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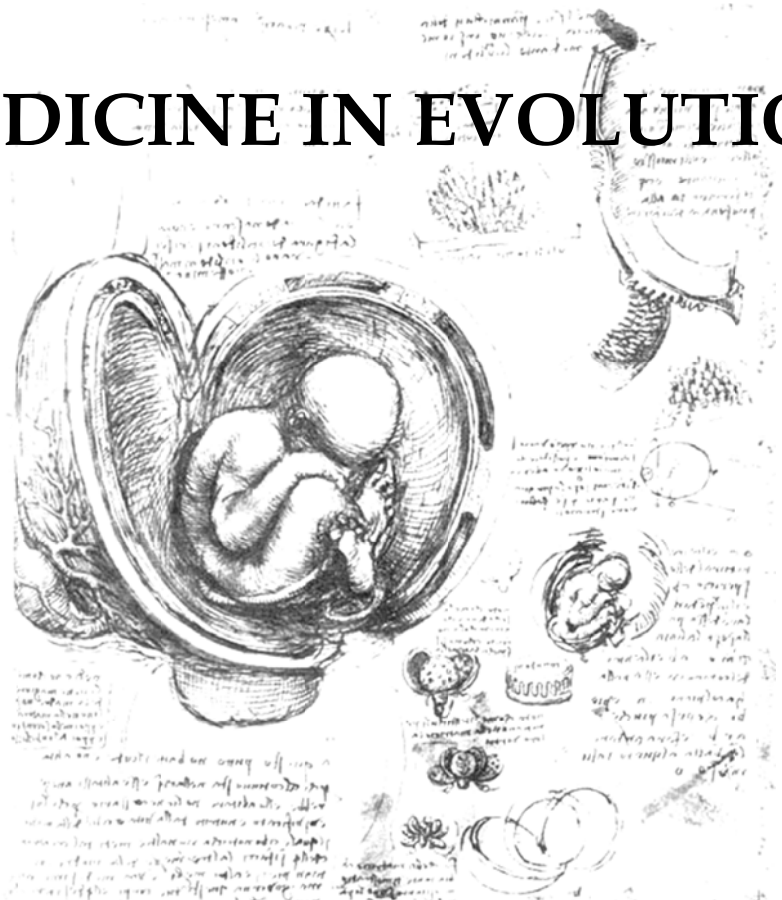

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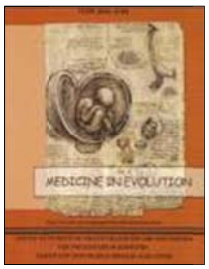
ARTICLES

A STUDY OF LONGITUDINAL UTILISATION OF NON-SELECTIVE AND COX-2-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: RESULTS FROM PRESCRIPTION DATA FROM A PHARMACY DATABASE



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ABSTRACT

Aim and objectives: *In our investigation we aimed to explore tendencies of prescribing non-steroidal anti-inflammatory drugs (NSAIDs), analysing prescription data from a pharmacy electronic database.*

Material and Methods: *We analysed the longitudinal prescribing of NSAIDs in an observational retrospective study. Data on prescription drug (NSAIDs) were obtained from a pharmacy electronic database located in Timişoara, during 2008 -2009.*

Results: *The study population consisted of 1150 patients (56.5% women) with at least one NSAIDs prescription recorded. A total of 1318 prescriptions related to ten different NSAIDs were evaluated. Ibuprofen was the most frequently prescribed NSAID, followed by ketoprofen, diclofenac, and celecoxib.*

Conclusions: *This study results showed the extent of the heterogeneity of drug utilization among NSAID users .The utilization degree of non-selective anti-inflammatory drugs versus COX -2 selective inhibitors remains still high.*

Key words: *non-steroidal antiinflammatory agents, selective cyclooxygenase-2 inhibitors, observational study.*

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most prescribed therapeutics in the world, being indicated in acute, subacute and chronic diseases.

Clinical studies evaluate the efficacy and safety of a drug on a large number of patients in a well defined and controlled frame. Moreover, observational epidemiological and post-marketing studies can achieve valuable information to validate or modulate the clinical trial results.

The extent of the heterogeneity of drug utilisation among the NSAIDs users have not been extensively studied according to literature. In our investigation we aimed to explore the longitudinal utilisation as well as tendencies of prescribing of non selective NSAIDs and selective COX-2 inhibitors using prescription information.

MATERIAL AND METHODS:

We retrospectively analysed prescription information using the electronic database of a middle size pharmacy located in Timisoara.

The study population consisted of 1150 patients included in five age groups with at least one prescription for a NSAID, recorded over one year, from November 1, 2008 up to October 31, 2009. The selected data include non-selective NSAIDs and COX-2 selective inhibitors prescribed by general practitioners in the study period.

We examined the use of 10 non-steroidal anti-inflammatory drugs: diclofenac, aceclofenac, ibuprofen, ketoprofen, piroxicam, meloxicam, lornoxicam, etoricoxib, celecoxib, and nimesulid. For each patient from the pharmacy electronic database the following information were extracted: type of NSAID, application form, strengths and amount of the drug and duration of therapy. In our investigation were recorded also the patients' characteristics: age, gender and indication for the NSAID dispensed for each patient.

The study participants were patients ranged from 0 years to 75 years and older, who submitted at least one prescription for a NSAID at any time during the study period.

For each NSAID it was indicated the Defined Daily Dose (DDD) which is the average daily dose for the main indication of the drug in adults.

In our study we evaluated the heterogeneity of NSAID prescriptions released by general practitioners as well as the utilisation degree of non-selective NSAID versus COX-2 selective inhibitors, over a period of one year, having as source of information a pharmacy database.

RESULTS:

One thousand one hundred and fifty patients were included as eligible to enter to this study. Each of them was recorded in the pharmacy database with at least one prescription for NSAID during a year study from November 1, 2008 up to October 31, 2009.

Table I shows the general characteristics of the patients. From the obtained data, men accounted for 43.47% (500 patients) and women for 56.53% (650 patients) of the study population.

As shown in the Table I the degree of utilisation of NSAIDs, expressed

as number of prescriptions / year, generally increases with the age of patient.

Seven hundred and five (61.30%) aged 0-44 years received one prescription during the study year. Patients 45-59 years (7.82%) had an average of 1.44 prescriptions / year with an NSAID. One hundred and ninety-one patients aged 60-74 years (16.60%) received an average of 1.40 prescriptions / year. Patients aged 75 years and older (14.26%) obtained on average 1.30 prescriptions / year.

Regarding the gender, a small difference in the degree of utilisation was observed between males (1.22 prescriptions / year) versus female 1.08 prescriptions / year.

In Figure 1 is shown representation by gender (M / F) of the patients treated with NSAIDs.

A total of 1318 prescriptions related to ten different NSAIDs were recorded for the 1150 patients, and were analysed. Significant differences were found between the different groups of NSAIDs used (non-selective, coxibs, other selective COX-2 inhibitors) and are shown in Figure 2.

The utilisation degree of non-selective NSAIDs is the highest, representing 83.00% from the total overall prescriptions. Secondly, comes with 10.00%, the coxib group (celecoxib and etoricoxib) and thirdly, with 7%, accounted other selective COX-2 inhibitors (meloxicam, nimesulid, lornoxicam).

Table 1 Utilisation of NSAIDs stratified by age and gender

Patient characteristics	Number of patients (%)	Number of prescription /year (mean)
Age groups		
0 - 17	567 (49.30)	567 (1)
18 - 44	138 (12.00)	138 (1)
45 - 59	90 (7.82)	130 (1.44)
60 - 74	191 (16.60)	269 (1.40)
≥ 75	164 (14.26)	214 (1.30)
Total number	1150 (100)	1318 (1.02)
Gender		
Male	500 (43.47)	612 (1.22)
Female	650 (56.52)	706 (1.08)

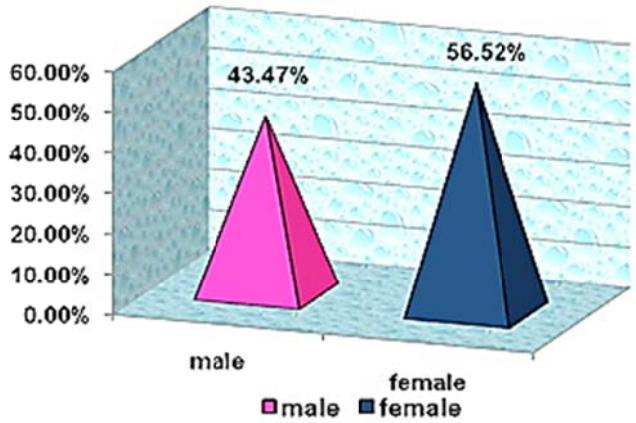

Fig.1 Representation by gender (M/F) of the patients who presented at the pharmacy at least one prescription with a NSAID, during the study period.

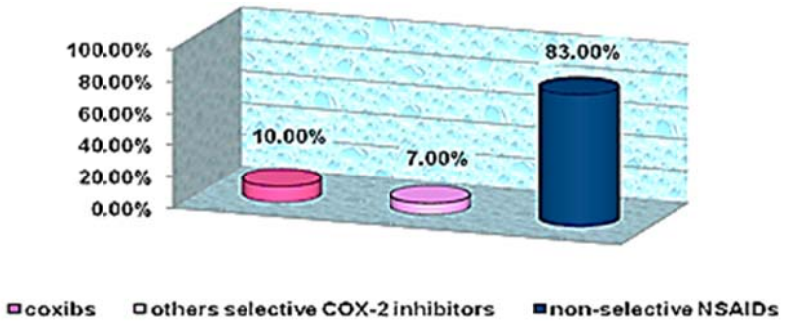

Fig.2 Utilisation degree of different NSAIDs

The most widely used NSAIDs, as shown in Table II, were ibuprofen, 56.00% (644 patients) and ketoprofen, 16.52% (190 patients). Third, comes diclofenac prescribed for 11.82% (136 patients) and fourth, celecoxib, 3.39% (39 patients). The most frequently prescribed application form was oral (97.39%) followed by suppositories (1.39%) and ampoules (1.21%).

Table 2 Total number of prescriptions stratified by type of NSAID, application form and DDD per prescription

NSAID	Number of patients (%)	Number of prescriptions / year (%)	DDD* (mg)
Type of NSAID			
Diclofenac	136 (11.82)	157 (11.91)	100
Aceclofenac	7 (0.60)	7 (0.53)	100
Ibuprofen	644 (56.00)	650 (49.31)	100 (children) 200 (adult)
Ketoprofen	190 (16.52)	245 (18.58)	200
Piroxicam	27 (2.34)	27 (2.04)	20
Meloxicam	38 (3.30)	59 (4.47)	7.5
Lornoxicam	4 (0.34)	4 (0.30)	8
Etoricoxib	29 (2.52)	45 (3.41)	90
Celecoxib	39 (3.39)	88 (6.67)	200
Nimesulid	36 (3.13)	36 (2.73)	100
Application form			
Oral	1120 (97.39)	1288 (97.72)	*DDD – Defined Daily Dose
Suppositories	16 (1.39)	16 (1.21)	
Ampoules	14 (1.21)	14 (1.06)	

Table III presents the top five most prescribed NSAIDs expressed in total number of prescriptions analysed in our study. According to the results of the present research project, ibuprofen was the most prescribed NSAID with 650 prescriptions, representing almost a half of the total number of prescriptions / year for the NSAIDs, submitted at the pharmacy.

Table 3 the top five prescribed NSAIDs among study patients expressed in total number of prescriptions analysed in the study period

Type of NSAID	Number of prescriptions (n)
1.Ibuprofen	650
2.Ketoprofen	245
3.Diclofenac	157
4.Celecoxib	88
5.Meloxicam	59

DISCUSSIONS:

One of the first studies regarding the extent of the heterogeneity of drug utilization among NSAIDs users has been done in four German pharmacies already in 1997 by Sift et al.[1] but their methodology differed from ours. They found, at that period, that diclofenac have been the most prescribed NSAID, followed by indometacin, ibuprofen and piroxicam.

In a more recent study (2006) Lamb[2] found that in 2006 among the top 200 drugs prescribed in the United States by number of prescripttions, the following order for NSAIDs drugs: celecoxib (43 rank), ibuprofen (70 rank) and naproxen (147 rank).

The analysis of the prescription data from a pharmacy source, over one year, showed that:

Almost half of patients (49.30 %) were aged 17 years or younger and were exposed to a NSAID for a short time, less than 30 days. Only ibuprofen has been prescribed for the utilisation in the paediatric use. Consequently, ibuprofen was found the most frequently prescribed NSAID in our study, but in the same time, it may have led to an overestimation of the utilisation degree of this NSAID. However, we consider that its prescription is properly chosen, according to the most recent data from the literature, which recommend ibuprofen in: children pain management of musculoskeletal injuries[3,4], children fever management[5,6] but also for its efficacy and safety in children and adults[7].

The multiple actions of ibuprofen in controlling inflammation combined with moderate inhibition of COX-1 and COX-2 and short residence time of the drug in the body account for the low gastrointestinal, cardiovascular events and renal risk for ibuprofen, especially at low doses[8]. The second prescribed NSAID in our study was ketoprofen, another non-selective NSAID, also available as a more potent S-enantiomer formulation and in a variety of application forms, with a potent antiinflammatory and antipyretic effects[9]. Ketoprofen has generally transient and asymptomatic adverse effects, more commonly in elderly[9].

The third more prescribed NSAID in this study was diclofenac a proven commonly prescribed NSAID that has analgesic, anti-inflammatory and antipyretic properties and which has been shown to be effective in treating a variety of acute and chronic pain and inflammatory conditions. Diclofenac is now available on different application forms and different pharmaceutical formulations. New extensive research shows that pharmacological activity of diclofenac goes beyond COX-inhibitions whose selectivity of COX-2 resembles of that of celecoxib. The incidence of serious gastrointestinal adverse effects did not differ for diclofenac and celecoxib[10]. An update research suggests that diclofenac can act also in a multimodal way and in some instances novel mechanism of action delineate its potentially unique qualities[11]. Unlike ibuprofen the drug is not recommended for children and does not interfere with antiplatelet effect of aspirin[12].

