascular endothelium, heart attack, and stroke [18].

Several independent studies have emerged showing that DNA methylation is an important aspect in CVD pathology. The altered

methylation pattern induced by CS could be detected before any noticeable atherosclerotic lesions were present, suggesting that DNA methylation plays a pivotal role in the CVD development [19].

CS results in endothelial dysfunction with impaired NO-dependent vasodilatory function and elevates various pro inflammatory cytokines involved in atherosclerosis with subsequent recruitment and transendothelial migration of leukocytes. Additionally, CS causes vascular smooth muscle cell stimulation/proliferation and increases oxidative modification of low density lipoproteins [20].

Experimental studies have shown that CS induces a pro inflammatory activation of brain endothelial cells, disrupting their normal function and initiating cerebral aneurysm formation [21]. Three major pathways were identified for this effect: free radical-mediated oxidative stress resulting in CS-induced inflammation [20], the increase in the wall shear stress leading to increased blood viscosity and blood volume [22] and the modulation of the expression of key endothelial enzymes involved in cerebrovascular inflammation [23-25].

CONCLUSIONS

Tobacco smoking is probably the best-documented preventable risk factor for cancer pulmonary and cardiovascular disease. Tobacco smoking harms through several mechanisms, from which most documented are the endothelial dysfunction, impairment in normal metabolic enzyme function generally resulting in altered cellular biochemistry, further leading to inflammation, apoptosis or necrosis. Cancer, mainly lung cancer, pulmonary impairment, among most documented is the chronic obstruction pulmonary disease and all cardiovascular diseases are the most frequent health risks associated with cigarette smoke exposure, therefore the present paper presents a few recent findings in that respect.

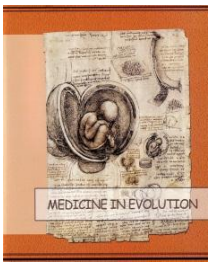
REFERENCES

1. Pryor W.A., Stone K., Cross C.E., Machlin L., Packer L. Oxidants in cigarette smoke: radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. 1993. Ann.N.Y.Acad.Sci.; 686:12–28
2. Birru R.L., Di Y.P. Pathogenic mechanism of second hand smoke induced inflammation and COPD. Front Physiol. 2012; 3(348), doi: 10.3389/fphys.2012.00348.
3. *** The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. 2006, Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. http://www.ncbi.nlm.nih.gov/books/NBK44324/
4. Stinn, W., Arts, J. H., Buettner, A., Duistermaat, E., Janssens, K., Kuper, C. F. Haussmann, H. J. Murine lung tumor response after exposure to cigarette mainstream smoke or its particulate and gas/vapor phase fractions. Toxicology. 2010; 275:10–20
5. Coggins, C. R. A further review of inhalation studies with cigarette smoke and lung cancer in experimental animals, including transgenic mice. Inhal. Toxicol. 2010; 22:974–983.
6. Guo X., Verkler T.L., Chen Y., Richter P.A., Polzin G.M., Moore M.M., Mei N. Mutagenicity of 11 cigarette smoke condensates in two versions of the

mouse lymphoma assay. Mutagenesis. 2011; 26:273–281.
7. Liu F., Killian J.K., Yang M., Walker R.L., Hong J.A., Zhang M., Davis S., Zhang Y., Hussain M., Xi S., Rao M., Meltzer P.A., Schrump D.S. Epigenomic alterations and gene expression profiles in respiratory epithelia exposed to cigarette smoke condensate. Oncogene. 2010; 29:3650–3664.
8. Phillips J.M., Goodman J.I. Inhalation of cigarette smoke induces regions of altered DNA methylation (RAMs) in SENCAR mouse lung. Toxicology. 2009; 260:7–15.
9. Adcock I.M., Caramori G., Barnes P.J. Chronic obstructive pulmonary disease and lung cancer: New molecular insights. Respiration. 2011; 81: 265–284
10. Young R.P., Hopkins R.J., Christmas T., Black P.N., Metcalf P., Gamble G.D.. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur. Respir. J. 2009; 34:380–386
11. Nadigel J., Audusseau S., Baglole C.J., Eidelman D.H., Hamid Q. IL-8 production in response to cigarette smoke is decreased in epithelial cells from COPD patients. Pulm Pharmacol Ther. 2013; pii: S1094-5539(13)00076-X. doi: 10.1016/j.pupt.2013.03.002. [Epub ahead of print]
12. Hossain M., Sathe T., Fazio V., Mazzone P, Weksler B., Janigro D., Rapp E., Cucullo L. Tobacco smoke: a critical etiological factor for vascular impairment at the blood-brain barrier. Brain Research. 2009; 1287: 192–205.
13. Braber S., Koelink P.J., Henricks P.A., Jackson P.L., Nijkamp F.P., Garssen J., Kraneveld A.D., Blalock J.E., Folkerts, G. Cigarette smoke induced lung emphysema in mice is associated with prolyl endopeptidase, an enzyme involved in collagen breakdown. Am. J. Physiol. Lung Cell Mol. Physiol. 2011; 300: L255–L265
14. Iida H., Iida M., Takenake M., Fukuoka N., Dobi S. Rho-kinase inhibitor and Nicotinamide Adenine Dinucleotide Phosphate oxidise inhibitor prevent impairment of endothelium-dependent cerebral vasodilation by acute cigarette smoking in rats. J.Renin-Angiotensin-Aldosterone Syst. 2008; 9(2): 89–94.
15. *** The Health Consequences of Smoking: A Report of the Surgeon General. 2004 U.S. Department of Health and Human Services. 2004. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. http://www.ncbi.nlm.nih.gov/books/NBK44695/
16. To M., Takagi D., Akashi K., Kano I., Haruki K., Barnes P.J., Ito K. 2013. Sputum PAI-1 elevation by oxidative stress-dependent NF-κB activation in chronic obstructive pulmonary disease. Chest. 2013, doi: 10.1378/chest.12-2381. [Epub ahead of print]
17. Das A., Dey N., Ghosh A., Das S., Chattopadhyay D.J., Chatterjee I.B. 2012. Molecular and Cellular Mechanisms of Cigarette Smoke-Induced Myocardial Injury: Prevention by Vitamin C, PLoS ONE 7(9): e44151. doi:10.1371/journal.pone.0044151
18. Van Eeden S., Leipsic J., Paul Man S.F., Sin D.D. The relationship between lung inflammation and cardiovascular disease. Am J Respir Crit Care Med. 2012; 186:11–16
19. Talikka M., Sierro N., Ivanov N.V., Chaudhary N., Peck M. J., Hoeng J., Coggins C. R. E., Peitsch M. C. Genomic impact of cigarette smoke, with application to three smoking-related diseases. Critical Reviews in Toxicology 2012; 42(10): 877–889.
20. Benowitz N.L. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Progress in Cardiovascular Diseases, 2003; 46(1): 91–111.
21. Chalouhi N., Ali M.S., Starke R.M., Jabbour P.M., Tjoumakaris S.I., Gonzalez L.F., Rosenwasser R.H., Koch W.J., Dumont A.S. Cigarette Smoke and Inflammation: Role in Cerebral Aneurysm Formation and Rupture. Mediators of Inflammation, 2012, Article ID 271582
22. Singh P.K., Marzo A., Howard B., Rufenacht D.A., Bijlenga P., Frangi A.F., Lawford P.V., Coley S.C., Hose D.R., Patel U.J. Effects of smoking and hypertension on wall shear stress and oscillatory shear index at the site of