On the top five the most prescribed NSAID in our study; the forth in rank is celecoxib, a selective COX-2 inhibitor. In our study the most prescribed strength was of 200mg. Celecoxib is a NSAID recommended for the treatment of rheumatoid arthritis and osteoarthritis, with a lower incidence, even in elderly patients, of gastrointestinal and cardiovascular events, compared with non-selective NSAIDs[13]. This coxib offers in the elderly an alternative to standard NSAID at this group of age. However, close attention should be pa-

id to intercurrent illnesses and to new prescriptions, that may reduce its safety and also for patients at high risk of ischemic heart disease or stroke, when coxibs are contraindicated[14]. The fifth in rank in this paper is meloxicam, according to the literature used in the treatment of osteoarthritis and rheumatoid arthritis[15,16].

This molecule has been shown to be COX-2 preferential inhibitor, particularly at its therapeutic dose[16].

CONCLUSIONS:

Our assessment of the longitudinal utilisation of non-selective and COX-2 selective NSAIDs can be summarized thus:

(1) a number of 1318 prescriptions related to ten different NSAIDs were analysed;
(2) the utilization of NSAIDs varies between age groups, gender, duration of the disease and different types and application forms of the NSAID;
(3) ibuprofen was the most frequently prescribed NSAID followed by ketprofen, diclofenac, celecoxib and meloxicam, in the study period;
(4) the utilization degree of non-selective NSAIDs accounted 83% from the total overall prescriptions.

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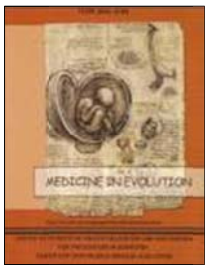
METABOLIC SYNDROME LINKED WITH SUBCLINICAL ATHEROSCLEROSIS AND CARDIO -VASCULAR RISK



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ABSTRACT

***Backgrounds and aims**: The metabolic syndrome (MetS) is a distinctive phenotype associated with an increased risk of vascular disease. The aim of the study was to investigate the association of clinically defined metabolic syndrome with subclinical atherosclerosis and the prediction of cardio-vascular risk.*

***Method and results**: Subclinical atherosclerosis was assessed by the common carotid intima-media thickness (IMT) and flow mediated vasodilation (FMD) by brachial artery in 116 participants with MetS without clinical changes of cardiovascular disease; on B-mode ultrasound images, with the use of a 10 MHz linear-array transducer in terms of fasting for 8 hours. The MetS was defined according to the IDF criteria. Subclinical atherosclerosis was considered by IMT greater than 0.9mm. Endothelial dysfunction was diagnosed if flow-mediated dilatation was less than 10%. Predictive cardiovascular risk factor is considered triglycerides/HDL-cholesterol > 3.5. 81 patients had predictive cadio-vascular risk factor present.The mean FMD was 5.38% ± 6.74. The mean value of IMT at the right common carotid was 0.939mm ± 4.18 and at the left common carotid was 0.912mm ± 2.07.*

***Conclusions**: Patients with metabolic syndrome have suclinical atherosclerosis, with increased endothelial dysfunction and modified common carotid intima-media thickness. FMD is corelated with the predictive cardio-vascular risk factor. Further studies are needed to understand the role of the MetS in the progression from subclinical to clinical atherosclerotic disease.*

***Key words**: metabolic syndrome, suclinical atherosclerosis, intima-media thickness, flow mediated vasodilation.*

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INTRODUCTION

The MetS is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure. MetS causes moderate increases in all-cause and CVD mortality. [1] In the general population, metabolic syndrome is associated with a marked increase in the risk not only of new onset diabetes mellitus but also of new onset office and daily-life hypertension, and left ventricular hypertrophy. [2]

Although MetS is related to CHD, there is no epidemiological justification for using it, rather than other criteria, as a risk predictor for CHD. [3] The underlying cause of the MetS remains controversial, but the syndrome helps identify individuals at high risk for cardiovascular disease (CVD) and type 2 diabetes. Development of atherosclerotic cardiovascular disease is a major cause of morbidity and mortality. Interestingly, components with the highest prevalence prior to MetS development, such as elevated blood pressure, are not necessarily the stronger risk factors.[4]

Endothelial dysfunction is now regarded as an early pivotal event in atherogenesis and has been shown to precede the development of clinically detectable atherosclerotic plaques in the coronary arteries [5], a major key in development of cardio-vascular and metabolic complications. Endothelial dysfunction of either the coronary, the peripheral, or the cerebral vasculature is a predictor of vascular events and appears to be a marker of uncontrolled atherosclerotic risk that adds to the burden of the genetic predisposition to cardiovascular disease.[6] Endothelial dysfunction is characterized by a reduction of the bioavailability of vasodilators, in particular, nitric oxide (NO), whereas endothelium-derived contracting factors are increased.[7] This imbalance leads to an impairment of endothelium-dependent vasodilation, which represents the functional characteristic of endothelial dysfunction. Impaired endothelial function may be a common denominator of pathogenesis of microvascular complications and atherosclerosis in T2DM. [8] A widely accepted, convenient marker of atherosclerosis is carotid artery intima-media thickness (IMT) [9] which is significantly associated with prevalent [10, 11] and incident [12] carotid plaques. The addition of IMT to the traditional criteria for the diagnosis of the MetS may help identify individuals who otherwise would not have been identified to be at high risk of CVD. [13] It is known that arterial stiffness is increased in patients with metabolic syndrome irrespective of the definition criteria [14]. Several analyses from the ARIC study have shown that the metabolic syndrome, as well as individual metabolic syndrome components, is predictive of the prevalence and incidence of coronary heart disease, ischemic stroke, carotid artery disease and diabetes. [15]

The aim of the study was to investigate the association of clinically defined metabolic syndrome with subclinical atherosclerosis.

MATERIAL AND METHODS:

The study enrolled 116 patients with MetS, 74 men (63.79%) and 42 women (36.20%) with a mean age of 50.70 ± 8.39. The MetS was defined according to the IDF criteria 2005: Central obesity (defined as waist circumference >94 cm

by male and >80 cm female) plus any two of the following four factors: raised TG level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality; reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality; raised blood pressure: systolic BP > 130 or diastolic BP > 85 mm Hg, or treatment of previously diagnosed hypertension; raised fasting plasma glucose (FPG) > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes (If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome).

Patients underwent ECG and ergonometric tests, negative for coronary disease. The exclusion criteria's were: smokers, chronicle arteriophaty of lower limbs, cerebrovascular disease (stroke), coronary disease, diabetes treated by insulin, kidney and liver failure, psychiatric disorders, malignancies, consumption of alcohol per day over 30gr. The method of assessing the endothelial dysfunction was flow mediated vasodilation. We measured the flow-mediated dilatation (FMD) of the brachial artery (endothelium dependent vasodilatation) on B-mode ultrasound images, with the use of a 10 MHz linear-array transducer in terms of fasting for 8 hours.

The vascular diameter in systolic and diastolic longitudinal plane was measured guided by the principle of "leading-edge", followed by determination of basal medium velocity by pulse Doppler (average of at least 3 determinations). To obtain stimulate blood flow in the brachial artery is placed the sphygmomanometer antecubital at the forearm. After recording the basal velocity average, the sphygmomanometer cuff was swollen above the systolic blood pressure (usually over 50 mm Hg) for 5 minutes, to achieve brachial artery ischemia. Dilation of the resistance vessels downstream through the mechanism of self sudden deflation of the cuff increased the blood flow in brachial artery (active hyperemia) and the shearing stress at this level with consecutive dilation of the brachial artery. The maximum velocity was measured by pulse Doppler in first 15 seconds of cuff deflation and maximum diameter of the brachial artery was determined at 45-60 seconds post hyperemia. The brachial artery diameter was measured in the same cardiac cycle to avoid variations caused by arterial compliance.[7,9,10] Endothelial dysfunction was diagnosed if flow-mediated dilatation was less than 10%.

We measured intima-media thickness at the left and right common carotid at 1cm of the bifurcation (average of at least 3 determinations) as well on B-mode ultrasound images with the use of a 10 MHz linear-array transducer. Subclinical atherosclerosis was considered by a common carotid intima-media thickness higher than 0.9 mm. Predictive cardiovascular risk factor is considered triglycerides/HDL-cholesterol > 3.5.

RESULTS:

After adjustment for covariates the mean FMD was 5.38% ± 6.74 by the patients with MetS enrolled in the study. The mean value of IMT at the right common carotid was 0.939mm ± 0.418 and at the left common carotid was 0.912 mm ± 0.207. 81 patients from the studied group had the predictive cardiovascular risk factor present, with a mean FMD of 2.82 ± 7.87%; a mean IMT

right of 8.58 ± 2.69mm and IMT left 8.81 ± 2.10mm. The rest of the enrolled patients had a mean FMD of 7.94 ± 4.92%; a mean IMT right of 9.03 ± 6.74mm and IMT left of 7.89 ± 2.13mm. From the statistical point of view we used ANOVA test with $p < 0.001$ significant.

Table 1 Characteristics of the study group

Parameters	Men	Women
Number	75	41
HDL	38.27 ± 9.64	43.39 ± 12.42
Triglycerides	204.09 ± 132.04	172.45 ± 76.79
Glycemia	128.20 ± 42.45	137.51 ± 55.55
Abdominal waist	113.10 ± 11.67	114.22 ± 14.50
BMI	31.93 ± 5.24	34.05 ± 5.89
IMT right	9.25 ± 2.57	9.66 ± 6.61
IMT left	9.27 ± 2.15	8.85 ± 1.94
FMD%	4.96 ± 6.55	6.61 ± 7.20

Table 2 Linking FMD and IMT with predictive cardiovascular risk factor in patients with MetS:

Parameters	patients with TG/HDL<3.5	patients with TG/HDL>3.5	p ANOVA
FMD	7.94 ± 4.92	2.82 ± 7.87	0.00056
IMT right	9.03 ± 6.74	8.58 ± 2.69	0.608
IMT left	7.89 ± 2.13	8.81 ± 2.10	0.031

Fig.1 IMT by a metabolic patient

DISCUSSIONS:

It was noted that on a multivariate analysis, a TG/HDL ratio > or = 3.5 was associated with the burden of CAD16, using a lipid ratio to determine the presence of endothelial disfunction the early event in atherogenesis could be very helpful.

CONCLUSIONS:

Patients with MetS have suclinical atherosclerosis present, with increased endothelial dysfunction and modified common carotid intima-media thickness. FMD is corelated with predictive cardiovascular risk factor in patients with MetS. Further studies are needed to understand the role of the MetS in the progression from subclinical to clinical atherosclerotic disease.

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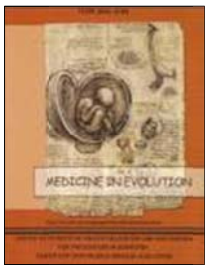
ONE-YEAR OBSERVATIONAL STUDY ON THE UTILISATION DEGREE AND CHARACTERISTICS OF CELECOXIB AND ETORICOXIB PRESCRIPTION USING AN ELECTRONIC PHARMACY DATABASE



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ABSTRACT

Aim and Objectives: *The aims of this study were to evaluate the utilization degree of coxibs (celecoxib, etoricoxib) and to examine their prescription characteristics, from an electronic pharmacy database.*

Material and Methods: *Were eligible for inclusion in this retrospective study, all coxib users, who received and submitted at least one prescription with a coxib, from November 2008 to October 2009. Was recorded information on pattern of prescription and patients characteristics?*

Results: *The eligible population consisted of 68 patients, and a number of 133 prescriptions with one of the two coxibs were analyzed. The highest utilization degree of coxibs was recorded at the age group 60-74 years (32.35%).*

Conclusions: *Celecoxib is the coxib of first choice, both in inflammatory acute and chronic diseases. The prevalence of coxibs incidental users showed a decreasing trend with advancing age. Prescription information could be an important source for the level of exposure, mainly in the long term treatments.*

Key words*: celecoxib, etoricoxib, observational study.*

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INTRODUCTION

Despite their toxicity, non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed groups of drugs by general practitioners.

Non-steroidal anti-inflammatory drugs that non-selectively inhibit COX-1 and COX-2 continue to be an important option for the management of pain. However, despite the potential advantages of NSAIDs, including the opioid-sparing effect, improved analgesia and attenuation of the inflammatory pain response, several side effects limit their use. Traditional NSAIDs predispose to ulcer formation and upper gastro-intestinal bleeding impaired coagulation, cardiovascular effects and renal dysfunction.

Selective cyclooxygenase-2 (COX-2) inhibitors were designed based on the hypothesis that selective inhibition of the COX-2 isoform should reduce pain and inflammation without compromising the integrity of the gastric mucosa. Celecoxib and etoricoxib are two COX-2 inhibitors (coxibs) with similar pharmacological properties but an improved gastro-intestinal safety profile compared with traditional NSAIDs[1,2]. They have shown excellent efficacy in relieving inflammation and associated pain, being prescribed for the relief of acute pain and symptoms of chronic inflammatory conditions such as osteoarthritis and rheumatoid arthritis[3,4,5,6].

To our knowledge there are few studies reporting the utilization degree of COX-2 selective inhibitors (coxibs) and their prescription pattern, using a pharmacy based approach.

AIM AND OBJECTIVES:

The aims of this observational study were to evaluate the utilisation degree of coxibs (celecoxib and etoricoxib) and to examine prescription characteristics of the two coxibs, from an electronic pharmacy database, over a period of one year.

MATERIAL AND METHODS:

We retrospectively analysed the data from the electronic database of a middle size pharmacy, located in Timisoara. Were eligible for inclusion in this study all the patients who were registered with at least one prescription with celecoxib or etoricoxib from November 1, 2008 up to October 31, 2009. For the study period were recorded from the electronic pharmacy database, the following information regarding each individual patient: type of coxib, application form, amount and strength of the drug, duration of therapy. They were 29 patients who received prescriptions of etoricoxib and 39 patients who received prescriptions for celecoxib. The number of patients treated with etoricoxib 60 mg was 7; seventeen patients with etoricoxib 90 mg and 5 patients with etoricoxib 120 mg. The number of patients treated with celecoxib 100 mg were 7 and with celecoxib 200 mg were 32 patients.

It was also recorded the patients' characteristics: age, gender and indications for prescribing the coxib treatment (acutely or chronically ill patient).

The level of exposure to coxibs over one year was taken for each patient.

The level of exposure to coxib treatment was established as the total duration of the NSAID therapy over one year.

Two categories were formed: incidental coxib users (duration of treatment of 1 to 30 days) and regular to continuous coxib users (more than 30 days).

In this study were included 68 patients with age between 18-92 years who received at least one prescription with a coxib during the mentioned study period.

RESULTS:

A total of 583 adult patients were identified, who were prescribed and submitted at the investigated pharmacy, at least one prescription with a non-steroidal anti-inflammatory drug, at any time during the study period.

The eligible population during a year study from November 1, 2008 up to October 31, 2009, consisted of 68 (11.66%) adult patients with at least one prescription for celecoxib or etoricoxib recorded in the electronic pharmacy database. Women accounted for 63.23% (43 patients) and men for 36.76% (25 patients) of the study population.

In Figure 1 is shown representtation by gender (M / F) of the patients treated with celecoxib or etoricoxib. The utilisation degree of the two coxibs (celecoxib, etoricoxib) during the study period stratified by age of the patients is presented in Figure 2.

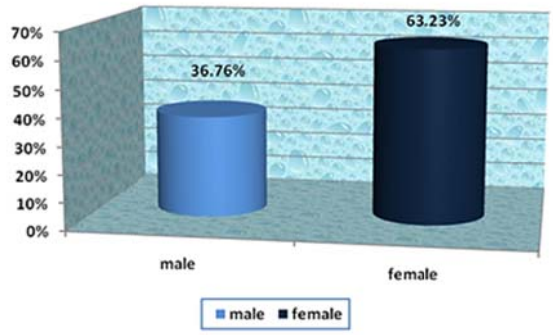

Fig.1 Representation by gender (M/F) of the patients treated with coxibs (celecoxib and etoricoxib) during the study period.

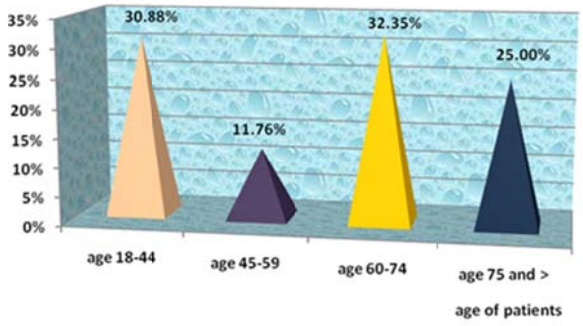

Fig.2 Representation of the utilisation degree of coxibs (celecoxib and etoricoxib) by age in the study period.

As shown in Figure 2 the utilization degree of the two coxibs is the highest for the age group 60-74 years (32.35%) and increased up to 57.35% for all the patients' ≥ 60 years of age. A total of 133 coxibs prescriptions, with celecoxib, or with etoricoxib, was registred for the 68 patients during the observational study, and were analysed. Celecoxib was the most commonly prescribed selective COX-2 inhibitor, during the study period being registered 88 (66.16%) prescriptions.

Figure 3 shows the utilisation degree of celecoxib versus etoricoxib by number of prescriptions / year in the study period.

Data regarding the level of exposure to each of the two analysed coxibs are shown in Figure 4. Forty-eight patients (70.58%) received one coxib (celecoxib or etoricoxib) prescription during the study period, 8 (11.76%) patients obtained two, 4 (5.88%) patients three or four, and 8 (11.76%) patients five or more prescriptions. Substantial differrences were also observed between different strength of the drug used.

Figure 5 shows the percentage distribution of patients treated with different concentration of etoricoxib. The most frequently strength prescribed was etoricoxib 90 mg (58.62%) followed by etoricoxib 60 mg (24.13%).

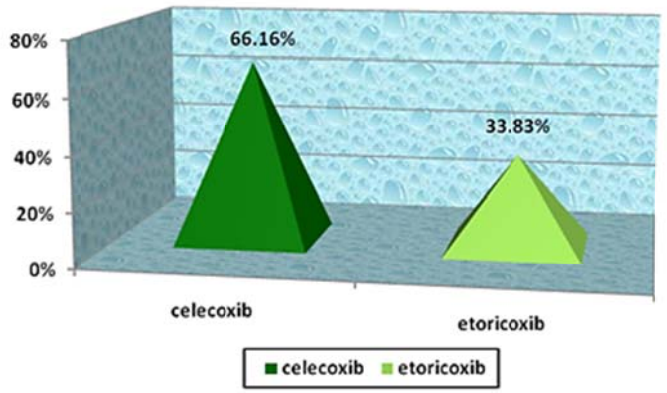

Fig.3. Utilization degree of celecoxib, versus etoricoxib by number of prescriptions/year in the study period

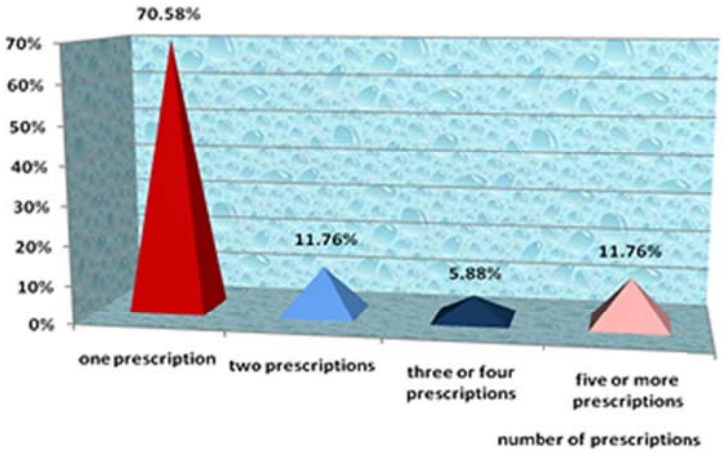

Fig.4. Duration of exposure. Figure includes percentage of patients for whom it was recorded at the pharmacy one or more prescriptions with coxibs during the study period.

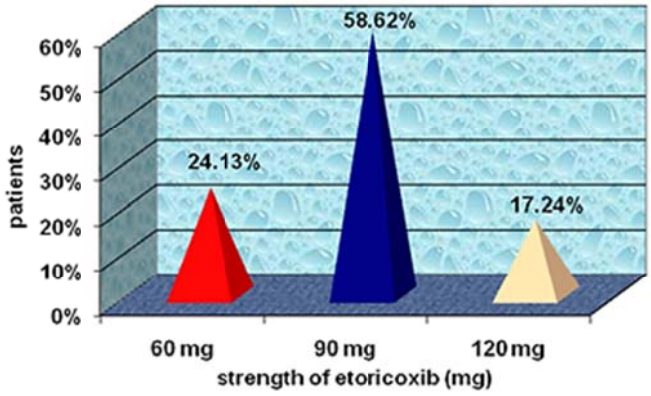

Fig.5. Strength of the drug used. Figure indicates percentage of patients treated with different concentrations of etoricoxib.

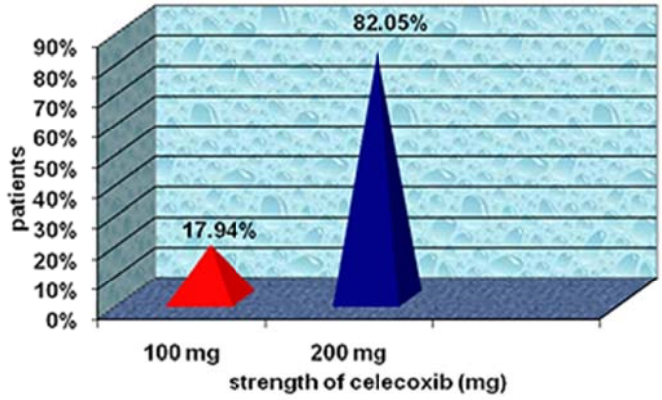

Fig.6. Strength of the drug used. Figure indicates percentage of patients treated with different concentrations of celecoxib.

In Figure 6 is shown the percentage distribution of patients treated with different strengths of celecoxib and by far, the most prescribed was the strength of celecoxib 200 mg (82.05%). The distribution of the patients treated with the two coxibs according with the evolutive type of the disease is shown in Figure 7.

Twenty-one patients (30.88%) acute cases, named incidental users, were exposed to one of the coxibs for a relatively short time, 30 days or less. Patients, who were defined as regular to continuous users, were exposed to one of the coxibs more than 30 days, accounted for 69.11% (47 patients).

The prevalence of incidental users showed a remarkably decreasing trend with advancing age (Fig. 8).

Of the study population, younger than 45 years of age (100.00%) were incidental users, compared with 58.82% of patients 75 years of age and older.

The safety of treatment with coxibs taking into account the level of exposure was also appreciated. Fifteen (38.46%) patients treated with celecoxib received two or more prescriptions: two patients received four respectively five prescriptions; two patients' received six prescriptions; two patient's received seven respectively eight pre-

scriptions; one patient received eleven prescriptions during the study period.

This number of prescriptions, almost all with celecoxib 200 mg, the generally maximum recommended dose of celecoxib, suggest a good tolerability for this drug. Five patients treated with etoricoxib 90 mg and even 120 mg, received three and more prescriptions.

One patient, aged 70 years, received eight prescriptions with etoricoxib 90 mg. It seems that both celecoxib and etoricoxib were well tolerated even by older patients.

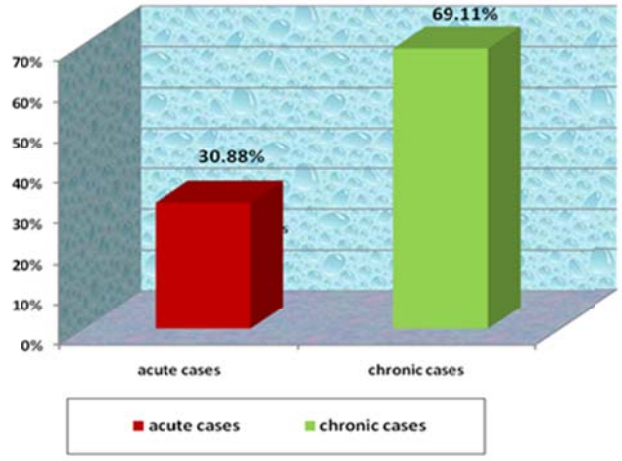

Fig.7. Coxibs (celecoxib and etoricoxib) distribution according with the evolutive type of the disease (acute cases and chronic cases).

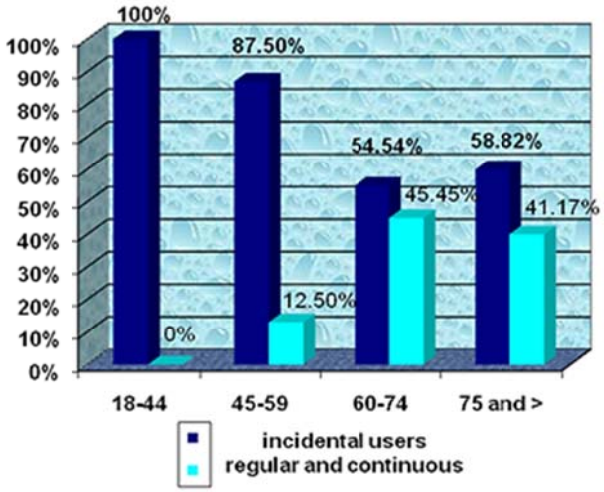

Fig.8. Prevalence of incidental and regular to continuous users of coxibs (celecoxib and etoricoxib). Incidental users = (1 – 30 days); regular and continuous = (> 30 days)..

DISCUSSIONS:

Coxibs are drugs prescribed in acute pain but mainly in the treatment of osteoarthritis and rheumatoid arthritis[6]. This study showed that, the two COX-2 selective inhibitors (celecoxib and etoricoxib) available to the market during the study period were more likely prescribed for chronic use in older, female patients. Celecoxib was the most commonly prescribed of the two avai-

lable coxibs. This current study provides useful information regarding characteristics of celecoxib and etoricoxib prescribing patterns, in a city from Romania, during the study period and the impact of COX-2 selective inhibitors prescription in the general practice. The relatively low prescribing rates for celecoxib and etoricoxib (11.66%) in the patients treated with a NSAID may also have been influenced by financial considerations.

Previous studies that investigated the utilization degree of non-steroidal anti-inflammatory drugs using a pharmacy based approach, shown the extent of the heterogeneity of drug utilization only among traditional NSAID users as, the selective COX-2 inhibitors were not yet available to the market during that time[7].

Other previous studies have investigated the features of NSAIDs prescription using a general practitioner based approach, identified in the group of the most prescribed NSAIDs at this level, only traditional NSAIDs (piroxicam, ketoprofen) and one preferential COX-2 inhibitor (nimesulid) but not coxibs, even they were already available during the study period[8].

The results of our study showed that pharmacy could be a good source to analyse the utilization degree and prescription characteristics of drugs, firstly because of the greater diversity of age strata patients and secondly, because of the difference of experience existing between general practitioners with one or another drug from the same group (e.g. coxibs).

CONCLUSIONS:

Our study results show the followings: The analysed coxibs (celecoxib and etoricoxib) were more likely prescribed for chronic use in older, female patients.

Celecoxib was the coxib of first choice both in inflammatory acute and chronic diseases. The prevalence of coxibs incidental users showed remarkably decreasing trend with advancing age. Prescription information could be an important source for the level of exposure, mainly in the long term treatments.

Although COX-2 selective inhibitors (coxibs) have been promoted as being more gastro-protective than the non-selective NSAIDs, the relative low prescribing rates suggest that prescribers have concerns over the place of COX-2 inhibitor therapy and their use is reserved to those patients particularly at risk of NSAID-induced gastro-intestinal toxicity.