intracranial aneurysm formation. Clin.Neurol.Neurosurg., 2010; 112(4): 306–313.
23. Sandhu H., Xu C.B., Edvinsson L. Upregulation of contractile endothelin type B receptors by lipid-soluble cigarette smoking particles in rat cerebral arteries via activation of MAPK. *Toxic/ol. App. Pharmacol.*, 2010; 249(1): 25–32.
24. Aoki T., Nishimura M., Kataoka H., Ishibashi R., Nozaki K., Miyamoto S. Complementary inhibition of cerebral aneurysm formation by eNOS and nNOS. *Lab. Invest.*, 2011; 91(4): 619–626
25. Xu C.B., Zheng J.P., Zhang W., Zhang Y., Edvinsson L. Lipid-soluble smoke particles upregulate vascular smooth muscle ETB receptors via activation of mitogen-activating protein kinases and NF-kappaB pathways. *Toxicol. Sci.*, 2008; 106(2): 546–555

ADIPONECTIN - MULTIPLE FACETS OF THE SAME CHALLENGING MOLECULE



BĂLĂŞESCU E.[1], RUSU M.C.[2], ION D.A.[3]

[1]MD, PhD stud., Division of Physiopathology (II), Department 2, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[2]MD, PhD, Dr.Hab., Assoc.Prof., Division of Anatomy, Department 1, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[3]MD, PhD, Prof., Division of Physiopathology (II), Department 2, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Background: Adiponectin's discovery in 1995 by Philipp Scherer marked a pivotal moment in understanding that the adipose tissue is not only a protective, supportive and energy storage structure but also a real endocrine organ.

Adiponectin (ADPN), one of the most important adipocytokine, mainly synthesized in white adipose tissue, is a signal molecule which activates lipid metabolism and plays a significant roles in many physio-pathological mechanisms at cellular level. Consequently, ADPN has proved its anti-diabetic, anti-inflammatory and antiatherogenic properties. Variations in the serum ADPN level depend on multiple factors (gender, age, ethnicity, BMI, health status). Medical research shows that genetic ADPN deficiency induces obesity and moreover, its low concentrations were associated with multiple phenotypic traits of the metabolic syndrome. Thus, hypoadiponectinemia could play a causal role in the development of obesity-related diseases.

Evidence Acquisition and Synthesis: Further to various medical researches, this paper aims at providing an overview concerning the implications of ADPN in the physiopathology of the metabolic syndrome and its complications. Besides, we emphasize aspects of ADPN molecular structure, the influence of AdipoQ gene and its variations upon the ADPN plasmatic concentration, the circulating forms and their biological functions, mechanisms of action and effects at the cellular level.

Conclusions: It has been demonstrated that ADPN protects health through its vasodilatory, anti-apoptotic, anti-inflammatory and anti-oxidative actions. Although an increased level of ADPN seems protective in the general population, the contradictory results between the plasmatic ADPN and the mortality risk in different subtypes of populations require further investigations.

Key words: *adipocytokines; metabolic syndrome; lipid metabolism*

Correspondence to:

M.C. Rusu
Address: "Carol Davila" University of Medicine and Pharmacy, 8 Bd.Eroilor Sanitari, RO-76241, Bucharest, Romania
Phone: +40722363705
E-mail address: anatomon@gmail.com

INTRODUCTION

Discovered in the mid-90's from four independent research groups, adiponectin (ADPN) is a protein hormone with polypeptide structure, secreted mainly by the adipose tissue. ADPN represents about 0.01% of the total plasma protein with a concentration between 5 to 30µg/ml. Starting from the molecular weight, structural similarity with serum complement, encoding gene and the place of synthesis, and respectively the method used for its isolation and purification, adiponectin has been named ACRP-30 (Scherer et al., 1995), ADIPOQ (Hu et al., 1996), APM1 (Yoshimoto et al., 1997), GBP28 (Nakano et al., 1996).

Molecular structure, multimeric forms of adiponectin

Adiponectin is a polypeptide showing several distinct domains: the N-terminal domain - a signal sequence involved in the extracellular secretion of ADPN; a short non-helical sequence which varies among species, a collagen-like repetitive region (Gly-X-Y), and C-terminal globular domain - a three-dimensional structure, similar to that of TNF-α.