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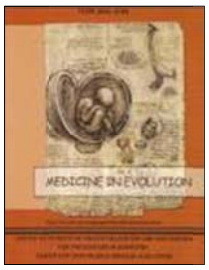
CHEMICAL COMPOSITION OF VOLATILE OILS ISOLATED FROM THE FRUITS OF TWO SWEET FENNEL ORGANIC CULTURE VARIANTS



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ABSTRACT

Introduction: *Sweet fennel (Foeniculum vulgare ssp. vulgare var. dulce Mill., Apiaceae) is a well-known aromatic and medicinal plant. It is used in phyto- and aromatherapy, but also in food industry due to volatile oil content of its fruits. The oil yield and chemical composition can be affected by different factors, such as: pedoclimatic conditions, agronomical practices, harvesting time or the type of processing.*

Aim: *In this study, we investigated the chemical composition of essential oils from fennel fruits collected from two organic culture variants.*

Materials and methods*: The experiment was performed in field of Agricultural Research and Development Centre, Secuieni-Piatra Neamt, Romania. The culture variants were made using seeds from fennel plants with variable age: eight (Fv1) and four (Fv2) years old plants. The seeds were sown in spring of the 2008 and the observations on phenophase and production were obtained in 2009, because the fennel is a biennial plant.The essential oils were isolated by hydrodistillation from dried fruits and characterized using gas cromatography coupled with mass spectroscopy (GC-MS). The fruit yield and the essential oil yield were also determined.*

Results and discussion*: The largest fruit production (1330 kg/ha) was achieved for Fv2 variant, while the highest essential oil yield (63.55 kg/ha) was obtained for Fv1 variant. In both volatile oils, the main components were t-anethole (53.91% and 49.54%, respectively), fenchone (27.45% and 23.33%, respectively) and D-limonene (2.69% and 5.08%, respectively).*

Conclusions*: The samples of sweet fennel volatile oil do not meet the requirements of the European Pharmacopoeia 6th ed. (min. 80% t-anethole and max.7.5% fenchone), nor those for its use in aromatherapy (0.5%-5% monoterpene ketones, mainly fenchone; 55%-85% aromatic ethers, mainly t-anethole).*

Key words*: Foeniculum vulgare, culture variants, essential oil.*

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INTRODUCTION

Sweet fennel (*Foeniculum vulgare* ssp. *vulgare* var. *dulce*, *Apiaceae*) is a well-known medicinal plant and spice used worldwide[2]. In 2009, the Institute for the History of Medicine from Würzburg University, Germany declared it "*the plant of the year*" and focused on summarizing all existing knowledge about the fennel, with a special emphasis on the pharmacological and clinical aspects [3]. Fennel fruits are used for expectorant, antispasmodic, galactagogue and carminative properties, but also as precious curative in infantile colic[4]. It has also been reported to possess anti-inflammatory, antioxidant and estrogen-like activities. The essential oil obtained from the fruits is used in phyto-and aromatherapy, food industry and as main source for trans-anethole, an aromatic substance of pharmaceutical and commercial value[5].

It is well-known that the essential oils composition depends upon external and internal factors affecting the plant, such as: environmental and climate conditions, season of collection, age of plants, the stage of fruits ripening or genetic data.

Consequently, the chemical variability may cause differences in terms of pharmacological action and/or pharmaceutical quality of the fennel fruits and their volatile oils[1].

AIM

As part of a broader research on the influence of environmental and crop factors on the production of the fruit and fennel essential oil, the current study investigated the importance of the seed material obtained from plants of different age.

MATERIAL AND METHODS:

Plant material

The samples of fennel fruits have been harvested in August 2009, by haymaking technique. After two days of storage, the plants have been subjected to the action of a threshing machine. The fruits were ventilated by turning on one side and the other with a shovel and dried up to a moisture standard content of 12%.

The sweet fennel crops were from the field of Agricultural Research and Development Centre, Secuieni, Piatra Neamt, Romania. The seed material was supplied by plants with different age: eight years (Fv1 sample) and four years old plants (Fv2 sample). The seeds were sown in April 22, 2008 and the plants have sprung in May 3, 2008. The observations on phenophase (fig. 1) and production were obtained in 2009, because the fennel is a biennial plant.

Isolation of volatile oils

The volatile oils were obtained from dried fruits by hydrodistillation in Clevenger apparatus (3 hours)[7]. The oil was dried over anhydrous sodium sulphate and kept in a dark glass bottle at 4°C until analysis. The essential oil content (mL/kg dried fruits) was determined.

GC-MS analysis

The constituents of the essential oils have been characterized using gas chromatograph and mass spectroscopy analysis (GC-MS). A 7890A Agilent type gas-chromatograph interfaced to a

5975C Agilent mass selective detector was used for mass spectral identifycation of the components of the volatile oils. DB-5 MS capillary column (30 m lenght x 0.25 mm i.d x 0.25 µm film thickness) was used for GC. Helium was the carrier gas at a flow rate of 1mL/min. The oven temperature was programmed as follows: from 35°C raised at 10°C/min. to 280°C (7.5 min hold). The injector temperature: 250°C; The sample injection volume: 0.2 µL. Split ratio: 50:1. The identification of the components was based on comparison of their mass spectra in the apex of each peak with those of analytical standards from Wiley Mass Spectral Library.

Fig.1 Images of sweet fennel phenophase

RESULTS AND DISCUSSION:

The 2008/2009 crop year has been characterized as a warm year in terms of temperature, with deviations from the multiannual average ranging between 0.2°C (May, June) and 2.7°C (February) and an annual average temperature of 9.9°C compared to an multiannual average of 8.6°C (fig.2).

In terms of rainfall, the 2008/2009 crop year was a droughty year, the deviations from the multiannual average varing from -38.8 mm (April) to 20.5 mm (June).

The rainfall was unevenly distributed during the vegetative period of the fennel (fig. 3).

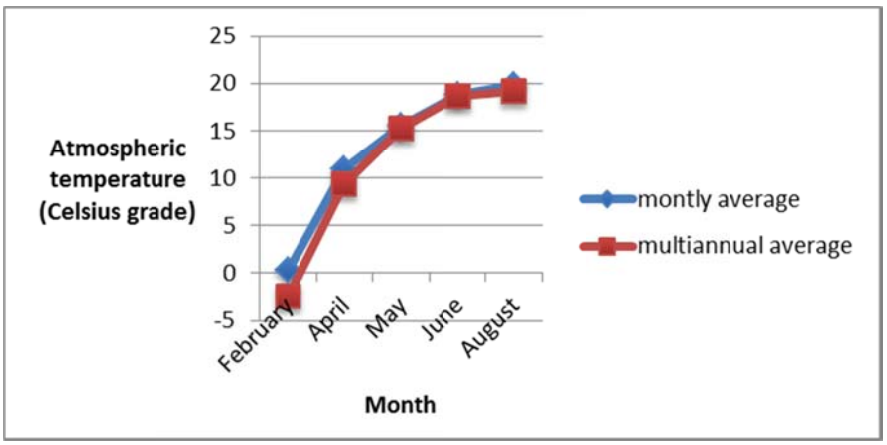

Fig. 2 - The variations of atmospheric temperature during the vegetative/fructification period of the fennel

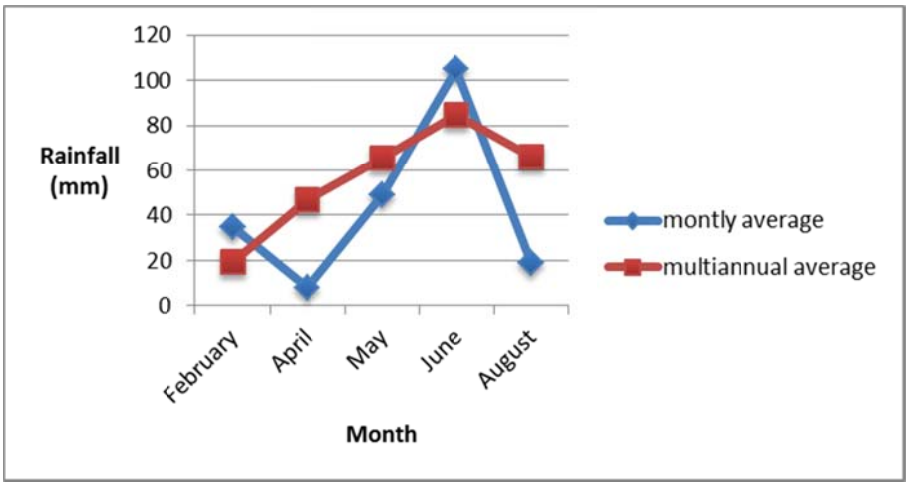

Fig. 3 - The variations of the rainfall (mm) during April-August 2009 at Secuieni crop field

The phenological observations indicated that in the second year of the crop, the sweet fennel had a short vegetative period (95 days) (table I).

The average number of fruits per umbel/plant, as well as the average height of plants were higher for Fv2 crop variant (table 2). Therefore, the largest fruits production (1330 kg/ha) was achieved for the same crop variant, but the highest essential oil yield was obtained for Fv1 crop (table II).

Table 1 The growing of sweet fennel plants during 2009 year

Phenological items	The onset of phenophase	Period (days)	Σ temperatures (°C)	Σ rainfall (mm)
The onset of the vegetative period	01.04.2009	-	-	-
The formation of the leaf rosettes	24.04.2009	23	166.3	10.0
The initiation of the flowering stems	18.05.2009	24	261.3	20.8
The onset of flowering	25.05.2009	7	114.2	6.0
The onset of fructification	13.06.2009	19	163.8	17.2
The fruit ripening (harvest)	05.07.2009	22	456.3	36.6
Sum	**01.04.-05.07**	**95**	**1161.8**	**90.6**

Table 2 The morphological and productivity features of the fennel crop variants

Crop variant	Average number of the fruits per umbel /plant	Average height of plants (cm)	Average fruits yield (kg/ha)	Yield of the essential oil (kg/ha)
Fv1	37	106	1260	63.55
Fv2	41	110	1330	61.92

The volatile oil content of the Fv1 and Fv2 dried fruits was 52 mL/kg and 48 mL/kg, respectively. Taking into account can say that the both crop variants can be considered highly productive in terms of volatile oils, as per the pharmacopoeial requirement (min. 20 mL/kg).

The constituents of fennel essential oils are shown in table III.

For both volatile oils, the main components were t-anethole (53.91% and 49.54%, respectively), fenchone (27.45% and 23.33%, respectively) and D-limonene (2.69% and 5.08%, respecttively) (table 3). The samples showed an unusually high content in fenchone (over 20%).

Table 3 The chemical composition of the essential oils obtained from sweet fennel fruits

RT (min)	Compound	%	
		Fv1	**Fv2**
5.273	α-pinene	1.76	2.31
5.498	camphene	0.25	0.28
6.095	β-pinene	1.11	1.35
6.329	α-phellandrene	0.38	0.45
6.640	p-cymene	0.17	0.23
6.718	D-limonene	2.69	5.08
7.168	γ-terpinene	0.64	0.77
7.350	t-sabinene hydrate	0.43	0.28
8.025	fenchone	27.45	23.33
8.525	camphor	1.86	1.33
9.497	estragole	7.03	9.19
9.964	carvone	-	2.99
10.336	p-anisaldehyde	0.30	0.43
11.046	t-anethole	53.91	49.54
11.877	p-acetonylanisole	-	0.37

Table 4 Pharmaceutical quality of sweet fennel fruits essential oil

Compound	Ph. Eur. 6th ed requirement	Samples	
		Fv1	**Fv2**
t-anethole	min. 80%	53.91	49.54
estragole	max. 10%	7.03	9.19
fenchone	max. 7.5%	27.45	23.33

Table 5 Composition (%) of fennel volatile oils by major component types

Component (%)	Samples	
	Fv1	**Fv2**
Monoterpenes	7.26	10.52
Monoterpenketones	29.31	27.65
Aromatic compounds	61.41	59.76

The compendial monograph for *Foeniculi dulcis fructus* (Ph. Eur., 6th ed.) specifies limits for three compounds: t-anethole, fenchone and estragole.

As indicated in table IV, none of the variants met the pharmacopeial requirements for t-anethole and fenchone[8].

Because of this issue, the volatile oils from these sweet fennel samples may be considered of lower quality. In fact, this is the situation of many volatile oils obtained from sweet fennel fruit's grown in Europe.

A grouping of the components by structural classes sho-wed a prevalence of aromatic compounds (59.76%-61.46 %) followed by monoterpenketones (27.65%-29.31%) table V.

For use in aromatherapy, the volatile oil of sweet fennel should contain 55%-85% aromatic ethers (mainly, t-

anethole), 15%-30% monoterpenes (mainly, α- and β-pinene, limonene), 0.5%-5% monoterpenketones (mainly, fenchone) and monoterpeneoxides up to 4% (predominantly, 1, 8-cineol)[6].

Considering these requirements, volatile oils from the fennel samples included in our study were not suitable for use in aromatherapy.

CONCLUSIONS:

The volatile oils of sweet fennel fruits harvested from the crops grown under same pedo-climatic conditions, but from seeds of different age (eight and four years) showed a distinct chemical composition. The most significant differences concerned the major compounds: t-anethole, fenchone, estragole and limonene.

Although the yield of volatile oil (kg/ha) was high, its quality did not meet requirements for pharmaceutical (Ph. Eur.) or aromatherapy use. The oils were suitable only for use in the food industry or for anethole extraction.

The anethole deficit and fenchone excess could not be considered a result of 2009 weather conditions. Previous research revealed same chemical characteristics for other samples of Romanian fennel, many of them from wholesale trade. It is likely that the seeds used for sowing in Romania originate from a poor chemovariety. For this reason, it is recommended that the farmers purchase controlled seeds from the Mediterranean area.

ACKNOWLEDGEMENTS

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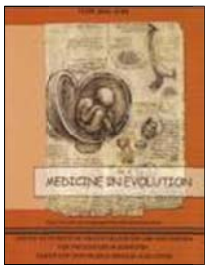
NEW STATISTICAL ANALYSIS METHODS FOR COMPARING ROMANIAN PHARMACY EDUCATION PROGRAMS



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ABSTRACT

*The **aim** of the study was to define new statistical metrics of correlation between the number of hours and credit points allocated to groups of disciplines in different faculties of pharmacy. In this research the **materials (entrance data)** used were curricula in academic year 2009/2010 at 6 faculties of pharmacy in Romania (Bucharest, Cluj, Craiova, Iaşi, Târgu-Mureş and Timişoara). Additionally to known statistical method (Helmert-Pearson x^2) for testing correlation we used new quantitative **methods** and defined new metrics (factors of similarity and dissimilarity) by analogy with metrics on dissolution curves and plasma levels curves in biopharmaceutical evaluations. It were evaluated, compared and correlated the numbers of teaching hours and credit hours allocated to four group of disciplines (BD – Basic Disciplines, PhTD - Pharmaceutical Technology Disciplines, MD – Medical Disciplines, SD – Social Disciplines).*

***Results.**The dissimilarity factor (f_1) took values from 0 to 0.8 which signifies lack of dissimilarity. The results of application of f_2 metric (the similarity factor) exceeded the threshold of 50, between non-similarity and similarity. Since the usual f_2 metric was not sensitive enough (discriminant), it was proposed replacement of threshold 50 with a 65 threshold, corresponding to a mean difference of 15%. The correlation coefficient r values were found within the range (0.88-1), which once again signifies a good correlation.*

***Conclusions.**"Function of pharmaceutical training" as the total volume of theoretical and practical hours calculated by summing the number of hours weighted by the number of credits, was not significantly different between faculties. We used the dissimilarity factor f_1 for comparing the data (differences between number of hours and number of credit points) but the results were difficult to interpret. The correlation coefficient r indicated that the data are correlated both within the same curriculum and between curricula at different universities. Structural analysis of pharmaceutical education in Romania showed in general, that after ten years of continuous tuning, hours and credits are similarly shared and correlated in the four main groups of pharmaceutical sciences in curricula.*

***Key Words:** comparison of pharmaceutical curricula, similarity, dissimilarity, correlation*

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INTRODUCTION

Academic pharmacy today finds itself in a dynamic and difficult environment. Forces and changes both within and external to the academic milieu are challenging faculties of pharmacy in their efforts to ensure the development and delivery of quality professional degree programs while simultaneously evolving to meet the ever changing needs of the health care environment and patient care.

Increased autonomy has been permitted, resulting in the emergence of new models for pharmaceutical education involving new pedagogy and technology. More emphasis is being placed on weaving an array of introductory and advanced pharmacy practice experiences throughout the curriculum and on developing the problem solving and critical thinking abilities of students. Emphasis has continued to be placed on key structural content and on outcomes assessment as a means for documenting success and quality of the training program [1].

This effort of modernization includes also, starting from the desired European common labor market, a tuning of curricula and educational methods across continent.

In comparing structures of academic curricula mathematical and statistical methods had to be used.

Correlations are frequently used because they can indicate a predictive relationship that can be exploited in practice. In general statistical usage, correlation can refer to any departure of two or more random variables from independence, but most commonly refers to a more specialized type of relationship between mean values. There are several correlation coefficients, measuring the degree of correlation. The most common of these is the Pearson correlation coefficient, which is sensitive mainly to a linear relationship between two variables [2, 3].

A correlation coefficient of 1 means that the two variables are perfectly correlated, if one grows so does the other and a -1 value signifies that the variables are perfectly inversely correlated (if one increases the other one decreases).

A non-zero correlation coefficient means that the variables are related, but unless the coefficient is either 1 or -1 there are other influences and the relationship between the two variables is not fixed. The closer the correlation coefficient is to zero the greater the uncertainty and low correlation coefficients means that the relationship is not certain enough to be useful.

Additionally to the above presented usual statistical procedures, the present paper tried to impose new comparison methods borrowed from biopharmacy.

The fit factors (f_1 and f_2) are applied in biopharmacy for comparing dissolution profiles [4, 5, 6, 7, 8]. These factors offer ease of calculation and a simple measure of similarity between pairs of dissolution profiles. This is well suited to the quantitative determination of 'similarity'.

In this paper we compared the number of hours and credit hours assigned in the curricula at six faculties of pharmacy in Romania, using statistical methods of structural and functional modeling.

Statistical and mathematical methods were applied for evaluation of structural and functional similarity and correlation hours - credit hours at each faculty and between institutions of higher pharmaceutical education in the aim of estimation the final result of a long period of tuning between curricula.

MATERIAL AND METHODS:

Materials: curricula in the 2009-2010 academic years from the faculties of pharmacy in six universities (Table I) [9-14].

Research methods were mathematical and statistical criteria of evaluation, comparison, correlation.

A functional model used in estimating the pharmaceutical training of human resources was build using a " *function of training*".

We defined the function

$$F_f = \sum_{i=1}^{n} \frac{n_c^i}{\sum_{j=1}^{n} n_c^i} n_i$$

Where n^i_c- represents the number of credit hours alocated to discipline *i* and n_i- number of hours in curricula for discipline *i*. As methods of comparison of structures we used metrics (factors of similarity f_1 and dissimilarity f_2) and the correlation coefficient r. Metrics (squared functions of sums and/or differences of certain data) were proposed to measure distances between sets of experimental data that characterize the evolution of various phenomena [15-18]. Metrics which can be applied to measure similarity and dissimilarity, include semi metrics, quasi metrics, different "metrics of probability" [3, 19] etc.

$$f_1 = \frac{\sum_{i=1}^{n} |\bar{X}_{ri} - \bar{X}_{ti}|}{\sum_{i=1}^{n} \bar{X}_{ri}}$$

Factor f_1 ,

Where n – represents the total sample studied; i – the disciplines studied; X_{ri} reference data; X_{ti} - tested data; is defined in biopharmacy for comparison of dissolution data.

Greater the f_1 values, greater is the dissimilarity. If f_1 is 0, the terms compared are identical and implicit similar. Similarity factor f_2 [6],

$$f_2 = 50 \lg \frac{100}{\sqrt{1 + \frac{\sum_{i=1}^{n} (\bar{X}_{ri} - \bar{X}_{ti})^2}{n}}},$$

Where n - total sample studied; i – the disciplines studied; X_{ri} - reference data; X_{ti} - tested data; is a compendial factor for comparison of dissolution curves. The value 50 was somewhat conventionally established in biopharmacy as the threshold between similarity and non-similarity starting from believes that a 10% mean difference is not significant therapeuticaly.

Values over 50 indicate similarity. If it is under 50, the result is considered as dissimi-larity.

The correlation coefficient r,

$$r = \frac{\sum_{i=1}^{n} X_i Y_i - \frac{\sum_{i=1}^{n} X_i \sum_{i=1}^{n} Y_i}{n}}{\left[\sum_{i=1}^{n} X_i^2 - \frac{\left(\sum_{i=1}^{n} X_i\right)^2}{n}\right]\left[\sum_{i=1}^{n} Y_i^2 - \frac{\left(\sum_{i=1}^{n} Y_i\right)^2}{n}\right]}$$

Where n - the sample studied; i – the disciplines studied; X_i, Y_i - data for comparison; was used in comparing structures.

The values of r vary between -1 and 1.

We determined the values of three functions (the function of pharmaceutical training, factors of similarity and dissimilarity) and the correlation coefficient r for four groups of disciplines (BD –Basic Disciplines, PhTD – Pharmaceutical Technology Disciplines, MD –Medical Disciplines and SD-Social Disciplines) at each of the six faculties.

RESULTS:

Applying the proposed new formula for determining the function of pharmaceutical training, we calculated this parameter for each of the six faculties, for four categories of pharmaceutical sciences.

For example, for a single discipline let it be mathematics calculus was:

$$F_{f\ Mathematics} = \frac{8\,credits}{136\,credits\,BD} 8\,hours = 0.5\,hours$$

The values of pharmaceutical training function for a given group vary between 2 hours and 16 hours, being smallest in the social sciences (SD).

Basic and Pharmaceutical technology sciences prevail (in number of hours and credit hours assigned) in education programs practically at all university centers: Craiova (F^{BD}_f = 16, F^{PhTD}_f = 14), Iași (F^{BD}_f = 15, F^{PhTD}_f = 16), Bucharest (F^{BD}_f = 14, F^{PhTD}_f = 14) and Timișoara (F^{BD}_f = 13, F^{PhTD}_f = 16).

Actually, the number of hours and the number of credits have to be strong correlated. The strengths of these correlations were checked using f_1 and f_2 factors.

According to data presented in Table II, dissimilarity factor (f_1) ranged from 0 (complete similarity) to 0.8 and values of the f_2 function are above the threshold 50, which confirms the similarity between the number of hours and assigned credits.

There was less similarity between the number of hours and credits provided in the curriculum for the group of basic sciences (BD).

The minimum value 76 was recorded at Timisoara.

Table 1 Values of pharmaceutical training function (F_f) on groups of disciplines

Faculties of Pharmacy	F_f				$F_f = \sum_{i=1}^{n} \frac{n_c^i}{\sum_{j=1}^{n} n_c^j} n^i$
	BD	PhTD	MD	SD	
Bucharest	14	14	12	5	
Cluj	12	14	11	4	
Craiova	16	14	11	4	
Iași	15	16	11	2	
Târgu-Mureș	12	13	11	5	
Timișoara	13	16	12	5	

Table 2 Values calculated for f_1 and f_2 metrics for comparison structure by hours with structure by credit hours at the four groups of sciences (BD, PhTD, MD, SD)

Faculties of Pharmacy	f_1 (Dissimilarity factor)				f_2 (Similarity factor)			
	BD	PhTD	MD	SD	BD	PhTD	MD	SD
Bucharest	0.1	0.1	0.07	0.2	88	93	96	97
Cluj	0.2	0.1	0.04	0.2	82	92	96	95
Craiova	0.2	0.1	0.09	0.2	80	87	93	98
Iaşi	0.2	0.07	0.11	0.3	84	96	88	90
Târgu-Mureş	0.1	0.07	0.04	0.8	85	94	97	98
Timișoara	0.2	0.2	0.13	0	76	83	91	100

The values of the correlation coefficient r as can be shown in Table III were within the range 0.88-1. It appears that there is a perfect interdependence between the number of hours and credits in the disciplines of Pharmaceutical Technology group studied at the Faculty of Pharmacy of Craiova, Iasi

and Targu-Mures, and the Social Sciences at university in Timisoara. The Medical disciplines (MD) presented a very good correlation between hours and credit hours in the education programs in all six faculties of pharmacy.

The correlation coefficient r values were lower at Social sciences, a minimum (r =88) occurring in Iasi.

Table 3 Values of the correlation coefficient (r) between hours and credit hours

Faculties of Pharmacy	r			
	BD	PhTD	MD	SD
Bucharest	0.97	0.99	0.99	0.99
Cluj	0.93	0.99	0.99	0.95
Craiova	0.96	1	0.99	0.99
Iaşi	0.98	1	0.98	0.88
Târgu-Mureş	0.96	1	0.99	0.99
Timişoara	0.91	0.99	0.98	1

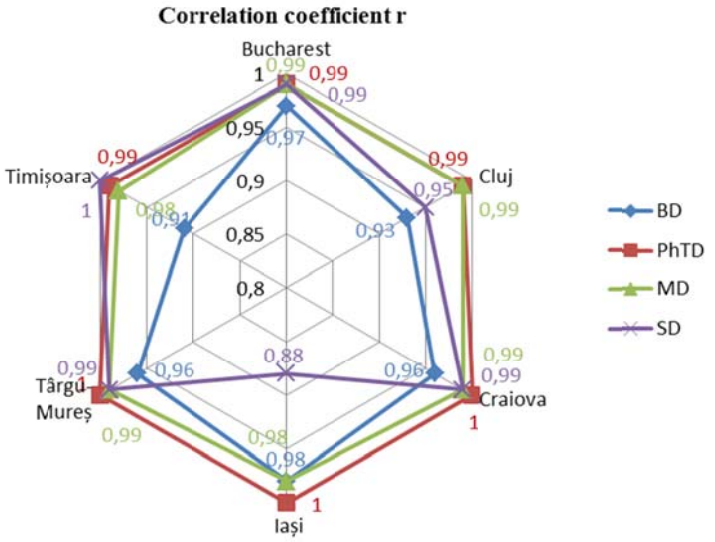

Fig.1 Values of the correlation coefficient (r) between structure by hours and structure by credit hours at faculties of pharmacy in Romania for groups of pharmaceutical sciences BD, PhTD, MD, SD

In all faculties included in the conducted study, we observed that in the four groups of disciplines, in the Medical disciplines there is the smallest dissimilarity between the number of hours and credits assigned (Bucharest: f_1=0.07 and r=0.99; in Cluj and Targu-Mures f_1=0.04 and r=0.99; in Iasi f_1=0.07 and r=0.98).

On the opposite side, the highest values of the factor was obtained at the Social sciences, where there was a large enough non-correlation between hours and credits provided in the pharmaceutical curricula (in Targu-Mures f_1=0.8 and r=0.99; in Iasi f_1=0.3 and r=0.88; in Bucharest and Cluj f_1=0.2 and r=0.99 respectively 0.95). Variation of factor f_1 values was uniform in the disciplines of Pharmaceutical Technology: in Bucharest and Cluj f_1=0.1 and r=0.99; Craiova f_1=0.1 and r=1; Iasi and Târgu-Mures f_1=0.07 and r=1; Timisoara f_1=0.2 and r=0.99.

Although the factor f_1 took the values 0.1 and 0.2, for the Basic disciplenes, we noticed that the results of the correlation coefficient r are more discri-

minant: Bucharest f_1=0.1 and r=0.97; Cluj f_1=0.2 and r=0.93; Craiova f_1=0.2 and r=0.96; Iasi f_1=0.2 and r=0.98; Targu-Mures f_1=0.1 and r=0.96; Timisoara f_1=0.2 and r=0.91.