It has been demonstrated the separation of ADPN in multimeric species (Waki et al., 2003). In the human or murine serum and the NIH-3T3 fibroblast cell line, ADPN molecules automatically join in initial groups of three giving rise to homo-trimers whose further association leads to high molecular weight structures. There were detected low molecular weight structures (LMW-about 180 kDa), medium molecular weight structures (MMW) - which contain disulfide bridges, and structures with high molecular weight (HMW - about 360 kDa) consisting of at least 12 - 18 subunits of adiponectin (Kadowaki and Yamauchi, 2005), (Waki et al., 2003). In humans, adiponectin mainly exists as hexamers and multimers, smaller complexes such as trimers, being virtually undetectable in serum (Trujillo and Scherer, 2005).

In the plasma, ADPN monomers are associated with disulfide bridges which connect the collagen domains, resulting from higher order multimeric structure, with the appearance of the "bouquet". Formation of ADPN oligomers depends on Cys-39-mediated disulfide bond formation (Pajvani et al., 2003). Secreted by adipocytes, ADPN exists in several glycosylated isoforms. In this respect, there was made the mapping of glycosylation sites to the amino acid Lysine (residues 68, 71, 80, 104) in the collagenic domain of ADPN, as well as surrounding consensus sequences GXKGE (D). (Mention should be made that each of these four Lys residues and consensus sequences GXKGE (D) are conserved in all species of ADPN). These Lysine residues were hydroxylated and subsequently glycosylated. The importance of hydroxylysine glycosylation was confirmed by analyzing mutations, which showed that replacement of Lys residues with the Arg, reduces the ability of ADPN to potentiate the inhibitory action of insulin on gluconeogenesis (Wang et al., 2002).

In human plasma there was detected a small amount of globular ADPN, and it was assumed that the globular fragment is generated by proteolytic cleavage (Fruebis et al., 2001). It was also shown that the cleavage of ADPN is done by leukocyte elastase, secreted by activated monocytes and/ or activated neutrophils (Kadowaki and Yamauchi, 2005), (Waki et al., 2005). Since most of the in vitro studies of ADPN effects used the full-lenght protein, it is unclear whether these effects are physiologically relevant, because neither full-length protein (produced by bacteria) nor globular domain (resulted through cleavage) do not aggregate in high molecular weight

forms (Lara-Castro et al., 2007), (Lara-Castro et al., 2006).

ADIPOQ GENE - VARIATIONS AND GENETIC POLYMORPHISMS

It has been shown that circulating ADPN level is determined in a proportion of 40% to 70% of the genetic factors (Heid et al., 2006), (Heid et al., 2010). In humans, ADPN is encoded by the ADIPOQ gene consisting of three exons and two introns. ADIPOQ gene covers a region of 17 kb and was located in chromosome region 3q27. After the mapping of genomic structural variation and the study of structural variants by a single nucleotide pairs (SNPs single nucleotide polymorfism), it has been shown that chromosomal region 3q27 is involved in susceptibility to type 2 diabetes, obesity, insulin resistance. In genome-wide studies, more than 10 SNPs have been reported, and among them, polymorphism 45 in exon 2 and polymorphism 276 in intron 2 were commonly associated with diabetes, obesity and cardiovascular disease (Gherman et al., 2013, Jung et al., 2006, Menzaghi et al., 2007, Gherman and Mironiuc, 2012).

Many studies tried to clarify the relationship between genetic variation – plasma ADPN level and obesity. A group of Japanese researchers reported lack of correlation between G / T polymorphism of exon 2, with changes in plasma ADPN and the presence of obesity (Takahashi et al., 2000). Further studies on non-diabetic populations, identified in the ADIPOQ gene one frequent polymorphism and two rare polymorphisms: a silent mutation T / G in the nucleotide 94 (exon 2) (~ 25% prevalence), a missense mutation T / C in the nucleotide 331 (exon 3) (Tyr111His, with a prevalence in the the German population of ~ 4%), a missense mutation T / C in the nucleotide 383 (exon 3), (Arg112Cys, with a prevalence in Japanese populations of ~ 0.5%). The prevalence of polymorphisms was about 50% (exon 2) and ~ 0.5% (exon 3). Polymorphism T / G in the exon 2 is very widespread, although not resulting in an amino acid change and affect plasma ADPN levels. To clarify whether polymorphism T / G in the exon 2 is associated with insulin sensitivity and whether it affects the relationship obesity- insulin resistance (dependent or not by the family history of type 2 diabetes), was analyzed correlation of insulin sensitivity - polymorphism T / G (GG + TG) versus wild-type controls (TT). As evidenced a significantly higher BMI in the population GG + GT and reduced insulin sensitivity compared with TT, it was concluded in individuals with no family history of diabetes, that this polymorphism may slightly increase the risk of obesity and also insulin resistance (Stumvoll et al., 2002). In the Japanese population by analyzing ADIPOQ gene, researchers have identified 10 common SNPs (Hara et al., 2002).

Similar associations of ADIPOQ gene with susceptibility to type 2 diabetes have been reported in other ethnic groups. In the Italian Caucasians, SNP 276 independent, or as haplotype with SNP45 (intron 2) showed that it is associated with obesity and insulin resistance in French Caucasians were described two SNPs in the promoter region of adiponectin gene, SNP-11377 and SNP-11391, significantly associated with low plasma ADPN and type 2 diabetes (Vasseur et al., 2002).

THE BIOLOGICAL ROLE OF ADIPONECTIN MULTIMERIC SPECIES

Initial epidemiological studies evaluated only total ADPN, to be further investigated how the multimeric forms of ADPN may exert different biological activity. Thus, the high molecular weight multimers (HMW) have been associated with favorable metabolic effects such as increased insulin sensitivity, reduction in visceral fat mass, reducing plasma levels of triglycerides and increasing HDL-cholesterol. It was shown (Trujillo and Scherer, 2005) that the HMW/ total ADPN ratio, was responsible of these favorable metabolic effects, and that the ratio, not the total ADPN, was correlated with insulin sensitivity in humans and mice. It was noted that this ratio was raised by thiazolidinediones, a therapy capable of improving hepatic insulin sensitivity manifested by decreasing fasting hepatic gluconeogenesis. Moreover, only the use of HMW, not LMW adiponectin, lowered blood glucose in rats (Lara-Castro et al., 2006).

Results of several in vitro studies show an important biological role of HMW compared to lower molecular weight forms. It was found that HMW species are more strongly correlated with insulin sensitivity, abdominal adiposity, HDL cholesterol, serum triglycerides and basal lipid oxidation rate. In addition to the HMW, although to a smaller extent, the LMW forms were also positively associated with insulin sensitivity and metabolic parameters and VLDL cholesterol and an increase of the concentration of LMW in response to a moderate weight loss was observed (Bobbert et al., 2005), (Pajvani et al., 2003); the trimer of ADPN was correlated with waist circumference and IL6 secretion in monocytes (Schober et al., 2007). Lodish et al. (Tsao et al., 2003) showed that the low molecular weight hexamer LMW as well as the HMW adiponectin are equally effective in the activation of nuclear factor NF-kB, and both the monomer and ADPN trimer are capable of stimulating AMP-kinase, while the LMW and HMW have no effect (Yamauchi et al., 2002).

In addition to total ADPN, its multimers can independently explain variability in metabolic traits among individuals and populations (Lara-Castro et al., 2008). It is not fully known what the distribution of ADPN multimers according to race and how to influence the relationship with insulin sensitivity and other metabolic traits. Recently, HMW was highly correlated with several features of the metabolic syndrome in European-Americans, and LMW and trimer forms were highly correlated with metabolic traits in African Americans (Lara-Castro et al., 2008).

In the ARIC Study (Atherosclerosis Risk in Communities Study) it has been found that increased blood levels of total and HMW adiponectin, were similarly associated with a lower incidence of type 2 diabetes over 9 years of follow up. Higher concentrations of total ADPN were associated with a lower incidence of diabetes, this combination having a similar magnitude in both sexes (male and female), white and African Americans. These results suggested that total ADPN serve as a link between fat accumulation and the likelihood of developing type 2 diabetes. Some researchers have shown that HMW and HMW / total ADPN ratio were inversely associated with risk of diabetes. Furthermore, HMW was more closely related to the development of type 2 diabetes as compared to the total ADPN (Zhu et al., 2010).

MECHANISMS OF ACTION AND CELLULAR EFFECTS OF ADIPONECTIN

Once secreted, ADPN aggregates into multimeric forms and circulates in high concentrations in the blood, its effects and its role in cellular lipid metabolism and atherosclerosis being intensively studied. ADP's effects occur after its binding to own receptors, which act by affecting the target AMP kinase, an important cellular metabolic rate control. There are two distinct ADPN receptors, ADIPOR1 and ADIPOR2. ADIPOR1 is ubiquitously expressed, whereas ADIPOR2 is most abundant in liver. T-cadherin, considered by most researchers as an ADPN ligand /binding protein, it is expressed and bind ADPN in muscle, but has no effects in the liver. Receptors expression is correlated with insulin, in particular in skeletal muscle and adipose tissue.

ADPN influences the level of plasma lipoproteins by altering the level and activity of some key enzymes responsible of the catabolism of triglyceride-rich lipoproteins and HDL cholesterol. It intervenes in atherosclerosis by affecting the plasmatic balance between potentially atherogenic respectively antiatherogenic lipoproteins and by modulating the cellular processes of pre-adipocytes differentiation.

Despite the various studies performed, the signalling pathways that mediate the metabolic effects of ADPN have not been fully elucidated. It has been shown that phosphorylation and activation of 5'-AMP protein kinase-activated (AMPK) is stimulated by both the globular domain of ADPN resulted from proteolytic cleavage and by full-length form of ADPN in skeletal muscle, only the latter being involved in AMPK activation in the liver. Thus, by activating AMPK, ADPN directly interferes with glucose metabolism and insulin sensitivity both in vitro and in vivo. In parallel with the activation of AMPK, ADPN stimulates phosphorylation of acetyl coenzyme A carboxylase (ACC), fatty acid oxidation, glucose and lactate uptake in myocytes, reducing the molecules involved in hepatic gluconeogenesis, resulting in a lower blood glucose in vivo (Yamauchi et al., 2002).

Higher levels of total ADPN and HMW were correlated with higher levels and larger HDL particles and low levels of LDL cholesterol and VLDL particles (Lara-Castro et al., 2006). ADPN intervenes in lipid metabolism by increasing plasma levels of HDL-cholesterol and triglycerides clearance; fatty acid lowering occurs due to basal lipid oxidation (β-oxidation) mechanism, that can explain its involvement in endothelial protection.

ADPN interferes with carbohydrate metabolism by decreasing gluconeogenesis and insulin sensitivity adjustment; through its insulin sensitizing action intervenes in glucose homeostasis. As an moderate increase in circulating levels of ADPN, inhibits both the expression of hepatic gluconeogenesis enzymes, and endogenous glucose production rate, it was concluded that the liver and not the muscle is the main place of ADPN bioactivity (Combs et al., 2001). Furthermore, Wang et al have shown that the ADPN 's effect on the liver requires hydroxylation and glycosylation of the collagen residues of ADPN (Wang et al., 2002), a finding that could explain the observation of the lack of impaired hepatic glucose metabolism in those studies that have used globular (cleaved collagen domain required for multimerization) or full-length bacterial ADPN (where are missing the post-translational modifications in the collagenic domain) (Trujillo and Scherer, 2005).