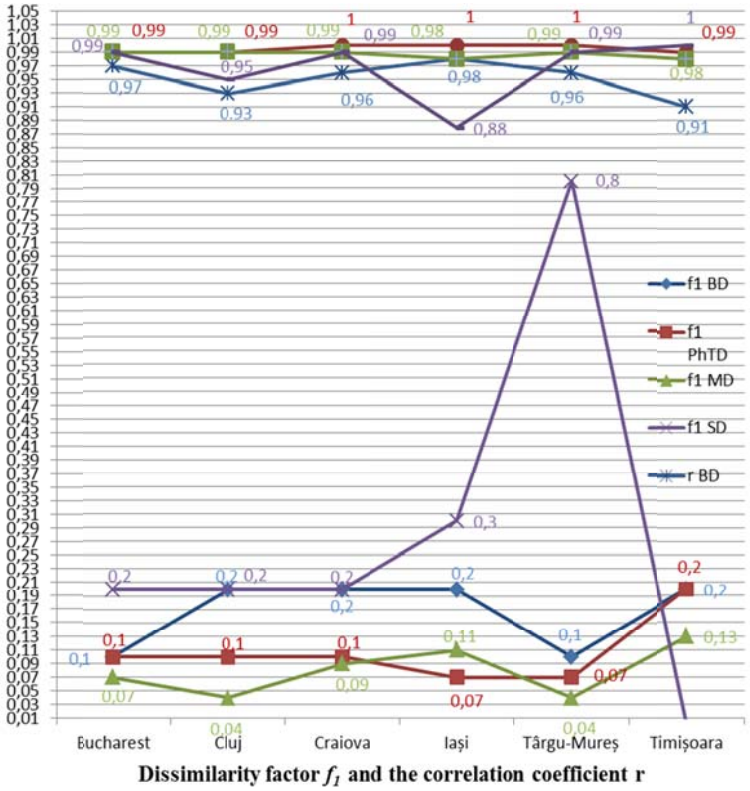

Fig.2 Values of the dissimilarity factor f_1 and of the correlation coefficient r. Since f_1 is a dissimilarity factor, if f_1 increases, the correlation coefficient, should decrease and this is largely verified as can be seen in Figure 2.

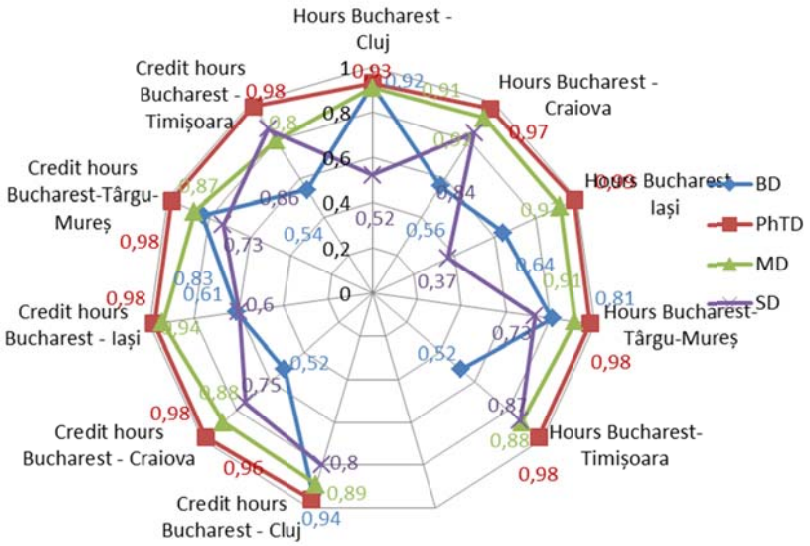

Fig.3 Values of the correlation coefficient r between the number of hours and credit hours assigned to groups of sciences at Faculty of Pharmacy at Bucharest in comparison with the other five academic centers in Romania.

The best correlations hours-credits between the Faculty of Pharmacy in Bucharest and the other Romanian faculties of pharmacy, were obtained for the disciplines of Pharmaceutical technology ($r \geq 0.98$ between Bucharest -Iași, Bucharest-Târgu-Mureș, Bucharest-Timișoara).

Medical sciences are better correlated as number of hours between Bucharest and Craiova (r_{ore}=0.92), Bucharest and Târgu-Mureș, respective Bucharest and Cluj (r_{Ore}=0.91). Credit hours are similary assigned for the medical disciplines in Bucharest and Iași ($r_{Credit-Hours}$=0.94) respective Bucharest and Târgu-Mureș ($r_{Credit-Hours}$=0.91).

The hours-credit hours structure for the Basic sciences is similar at faculties in Bucharest and Cluj (r_{Hours}=0.92; $r_{Credit-Hours}$=0.94). Regarding the Social disciplines we observed a good correlation in the number of hours between Bucharest and Timișoara.

CONCLUSIONS:

A comparison of structures of curricula can be performed using usual statistical techniques for testing correlation. New comparison methods using metrics from biopharmacy are applicable also, biopharmaceutical metrics being more sensitive to differences than usual statistical parameters.

The pharmaceutical training function, defined in this paper, refers only to global aspects of education and not to the quality of structure of curricula. This function makes a correction of the structure of curricula, for different disciplines in accordance with the assignned number of credit hours.

An increase in values of the training function indicates a students´ overloading with mandatory and supervised program and decreasing the role played by individual training. When the number of hours is fixed and the credit structure differs significantly from that of hours of course, laboratory/seminar and practice, aspect seen in most disciplines, this function reflects the share of time and mode of implication in educational process of students.

Because the normal range of variation of f_1 function is not known, the results were difficult to interpret. According to data presented in tables we observed that with the increasing degree of dissimilarity (measured by the factor f_1) decreases the correlation between hours and credits allocated (as measured by the correlation coefficient r).

The correlation coefficient r indicated that the data are correlated both within the same curriculum, (r BD = 0.97 Bucharest, Cluj r BD = 0.93) and between curricula at different universities (Bucharest, Cluj, r BD = 0.92 hours respectively credits r BD = 0.94). Lower correlations were found for social subjects.

The correlation factor did not put in evidence any trends or differences in structure and uniformity, being less sensitive than biopharmaceutical metrics. The values of the parameter f_2 overcome the threshold of 50 (range between similarity and non similarity), ranging between 82 and 97 in all four groups of disciplines and for a more discriminant power a threshold of 65 would be more adequate.

As a general characterization tuning succeeded in global distribution of hours between groups of disciplines but still further efforts had to be made for a better structural and qualitative concordance.

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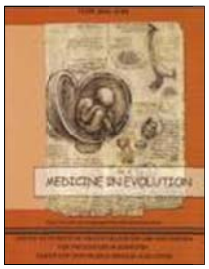
UV ABSORPTION CHEMICAL-TOXICOLOGICAL STUDY OF TRAMADOL AND PENTAZOCINE IN HUMAN PLASMA



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ABSTRACT

Aim: *This study aims at developing methods for dosage of tramadol and pentazocine by UV-absorption spectrophotometry, taking into consideration the possibility to transfer the developed methods to human plasma.*

Materials and methods: *The study was performed by UV absorption spectrophotometry for pentazocine and tramadol as such and following liquid / liquid extraction with chloroform at alkaline pH from human plasma.*

Results: *Tramadol has a maximum absorption in methanol at 272 nm, and pentazocine in water at 278 nm. Calibration curves in the range 0.5 to 20 µg/mL are linear, and the correlation coefficients are over 0.99.*

Conclusions: *The tested methods are acceptable in sensitivity, accuracy and precision, and can be used for the quantification of tramadol and pentazocine in plasma. Basic validation parameters were also settled for the methods.*

Key words: *tramadol, pentazocine, UV assay, human plasma, validation.*

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INTRODUCTION

Tramadol and pentazocine are opioid synthetic analgesics currently used in moderate to severe pain management (McCarberg, 2007).

Lately an abuse increase of tramadol and pentazocine use has been observed (Shadnia, 2008), even if the two medicines have a well-defined prescription regimen due to their addictive potential.

Tramadol belongs to the aminocyclohexanol group of chemically synthetized biological active agents and, despite its chemical structure which is not related to opioids, has opioid-like effects, acting particularly as a μ-receptor agonist (Hennies, 1988) and inhibitor of noradrenaline and serotonin reuptake (Bamigbade, 1997).

Pentazocine belongs to the benzomorphan class of opioids, acting as a partial agonist-antagonist of the opioid receptors. Therapeutic and / or toxic monitoring of both drugs is more difficult as simple methods have often too high detection limits so that they are useless in the above mentioned procedures (Moffat, 2004). The paper presents two UV spectrophotometric methods for the assay of tramadol and pentazocine in human plasma for the evaluation of toxic drug concentrations basic validation parameters for the assay.

MATERIAL AND METHODS:

Tramadol hydrochloride (pharmaceutical purity) was a gift from LaborMed Pharma; pentazocine lactate (Fortral injections from KRKA, containning 30 mg pentazocine) was used for the assay. Normal human plasma was obtained from the "C.T.Nicolau" National Hematologic Institute. All reagents used for the extraction procedure were of analytical grade.

The UV spectra were performed on a Varian Cary 100 Bio spectrophotometer.

RESULTS:

Pentazocine – Solutions of 0.5 to 20 μg/mL of pentazocine have been obtained in double distillated water, and their UV spectra were plotted against water in the range 240 – 300 nm (Fig.1). Pentazocine displays an UV absorption band having a maximum absorption peak at 278 nm and a shoulder which could not be resolved, at about 283 nm. The calibration curve, performed on 5 replicates for each concentration, proved to be linear in the range, having a correlation coefficient of 0.998. The parameters of the regression curve, as well as the detection and quantification limits determined following the ICH Q2 (R1) guidelines [1], are systematically presented in Table 1.

For the assay in human plasma, as the peak maximum is situated in the range of protein absorption maximum (280 nm), it is obvious that pentazocine can be spectrophotometrically evaluated at the 278 maximum only following an extraction procedure. That is why we prepared normal human plasma samples spiked with pentazocine for evaluating the possibility to get a simple method assay of the drug in human plasma for toxicological purposes. The samples were prepared as following: appropriate volumes of 3 mg/mL pen-

tazocine stock solution were mildly vortex-mixed with 1 mL of 1:10 diluted normal human plasma (in double distillated water). Pentazocine was extracted with 2 mL of chloroform at alkaline pH (100 µL 6 M NaOH) in the presence of 0.8 g NaCl, the extract was dried under nitrogen, then the residue was redissolved in water and analyzed. The parameters obtained for the assay are systematically presented in Table 1.

Tramadol – The same procedure was followed for the assay of tramadol. Solutions of 0.5 to 20 µg/mL of tramadol hydrochloride have been obtainned in methanol.

UV spectra of tramadol display two maximum absorption peaks, at 273 nm and 279 nm (Fig. 2). As the 273 peak is generally better resolved than 279 nm peak, we choose the first one for the assay. The calibration curve, performed on 5 replicates for each concentration, was linear in the range 0.5 to 20 µg / mL, having a 0.9998 correlation coefficient. The validation parameters obtained for tramadol is also presented in Table 1.

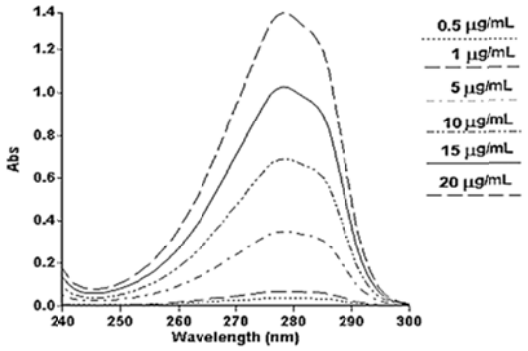


Fig.1 UV spectra of pentazocine in water.

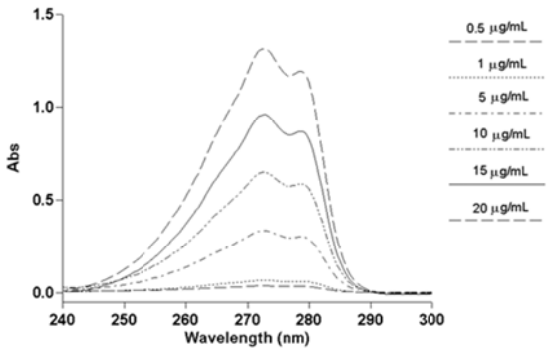


Fig.2 UV spectra of tramadol in methanol.

Human plasma samples spiked with tramadol were prepared in a similar manner to that one described for pentazocine, with the difference that the final solutions were obtained in methanol instead of water. The change was needed as the re-dissolving in water results in the precipitation of the extracted sample. The overall obtained results are presented in Table 1.

Validation parameters – The validation of the assay methods (pentazocine and tramadol from human plasma, following liquid/liquid extraction at alkaline pH) was performed for the following parameters: selectivity, linearity, detection and quantification limits, accuracy (expressed as recovery coefficient) and precision (expressed as relative standard deviation of 5 replicates of the same concentration).

All parameters are presented in Table 1 and discussed below.

Selectivity of the methods can be considered from Figure 3, where one can observe there is a clear difference between the spectra of the extracted compounds and the corresponding extracted blank samples. The methods display a rather good sensibility (detection limits around 300 ng/mL), considering the blood concentration range reported (Winek, 2001) as toxic for pentazocine (2-5 µg/mL) or therapeutic (0.03-1 µg/mL for pentazocine and 0.1-0.6 for tramadol).

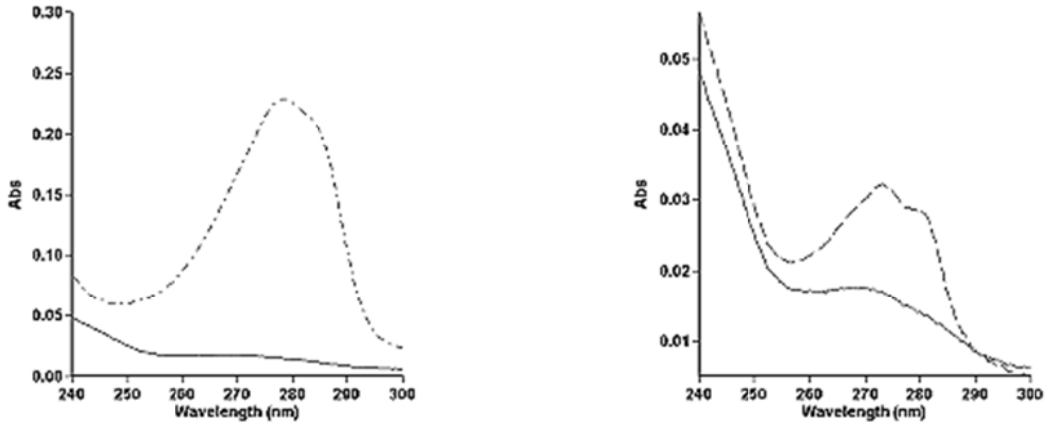
The method is precise, as the relative standard deviation of 5 replicates

is below 5%, which is a very good degree of repeatability.