ADPN has an insulin sensitized effect on the liver, an effect dependent of its presence in the form of higher

order structures (LMW and HMW). The heaviness of these structures serve as an indicator of systemic insulin sensitivity (Trujillo and Scherer, 2005). Scherer at al. have demonstrated that ADPN has the ability to decrease hepatic expression of enzymes involved in gluconeogenesis - PEPCK and mRNA G6Pase, and that a moderate increase in circulating levels of ADPN, inhibits both the expression of hepatic gluconeogenesis enzymes (Combs et al., 2001), and endogenous glucose production rate.

In obese mice, by lowering triglycerides content in their muscle and liver, ADPN decreases insulin resistance. This effect is mediated by stimulation of some molecules involved in fatty acid transport and combustion (CD36, respectively coenzim Acyl-A oxidase) and those that determine the transformation of energy into heat (UCP-2 uncoupling protein 2, a mitochondrial protein that belongs to the family of mitochondrial "anionic carriers" ubiquitously widespread, having a regulatory role in insulin secretion) (Kadowaki and Yamauchi, 2005), (Yamauchi et al., 2001), (Rousset et al., 2004).

In lipoatrophic mice treated with ADPN, it was observed in the skeletal muscle an increased insulin-induced tyrosine phosphorylation of insulin receptor, followed by many phosphorylations in the PI3K pathway, with partial reversibility of insulin sensitivity. Insulin resistance was completely reversed by administration of physiological doses of adiponectin and leptin, but only partially reversible by administering each of them (Yamauchi et al., 2001). Since increased tissue triglyceride content leads to insulin-stimulated activation of phosphatidyl inositol 3 kinase, subsequent translocation of glucose transporter 4 with increasing takeover of glucose and insulin resistance occurence, it was concluded that the decrease in triglyceride content in muscle could help decrease insulin resistance by improving insulin signal transduction (Kadowaki and Yamauchi, 2005).

In in vitro studies, by exposure of C2C12 myocytes to adiponectin for different periods of time (Yamauchi et al., 2003), it has been observed that fatty acid oxidation caused by adiponectin has different processes as substrate. The exposure for a short period of time has as a substrat AMPK activation, while a 6 hour treatment with adipnectin resulted in a significant increase in endogenous ligands of PPARα activity with the same effect (Kadowaki and Yamauchi, 2005), (Yamauchi et al., 2003). PPAR α activation promotes the acquisition and fatty acid catabolism by their β-oxidation at the peroxisome and mitochondrial level, by increasing the activity of the genes responsible for their transport, binding and activation, the most important being PDK4 (pyruvate dehydrogenase involved in inhibition, decreased conversion of pyruvate, glucose conservation by limiting its transformation into acetyl-CoA, peroxisome-acyl-CoA oxidase1 (ACOX1) and carnitine palmitoyl-transferase1 (CPT1A) (Rakhshandehroo et al., 2010).

Because of its antiatherogenic properties, ADPN was considered a genuine endogenous modulator of vascular remodeling. The exact mechanisms of protection are not yet fully known, so some studies have sought to identify correlations between plasma levels of ADPN and vascular damage at coronary (Wolk et al., 2007), (Kumada et al., 2003), (Pischon et al., 2004), cerebral (Efstathiou et al., 2005), and peripheral level (Dieplinger et al., 2006), (Gherman et al., 2013).

It has been demonstrated that ADPN acts as an endogenous antithrombotic factor, this effect being proven by the reducing in thrombus formation (in vivo) and inhibition of platelet aggregation (in vitro) (Kato et al., 2006). ADPN is involved in maintaining of the balance between

hemostasis and fibrinolysis. By joining to the vascular lesion (Okamoto et al., 2000), ADPN decreases vascular inflammation, monocyte-macrophage infiltration, apoptosis, and also stimulates the tissue inhibitor of metalloproteinase-1 by human macrophages (Kumada et al., 2004), thus protecting by the erosion and breakage of fibrous head of atherom plaque.

At endothelial level, ADPN suppresses phosphorylation of IkBα (induced TNF-α) and subsequent activation of NF-kB, without affecting other signals of phosphorylation, TNF-α mediated, including Jun N-terminal kinase, p38 kinase and PKB. This inhibitory effect of ADPN is accompanied by the accumulation of cAMP and is blocked by the adenylate cyclase inhibitor and the protein kinase A inhibitor. ADPN interferes with monocyte-macrophage system and foamy cell appearance (as result of loading macrophages with cholesterol (Ouchi et al., 2000), (Ouchi et al., 1999). In addition, ADPN intervenes in the process of atherogenesis and nitric oxide production (Wolk et al., 2007),(Ouchi et al., 2004), suppression of endothelial cell apoptosis (HMW forms, suppression of vascular smooth muscle cells proliferation in the intima (Matsuda et al., 2002), and in the angiogenesis. Thus, ADPN has the ability to modulate endothelial inflammatory response by cross action of both signaling pathways cAMP-PKA and NF-kappaB (Ouchi et al., 2000). Adhering to the damaged endothelium, ADPN inhibits the endothelial inflammatory response specific to the atherogenesis process (Okamoto et al., 2000).

By its antiproliferative and antiapopotic effects, maintaining the normal functioning of endothelial cells, (inhibition of TNF-α, inhibition of nuclear factor kB, decreased production of IL-6, stimulating secretion of endothelial NO), ADPN leads to plaque stabilization (Wolk et al., 2007).

CONCLUSIONS

ADPN has a beneficial effect through its vasodilators, anti-apoptotic, anti-inflammatory, antioxidant and insulin-sensitizing actions. Although increased plasma levels of ADPN seem to have a protective effect in the general population, and increased concentration of ADPN observed in centenarians, was associated with decreased incidence of dyslipidemia, cardiovascular diseases, hypertension and diabetes, there have been reported contradictory results about the correlation between ADPN and the risk of mortality. At the onset of acute conditions with vital risk, persistent low plasma levels of ADPN are accompanied by a poor prognosis, but in chronic disease (with hypoadiponectinaemia), increased plasma levels of ADPN are a predictor of overall and/or cardiovascular mortality. Significance of different serum levels of ADPN in different circumstances is not fully elucidated, one possible explanation being related to the variation of ADPN protective isoforms, but further studies are needed to clarify this discrepancy.

Acknowledgements

This study was supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/82839 (author #1).

REFERENCES

1. Bobbert T, Rochlitz H, Wegewitz U, Akpulat S, Mai K, Weickert MO, Mohlig M, Pfeiffer AF, Spranger J. Changes of adiponectin oligomer composition by moderate weight reduction. Diabetes. 2005;54(9):2712-2719.
2. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest. 2001;108(12):1875-1881.
3. Dieplinger B, Poelz W, Haltmayer M, Mueller T. Hypoadiponectinemia is associated with symptomatic atherosclerotic peripheral arterial disease. Clin Chem Lab Med. 2006;44(7):830-833.
4. Efstathiou SP, Tsioulos DI, Tsiakou AG, Gratsias YE, Pefanis AV, Mountokalakis TD. Plasma adiponectin levels and five-year survival after first-ever ischemic stroke. Stroke. 2005;36(9):1915-1919.
5. Gherman CD, Mironiuc AI. Evaluation of serum adipokines in peripheral arterial occlusive disease. Mediators Inflamm. 2012;2012(257808.
6. Gherman CD, Pamfil D, Bolboaca SD. Association of atherosclerotic peripheral arterial disease with adiponectin genes SNP+45 and SNP+276: a case-control study. Biomed Res Int. 2013;2013(501203.
7. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem. 1996;271(18):10697-10703.
8. Jung CH, Rhee EJ, Kim SY, Shin HS, Kim BJ, Sung KC, Kim BS, Lee WY, Kang JH, Oh KW, Lee MH, Kim SW, Park JR. Associations between two single nucleotide polymorphisms of adiponectin gene and coronary artery diseases. Endocr J. 2006;53(5):671-677.
9. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev. 2005;26(3):439-451.
10. Kato H, Kashiwagi H, Shiraga M, Tadokoro S, Kamae T, Ujiie H, Honda S, Miyata S, Ijiri Y, Yamamoto J, Maeda N, Funahashi T, Kurata Y, Shimomura I, Tomiyama Y, Kanakura Y. Adiponectin acts as an endogenous antithrombotic factor. Arterioscler Thromb Vasc Biol. 2006;26(1):224-230.
11. Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, Maeda K, Nagaretani H, Kishida K, Maeda N, Nagasawa A, Funahashi T, Matsuzawa Y. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation. 2004;109(17):2046-2049.
12. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Funahashi T, Matsuzawa Y. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol. 2003;23(1):85-89.
13. Lara-Castro C, Doud EC, Tapia PC, Munoz AJ, Fernandez JR, Hunter GR, Gower BA, Garvey WT. Adiponectin multimers and metabolic syndrome traits: relative adiponectin resistance in African Americans. Obesity (Silver Spring). 2008;16(12):2616-2623.
14. Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Curr Opin Lipidol. 2007;18(3):263-270.
15. Lara-Castro C, Luo N, Wallace P, Klein RL, Garvey WT. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. Diabetes. 2006;55(1):249-259.
16. Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, Kumada M, Okamoto Y, Nagaretani H, Nishizawa H, Kishida K, Komuro R, Ouchi N, Kihara S, Nagai R, Funahashi T, Matsuzawa Y. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. The Journal of biological chemistry. 2002;277(40):37487-37491.
17. Menzaghi C, Trischitta V, Doria A. Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. Diabetes. 2007;56(5):1198-1209.
18. Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from

human plasma. Journal of biochemistry. 1996;120(4):803-812.
19. Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M, Igura T, Inui Y, Kihara S, Nakamura T, Yamashita S, Miyagawa J, Funahashi T, Matsuzawa Y. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2000;32(2):47-50.
20. Ouchi N, Kihara S, Arita Y, Maeda K,
21. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA. 2004;291(14):1730-1737.
22. Rakhshandehroo M, Knoch B, Muller M, Kersten S. Peroxisome proliferator-activated receptor alpha target genes. PPAR Res. 2010;2010(
23. Rousset S, Alves-Guerra MC, Mozo J, Miroux B, Cassard-Doulcier AM, Bouillaud F, Ricquier D. The biology of mitochondrial uncoupling proteins. Diabetes. 2004;53 Suppl 1(S130-135.
24. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem. 1995;270(45):26746-26749.
25. Schober F, Neumeier M, Weigert J, Wurm S, Wanninger J, Schaffler A, Dada A, Liebisch G, Schmitz G, Aslanidis C, Buechler C. Low molecular weight adiponectin negatively correlates with the waist circumference and monocytic IL-6 release. Biochem Biophys Res Commun. 2007;361(4):968-973.
26. Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, Machicao F, Haring H. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes. 2002;51(1):37-41.
27. Takahashi M, Arita Y, Yamagata K, Matsukawa Y, Okutomi K, Horie M, Shimomura I, Hotta K, Kuriyama H, Kihara S, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Genomic structure and mutations in adipose-specific gene, adiponectin. Int J Obes Relat Metab Disord. 2000;24(7):861-868.
28. Trujillo ME, Scherer PE. Adiponectin--journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. J Intern Med. 2005;257(2):167-175.
29. Tsao TS, Tomas E, Murrey HE, Hug C, Lee DH, Ruderman NB, Heuser JE, Lodish HF. Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity. Different oligomers activate different signal transduction pathways. J Biol Chem. 2003;278(50):50810-50817.
30. Wang Y, Xu A, Knight C, Xu LY, Cooper GJ. Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin. Potential role in the modulation of its insulin-sensitizing activity. J Biol Chem. 2002;277(22):19521-19529.
31. Wolk R, Berger P, Lennon RJ, Brilakis ES, Davison DE, Somers VK. Association between plasma adiponectin levels and unstable coronary syndromes. Eur Heart J. 2007;28(3):292-298.
32. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002;8(11):1288-1295.