The recovery coefficients are rather low, probably due to losses of the substance both by protein binding and the extraction procedure. A bioanalytical validation for the method is needed in this case.

Table 1 Validation parameters obtained for pentazocine and tramadol assay from human plasma, following liquid/liquid extraction

Substance / **Parameter**		**Pentazocine**	**Tramadol**
Selectivity		Figure 3 a	Figure 3 b
Linearity	**Range (µg/mL)**	0.5 – 20	0.5 - 20
	Equation	Y=0.0687x +0.0038	Y=0.065x+0.0037
	Correlation	0.998	0.9995
DL (µg/mL)		0.091	0.112
QL (µg/mL)		0.303	0.338
Accuracy (mean recovery coefficient, %)		32.8	65.3
Precision (mean RSD, %)		2.1	4.7



a b

Fig.3 Demonstration of method specificity for pentazocine (a) and tramadol (b). Dotted line represents the spectra of the extracted drugs and full lines the spectra of corresponding extracted plasma blank samples.

CONCLUSIONS:

Assay methods for pentazocine in water and tramadol in methanol by UV absorption spectroscopy following extraction from human plasma with chloroform at alkaline pH are described.

The methods are selective (extracted drug spectra are different from corresponding extracted blank spectra), linear within the range 0.5-20 µg/mL, sensitive, having quantification limits of 0.3 µg/mL and precise.

Accuracy, expressed as mean recovery coefficient, is rather poor, a bioanalytical validation of the method being necessary in the case of the two drugs.

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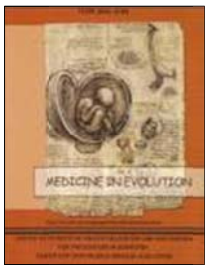
PHYSICO – CHEMICAL STUDIES OF KETOPROFEN – β – CYCLODEXTRIN INCLUSION COMPOUNDS



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ABSTRACT

***Purpose**: The aim o f this study is the complexation of ketoprofen with β-cyclodextrin and the characterization of the complexes formed, in terms of increasing ketoprofen bioavailability, stability and its solubility.*

***Matherials and methods**: Two molar concentrations (1:1 and 2:1) of ketoprofen and β-cyclodextrin were used in this study for inclusions compounds. The precipitate substances were study by FT-IR spectroscopy, DSC thermograms, SEM microscopy and solubility in water.*

***Results**: FT-IR analisys, DSC thermograms and SEM microscopy demonstrate the complexes formation between ketoprofen and β-cyclodextrin. Inclusion complexes solubility depends on temperature and molar concentration of substances.*

***Conclusions**: Compounds formed showed good ketoprofen inclusion in cyclodextrin cavity and a high solubility in water at different temperatures.*

Keywords: ketoprofen, β-cyclodextrin, complexes, solubility

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INTRODUCTION

NSAID medication ranked first in the treatment of pain associated with spinal pathology and beyond. Ketoprofen is an NSAID very effective in the treatment of pain associated with joint pathology but has the disadvantage of low solubility and gastric irritability.

Drugs with limited oral bioavailability due to low solubility and dissolution rate can be complexed with cyclodextrins to improve their absorption.

Inclusion of medicinal substances in various complexes, reduce recrystallization of active drugs, increasing their solubility in water and also reducing the gastric irritability orally administered drugs [1, 3, 5].

PURPOSE

The aim o f this study is the complexation of ketoprofen with β cyclodextrin and the characterization of the complexes formed, in terms of increasing ketoprofen bioavailability, stability and its solubility.

MATERIAL AND METHODS:

In order to formulate, prepare and characterize of new extended-release tablet of ketoprofen we use the method of ketoprofen inclusion in compound with β cyclodextrin. The substances included in the study had the following origin: ketoprofen (Bidachem, Italy), β-cyclodextrin (Fluka, Ph. Eur.) distilled water (FRX), and the apparatus used consisted of: type magnetic stirrer AM4 from Velp Scientific, analysis device DuPont (Wilmington, DE) model 910, Bruker FT-IR interferometer 66, the oven, Berzelius glasses.

Inclusion complexes were conducted by using magnetic stirring of ketoprofen, β-cyclodextrin and distilled water. Are used two molar concentrations of ketoprofen with cyclodextrin (1:1 and 2:1) and two methods of preparation by precipitation in solution and suspension. In order to obtain the shake magnetic complexes in solution were prepared β-cyclodextrin solution at a concentration of 1.5% using distilled water, plus an active substance-ketoprofen. For the shake of the magnetic suspension were prepared suspensions of β-cyclodextrin concentration of 5% in distilled water, plus ketoprofen (Table 1).

Dispersions were subjected to shaking at room temperature for 33 hours. Precipitate appeared in the reaction medium was isolated by filtration, washed with distilled water, dried at 50 ° C and characterized by FTIR spectroscopy, DSC tomograms, SEM microscopy and solubility in water at different temperatures. For spectroscopic studies, we used the device Bruker FT-106 module, equipped with Ge detector cooled with liquid nitrogen and connected to the Bruker FT-IR 66 interferometer (with a spectral resolution of 2 cm-1). 5 mg of each substance were taken so intimately mixed with 500 mg KBr and then were pressed in disc form. For each sample were recorded FT-IR spectra with that device.

Thermal behavior of ketoprofen, β-cyclodextrin and ketoprofen-β-cyclodextrin inclusion compounds was examined using an analysis device DuPont (Wilmington, DE) model 910. Argon gas is used in DSC analysis with a hea-

ting rate of 10 ° C / min and a flow rate of 35 cc / min.

Fusion energy has been calculated from the area of signal sites endothermic peak of DSC curves, calibration device was made using a sample of indium as a standard melting temperature and heat.

Samples were taken from all those powders with a weight of 5 mg and the examination was conducted at temperature ranges between 50 and 350 ° C. It took into account the melting points for ketoprofen (for = 96 ° C) and β-cyclodextrin (pt = 298 ° C).

Solubility was studied under the Romanian Pharmacopoeia X edition and its representation, was chosen as a graphical method, simulated surface response of mass influence on the solubility of their complexes is achieved through software MathCAD.

Table 1. The quantities (g) of β cyclodextrin (β-CD) and ketoprofen used in study

Distiled water (30 ml)	Ketoprofen	Molar raport
0,45g β-CD	0,0972 g	1:1
0,45g β-CD	0,1944 g	1:2
1g β-CD	0,216 g	1:1
1g β-CD	0,432 g	1:2

RESULTS

Ketoprofen inclusion compounds of β-cyclodextrin obtained by two methods using magnetic stirring solution and the suspension is in the form of white powder, odorless. The water solubility of compounds inclusion was determined according Romanian Pharmacopoeia ed. X. (Table 2).

Table 2. Phisico-chemical characteristics of ketoprofen-β-cyclodextrin complexes

Substance /Inclusion compounds	Solubility		Melting point (p.t.),°C
	20 °C	50 °C	
ketoprofen	-	0,05:100	96
β-CD	-	1,5:100	298
Complex I (metd. I)1:1	0,01:80	0,01:30	219
ComplexII (metd. I) 2:1	0,01:150	0,01:130	60
Complex III (metd. II) 1:1	0,01:40	0,01:40	50
Complex IV (metd. II) 2:1	0,01:100	0,01:80	90

FTIR spectroscopy was performed for confirmation or rejection of the formation of inclusion compounds ketoprofen-β-cyclodextrin by preparation methods used, but also to assess the quality of the complexes formed [2, 4].

Since the formation of inclusion complexes with ketoprofen involve changes in absorption bands in FT-IR spectrum of ketoprofen in the C=C bonds, C=O and -CH, are used the graphic below for complexes of interest related to its spectrum.

In Figure 1, were represented FT-IR spectra of inclusion complexes of ketoprofen- β-cyclodextrin obtained by magnetic stirring, and showed that the areas of 750-1750 cm-1 and 2950-3150 cm-1 shows differences that are due to characteristic groups involved in the bonds C=C, C=O and -CH. C = C bonds recorded peaks identical with

those of ketoprofen (1550 cm-1) for complex I, (method I), molar rapport 1:1 and complex II, (method I), molar rapport 2:1 followed by lower peaks evident in the case of complex III (method II) 1:1 and complex IV (metd. II) 2:1, which demonstrates that these complexes have included well-ketoprofen. Peak specific sites C = C bonds (1680 cm-1) is reduced from complex I, (method I), molar rapport 1:1 to complex IV, (method II), molar rapport 2:1 which indicates that at this level, the ketoporfen was included in all complexes. C = O bonds recorded decreases of the peak at 1700 cm-1 sites for all complexes, as is the case with -CH bonds (860 cm-1, 1370 cm-1 and 3200 cm-1) showing the same efficiency in the ketoprofen inclusion.

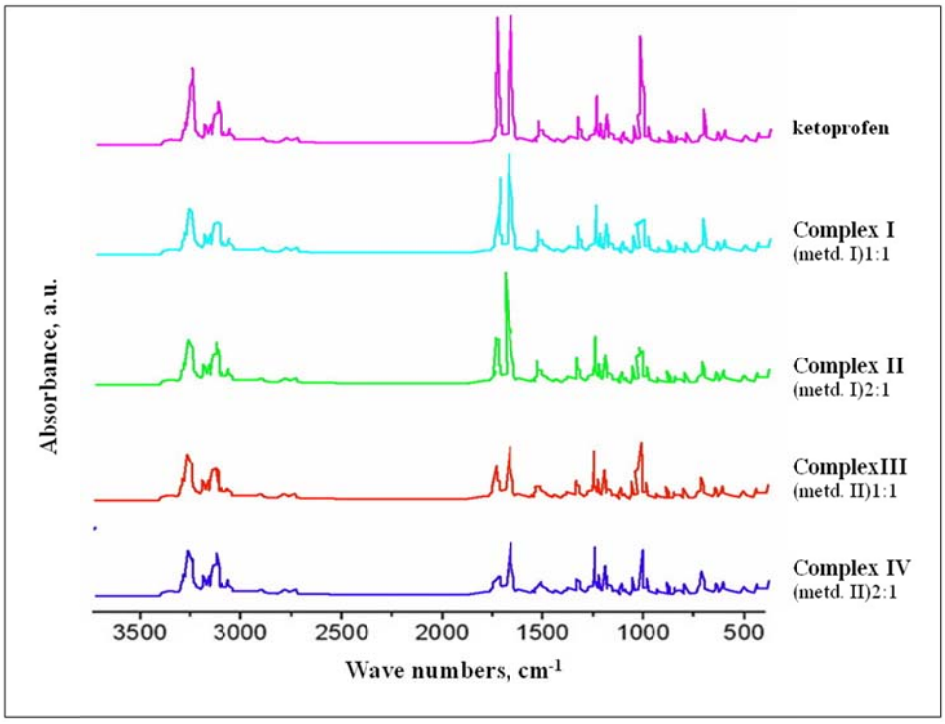

Fig.1 The FT-IR spectra of inclusion complexes of ketoprofen- β-cyclodextrin.

Differences between the curves recorded for ketoprofen-β-cyclodextrin complex obtained by method I and complex obtained by the method II, on the one hand, support the formation of inclusion complexes. Hydrogen bonds are stronger in the case of method II (860 cm-1, 1370 cm-1and 3200 cm-1), which shows a higher efficiency for this method in obtaining the inclusion compounds.

Analysis thermograms of pure components and complexes ketoprofen- β-cyclodextrin obtained by mixing magnetic revealed following information: curve DSC ketoprofen indicating the status of crystalline substance with a melting point characteristic at 96 ° C, curve DSC β-cyclodextrin recorded a peak for the melting specific 298 ° C.

The DSC curves analyzed for ketoprofen, β-cyclodextrin and inclusion compounds ketoprofen-β-ciclodextrin, it was established that best ketoprofen was included in complexes I and II (Fig. 2).

Also observed an endothermic peak characteristic of crystallization water loss through curves and β-cyclodextrin complexes within 40-110 ° C,

which corresponds to the residual moisture range <100 ° C. For these complexes we have an adder range of interest, the range of water included in the cyclodextrin cavity and for this the interval area corresponding to> 100 ° C.

In addition, the DSC curve of β-cyclodextrin is present an endothermic peak that characterizes the substance melting at about 298 ° C. In all four cases of the complexes there is an essential reduction or complete disappearrance of endothermic effects related to melting of the complexes formed ketoprofen-β-cyclodextrin (magnetic stirring), indicating interaction of ketoprofen with β-cyclodextrin and training complexes.