INSTRUCTIONS FOR AUTHORS

The journal publishes general reviews, studies and clinical, epidemiological, experimental and laboratory research, clinical case presentation, papers from the history of medicine, reviews, scientific and technical state-of-the-art articles, medical informations and opinions. Only papers which have not been published or sent for publishing in other journals are accepted. The authors are responsable for the opinions expressed in the papers. ***The paper must be edited both in Romanian and in English; the English version will be supervised by our collaborator Dana Brehar-Cioflec, MD, PhD; typed on white A$_4$ paper (fonts - Times New Roman 12, Romanian characters, line spacing 1.5, upper and lower margins 2cm, left border 3cm, right border 2cm) and on CD, DVD or Memory Stick***.

Manuscripts will not exceed:

- general reviews: 6-8 pages
- studies and researches: 5-7 pages
- case presentations: 2-4 pages
- reviews, scientific and technical state-of-the-art articles, medical informations and opinions: 1-2 pages.

The paper will be edited according to international editing rules for manuscripts. The title will be written in capital characters and it will be followed by the name and surname of the author (authors), followed by their place of work (place where the paper has been elaborated). Studies and researches will be followed by a brief abstract, followed by 3-4 key-words.

The body of the paper will be structured on the following chapters: introduction, aim, objectives, material and method, results and discussions, conclusions. The references will be presented alphabetically and in conformity to the Vancouver Convention, including:

- for articles: name of the authors and surname initials, title of the article in the original language, title of the journal according to the international abreviation system, year of issue, volume, number, pages;
- for books: name of the authors and surname initials, volume, publisher (editors), city of publishing, year of issue.

Citation of references inside the body of the paper will be put between brackets, Harward style (author, year) or Vancouver style (number in square brackets or superscript). Cited reference titles will be selected, maximum 6 for studies and case presentations and 12 for general reviews. Acceptance, rejection or the need of alterations in sent materials, or in inconography, will be comunicated to the authors in due time. For this, the authors will indicate the person and address for corespondence (phone number, e-mail address). Given the less pleasant experience of the editorial board with some articles being rejected because they did not meet publishing criteria, we decided to support those who intend to publish in this journal by detailing the way such a paper should be elaborated, as well as our requirements.

Except some particular aspects concerning this journal, the following details are general requirements asked or imposed by other journals as well. Conditions to be met in order to propose a paper for publishing. The main author has the

responsability to make sure the article has been approved by all the other authors. The journal will have copyright for papers accepted for publishing. The editorial board reservs the right to change the style and dimensions of an article (major changes will be discussed with the main author) and to decide the date of issue.

2. FIRST PUBLICATION

The editorial board will not consider a paper already reported in a published general review or described in a paper proposed to or accepted by another journal. This does not exclude papers which have been rejected by other journals. Also, papers which have been presented at a scientific meeting will be accepted for discussion if they have not been entirely or partially published in a similar publication. „Multiple" publishing of the same study is seldom justified. One of the possible justifications is publishing in a second language but only if the following conditions are met:

- Editors of both journals involved are fully informed;
- Priority of the initial publication will be respected by a minimum publishing interval of two weeks;
- For the second publication, a shortened version will suffice;
- The second version strictly reflects data and interpretations in the first;
- A footnote may state: „This article is based upon a study initially published in [title of the journal]".

3. PATERNITY

Paternity must reflect the common decision of the coauthors. Each author must have participated enough to take public responsability for the content. A paper with collective paternity must have a key person responsable for the article.

4. COPYRIGHT

In order to reproduce materials from other sources, written agreement from the copyright owner must be obtained:

- photographer – for unpublished photographs;
- hospital where the photographer (physician) is employed – for unpublished photographs performed during the employment period;
- initial publisher – for a table, picture or text which have previously been published elsewhere.

5. ETHICAL ASPECTS

Do not use name of patients, initials or hospital observation charts numbers. If a photograph of a body part which could allow direct or deductive recognition of the patient needs publishing, then the paper must be accompanied by the written consent of the patient and clinician, as well.

6. PRESENTING THE MANUSCRIPT

For the journal *„Medicine in evolution"*, the manuscript must be typed double spaced, on white A_4 paper – 210 x 297mm, on one side (2.5cm upper and lower borders, 3cm left and 2cm right border, respectively), in clear characters, no further corrections or addings. It is advisable that articles are presented on CD or other data transfer methods, in Word format, 12 Times New Roman fonts - using Romanian characters – respecting the same page order, accompanied by a printed version. Graphs – black and white or coloured – may be generated in MS Excel or MS Graph, inserted in the body of the paper or presented in a different file.
Infected materials will not be used.

6.1. FIRST PAGE (TITLE PAGE)

Together with the title and names of the authors, the first page must include the affiliation, professional and university degree (if applicable), marked by asterisc for every author; it is advisable to give at least a phone and/or fax number or e-mail address of the first author who may be contacted by the editors for additional recommendations or explanations.

6.2. ABSTARCT OF THE PAPER

6.2.1 Recommendations for original studies

Original studies must include a structured abstarct of maximum 150 words, containing the following titles and informations:

- Aim and objectives;
- Material and methods;
- Results;
- Conclusions;
- Key words: give 3-5 key words;
- The abstract will be translated into an international circulation language.

6.3 CONTENT OF THE PAPER

6.3.1 For original articles

The text will usually be divided into sections:

- Introduction – presentation of general aspects, in the context of the approached theme
- Aim and objectives – Define the aim of the article. Briefly expose the rationale of the presented study or observation. Make strictly pertinent referals and do not exhaustively review the subject. Do not include data or conclusions from the paper.
- Material and methods – Describe the selection of observations or subjects for the experiment (including controls). Identify methods, equipments (with the name and address of the manufacturer in brackets) and give sufficient details on procedures. Give references for the selected methods, including statistical methods; offer details and brief descriptions for previously published methods which are not well known; describe new or

substantially modified methods, justify their use and assess their limitations. Precisely identify all used drugs and chemicals, including generic names, dosage and administration ways. Describe statistical methods with sufficient details for reported results to be verified. Whenever possible, quantify discovered aspects and present them with appropriate measurement indicators for the uncertainty or error of measurement (such as confidence intervals).

- Results – Present results in a logical succession as text, tables and illustrations. Emphasize or briefly describe only important observations.
- Discussions – Underline new, important aspects of the study. Do not repeat in detail data which have been presented in previous sections. Include implications of revealed aspects and their limitations, including implications for future studies. Connect your observations to other relevant studies. Relate the results to the aim proposed for the study.
- Conclusions – organize conclusions which emerge from the study. In the end state: a) contributions to be acknowledged but which do not justify paternity right; b) thanks for technical support; c) thanks for financial or material support.

6.3.2 Indications for case reports

Themes may be selected from all medical fields. Manuscripts which offer a special gain for daily activity will have priority. The title must be clearly, precisely stated. It may be completed by a subtitle. It is advisable to include in the key words of the title the main message, the special element which may be observed from the case evolution. The content of a case report must be divided into three parts:

- Introduction – It must include a maximum of 15 typed rows (half page). Here, the main medical problem is summarized in order to place the case in a specific domain.
- Case report – It contains essential specific information on the case.
- In order to make a logical, chronological and didactical case report the following 5 chapters are needed:

  I. Anamnesis;
  II. Clinical examination data;
  III. Laboratory data;
  IV. Additional paraclinical investigations;
  V. Treatment and evolution.
- Discussions – The reason for the case report must be stated. The report must be patient-centered. Occasional deviations from typical (characteristic) evolutions, nosologically important facts must be presented in such a manner to expose the clinical picture as completely as possible. The case report must not appear as an appendix of a general review. Dimensions of a case report: maximum 6-8 typed pages, 30 rows of 60 characters/page.

6.4. MEASUREMENT UNITS, SYMBOLS, ABREVIATIONS

All measurements must be expressed in International System (IS) units. Abreviations must be fully explained when first used.

6.5. TABLES

Tables are noted with Roman figures and they will have a brief and concise title, concordant with their content.

6.6. ILLUSTRATIONS

Number all illustrations in Arabic figures in a single succession. Apply a label on the back side of every illustration, containing its number and an arrow indicating the upper side. Coloured illustrations may be accepted but it is the choice of the editors, according to particular technical abilities of each journal issue, or it may involve a fee in special cases.

6.7. EXPLANATIONS FOR DRAWINGS AND GRAPHS

Explanation for drawings and graphs must be clear and in readable dimensions, considering the necessary publishing shrinkage.

6.8. PHOTOGRAPHS

Offer glossy, good quality photographs. Any annotation, inscription, etc. must contrast with the ground. Microphotographs must include a scale marker.

6.9. ILLUSTRATION LEGENDS

Include explanations for each used symbol, etc. Identify the printing method for microphotographs.

6.10. REFERENCES

A numbered list of references must be provided at the end of the paper. The list should be arranged in the order of citation in the text of the publication, assignment or essay, not in alphabetical order(according to the Vancouver rules). List only one reference per reference number. It is very important that you use the correct punctuation and that the order of details in the references is also correct.

- Books - Standard format - #. Author of Part, AA. Title of chapter or part. In: Editor A, Editor B, editors. Title: subtitle of Book. Edition(if not the first). Place of publication: Publisher; Year. p. page numbers.
- Journal Articles - Standard format - #. Author of article AA, Author of article BB, Author of article CC. Title of article. Abbreviated Title of Journal. year; vol(issue):page number(s).
- E-Books - Standard format - #. Author A, Author B. Title of e-book [format]. Place: Publisher; Date of original publication [cited year abbreviated month day]. Available from : Source. URL.
- E-Journals - Standard format - #. Author A, Author B. Title of article. Abbreviated Title of Journal [format]. year [cited year abbreviated month

day];vol(no):page numbers[estimated if necessary]. Available from: Database Name (if appropriate). URL.

- Internet Documents - Standard format - #. Author A, Author B. Document title. Webpage name [format]. Source/production information; Date of internet publication [cited year month day]. Available from: URL.

7. COPIES FOR PUBLISHING

In order to accelerate publishing, the main author will send a set of printed sheets presenting the final version of the paper, as it will appear in the journal. It is really helpful that texts to be also sent on electronic support, diacritic characters mandatory.

8. REJECTION OF PAPERS

If a paper does not meet publishing conditions, whatever these may be, the editors will notify the first author on this fact, without the obligation of returning the material. Original photographs or the whole material will be returned only if the author comes to the editor and takes them.

Papers submitted for publishing will be addressed to:

Prof. Angela Codruta Podariu, DMD, PhD

Journal Medicine in evolution
Department of Preventive, Community Dental Medicine and Oral Health
Splaiul Tudor Vladimirescu no. 14 A
300041, Timişoara
Phone: 0256-204950
Email: proiectetm@yahoo.com

Dana Brehar-Cioflec, MD, PhD

Institute of Public Health *"Prof. Dr. Leonida Georgescu"* Timişoara
Bd. Victor Babeş no. 16
300226, Timişoara
Phone: 0256-492101
Email: dcioflec@yahoo.com