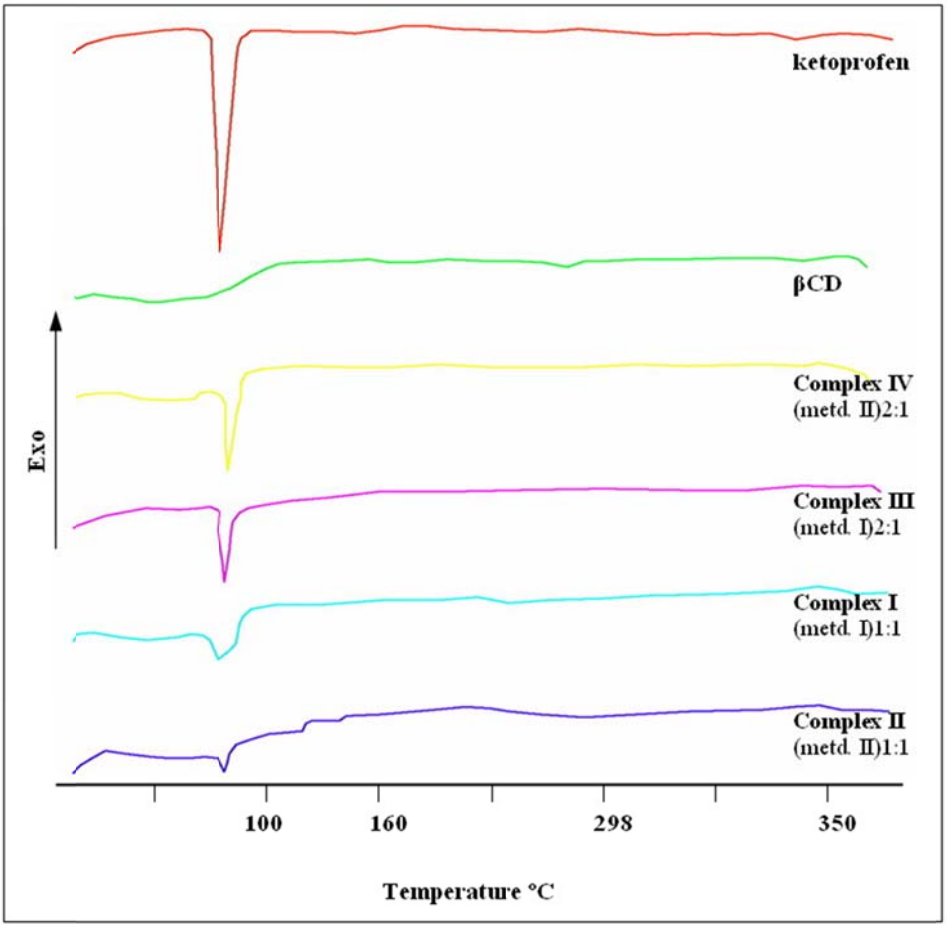

Fig.2 The DSC thermograms for ketoprofen, β-cyclodextrin and inclusion compounds ketoprofen-β-ciclodextrina.

The DSC curves analyzed, it was established that best ketoprofen was included in complexes I and II, these complexes will therefore only be achieved SEM microscopic analysis.

According to SEM images formed complexes have variable shape, condensed matter, stands the comprehensive inclusion of ketoprofen and the absence of pure substances. To determine the effectiveness of cyclodextrin inclusion complexes with ketoprofen the solubility of complexes formed was determined and representted using MathCAD soft. It was observed that increased temperature (50°C), ketoprofen solubility of β-cyclodextrin complex (1:1) obtained by method II increased, while the complex obtained by method I remains constant.

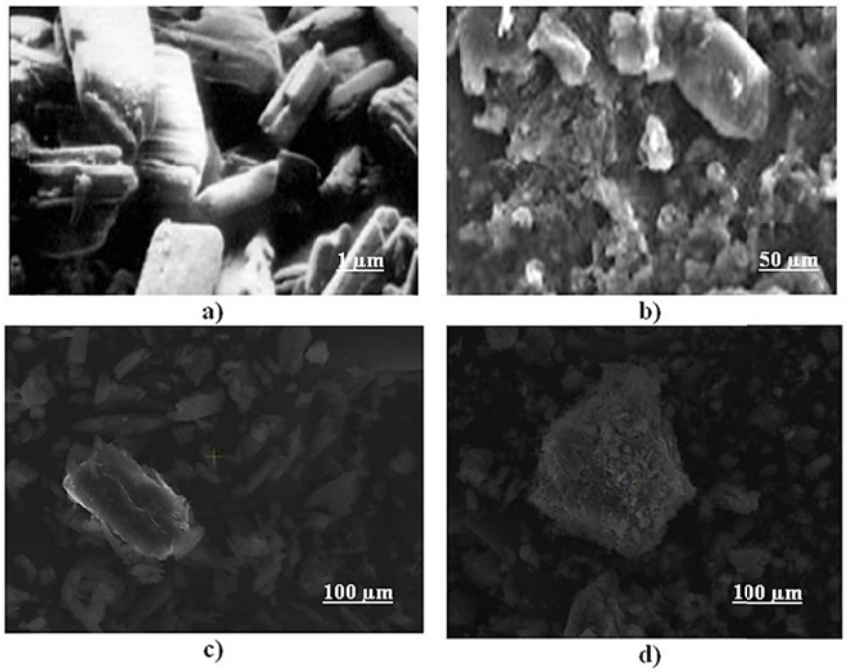

Fig.3 SEM images for ketoprofen (a), β-cyclodextrin (b), complex I (c) and II (d).

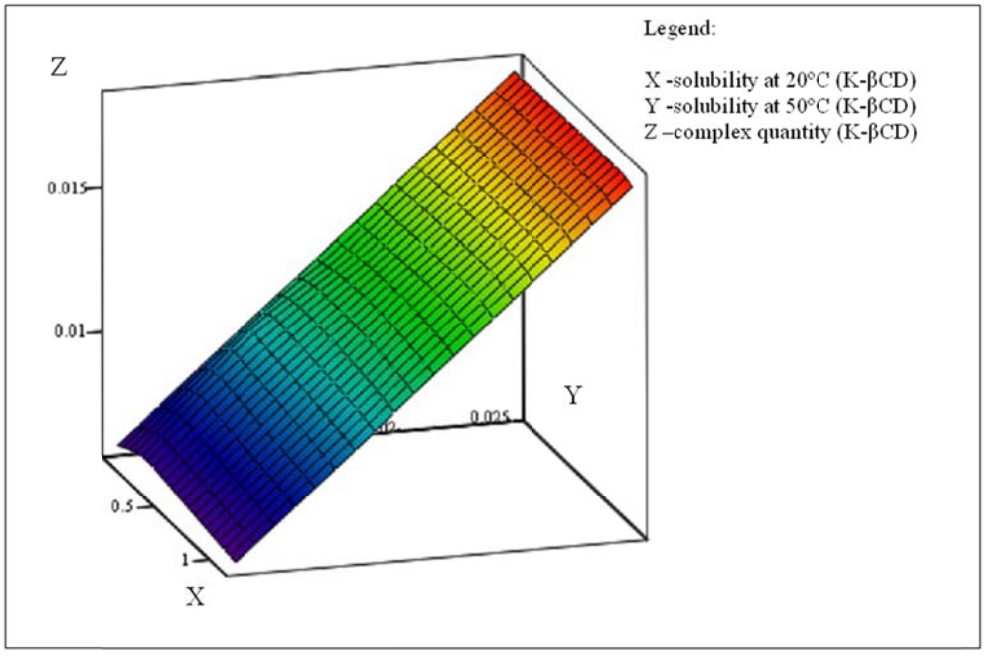

Fig.4 Response surface of K-βCD complex mass influence on its solubility at 20 ° C and 50 ° C.

DISCUSSIONS:

From the standpoint of the chemical method used, the most effective method is to incorporate ketoprofen suspension. The FT-IR spectra of inclusion complexes of ketoprofen with β-cyclodextrin obtained shows that: the fields 1550 - 1750 cm-1 and 2950-3150 cm-1 peaks changes occur, which is due to

groups involved in the connection C = C, C = O and CH. Specific peaks of these molecular links are changed, for each type of complex in hand, proving a good inclusion of ketoprofen. From the DSC curves it was found that ketoprofen was included best in complexes I and II. SEM microscopic evaluation method showed the formation of inclusion complexes of ketoprofen and β-cyclodextrin, all structures studied shows variable shapes, different specific structures of ketoprofen easily, which shows that it was included in the cyclodextrin cavity.

Compared to the pure active principle, the complex obtained by the method I remain slightly soluble, while the complex obtained by method II has a much higher solubility.

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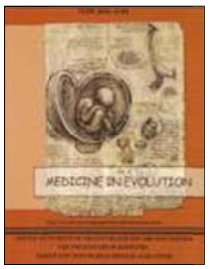
SUPERVISED LIFESTYLE INTERVENTION EFFECTIVENESS IN REDUCING CARDIOMETABOLIC RISK OF PATIENTS WITH METABOLIC SYNDROME



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ABSTRACT

Aim: *The present study is aiming to evaluate the effectiveness of a supervised lifestyle intervention programme for reducing cardiometabolic risk in patients with metabolic syndrome.*

Materials and methods: *Forty-three young metabolic syndromes patients were included in a 6 months lifestyle intervention study. We evaluate blood lipids, resting blood pressure and heart rate, fasting blood glucose before and after 6 months of intervention. An incremental cardio-pulmonary exercise test was performed by each patient in order to recommend proper effort intensity of the exercise programme. All subjects participated in a 6 months interval exercise training programme. General indications regarding healthy diet were set for each patient.*

Results: *We noticed at the end of the study a significant improvement in mean weight, body mass index, waist circumference, systolic and diastolic blood pressure, fasting blood glucose, HDL cholesterol, LDL cholesterol and heart rate.*

Conclusions: *Intensive lifestyle intervention programmes can be the key for better results in metabolic syndrome management of young patients.*

Key words: *lifestyle, exercise training, blood pressure, cholesterol.*

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INTRODUCTION

It is estimated that 2 million youth, most of whom are overweight, meet the criteria for MetSyn based upon an analysis of the National Health and Nutrition Examination Survey (1999 –2000) data and using the ATP-III definition modified for age.[1]

Metabolic syndrome (MetSyn) is a cluster of cardiovascular risk factors including high blood pressure, dyslipidemia, hyperglycemia, and central obesity.[2] According to Adult Treatment Panel III (ATP III), MetSyn is diagnosed when three or more metabolic abnormallities (impaired glucose metabolism, elevated blood pressure, hypertriglyceridemia, low HDL cholesterol and central obesity) cluster in the same person.[3]

MetSyn confers an increased risk for the development of diabetes mellitus and for cardiovascular morbidity and mortality.[4-7] In a population based cohort study the odds ratio (adjusted for age, sex and follow-up duration) for the development of diabetes in patients with impaired fasting glucose was 10.[8] The presence of the metabolic syndrome at baseline increased the risk for the development of diabetes mellitus almost 2-fold in American Indians and in Finnish men almost 4-fold increase was shown.[9]

Franks and colleagues, evaluating risk factors associated with the MS in a group of young non-diabetic patients, found features of the MS predict development of subsequent type 2 diabetes.[10]

Several studies shows that obesity associated with insulin resistance and type 2 diabetes mellitus has largely increased in populations which have started consuming high-calorie diets and reduced physical activity.[11] Dyslipidemia is the most common MetSyn factor present in youth, especially due to the increase in overweight and obesity prevalence in this age range. In adults, a "dyslipidemic triad" is widely described as part of the MS, consisting of elevated Triglycerides, low HDL-cholesterol and high LDL-cholesterol levels with rather qualitative changes, such as small dense particles which are more atherogenic.[12,13] This triad confers an increased risk for ischemic heart disease in affected adults.

Increased resting heart rate (HR) and high blood pressure (BP) are two important hemodynamic parameters for cardiovascular risk progression of atherosclerosis. Hypertension and its complications are largely responsible for morbidity and mortality of all age groups.[2, 14] Indeed hypertension is a major independent risk factor for coronary heart disease, stroke, and renal disease.[15, 17] More than this, when coexisting high blood pressure and metabolic risk factors potentiate each other, leading to a total cardiovascular risk which is greater than the sum of its individual components.[18, 19]

Prospective observational studies have demonstrated that subjects with high normal BP have a greater incidence of cardiovascular disease compared to people with normal or optimal blood pressure.[20, 21] Subjects in this category should be advised to implement intense lifestyle measures because of the relatively high chance these individuals have to progress to hypertension.[22, 23]

The association of BMI and hypertension is greater among men below 45 years of age and in this subpopulation, 60% of the hypertension cases can be attributed to excess weight. In women under 45 years old, the impact of weight gain on the prevalence of arterial hypertension is lower, compared to men.[11] Based on adult data; it seems likely that early identification of youth

with the MS, adoption of a healthy lifestyle and, appropriate medical intervention in those with the highest risk may help decrease long-term vascular disease.[24]

It is a well established fact that sedentary lifestyle contributes to increased risk of hypertension. Lack of physical fitness is a strong predictor of cardiovascular mortality independent of blood pressure and other risk factors.[25] However few studies have assessed the benefit of exercise training in high normal BP stages of young patients. Every component of MetSyn needs a specific treatment and treating one of it has a chain effect, influencing all the other. An important role in MetSyn treatment is played by the lifestyle intervention including healthy diet and increase in physical activity. Several studies have shown that increasing physical activity we can improve each MetSyn risk factor.[8, 9, 26]

Poor fitness is associated with development of CVD risk factors in young adults.[27]

Regarding cardiovascular risk factors related to excess weight and metabolic syndrome, different studies have shown that, at any age, the number of risk factors is inversely related to physical activity and to physical conditioning. [28, 29]

AIM:

The present study is aiming to evaluate the effectiveness of a supervised lifestyle intervention programme for reducing cardiometabolic risk in patients with metabolic syndrome.

MATERIAL AND METHODS:

Forty-three young patients (18-25 years old) previously diagnosed with metabolic syndromes (diagnosed according to NCEP-ATPIII criteria [3]) were included in the prospective intervenetional study. The patients were invited to participate in a 6 months lifestyle intervention programme, in order to promote changes in their sedentary lifestyle and nutritional habits. The basic requirements for the patients to participate were motivation and high attendance to the exercise training sessions.

None of the patients were on antihypertensive medication before and during the study. The patients were free of cardiac and pulmonary disease and presented a normal tensional response to the exercise.

Blood lipids were evaluated before and after 6 months of intervention using a portable spectrophotometer (CardioCheck, USA). Blood pressure vas measured using a sphygmomanometer (Boso-classico, Germany) after 5 minutes of rest in sitting position. The same investigator measured blood pressure for all investigated patients. For body composition assessment we use a multi-frequency bio-impedance body composition analyzer (InBody720, South Korea). Using a diverse range of frequency from 1 kHz to 1 MHz, the In Body720 measures accurately the balance between body water, protein, body fat, mineral and muscle mass. In the present study we used body composition in order to analyze the progression in weight, waist circumference, body mass index, for each patient.

Incremental exercise test: All patients performed two incremental cardio-

pulmonary exercise tests (CPET), before and after 6 months of exercise training, using an electronically braked cycle ergometer (Lode Corival, the Netherlands). Three hours after a light breakfast, each subject performed a CPET (breath by breath spiroergometer device - Cortex Metalyzer 3B, Germany) up to exhaustion to determine his maximal V'O2, the anaerobic threshold (V'O2_AT) and respiratory compensation point (V'O2_RCP), which were used to determine the proper exercise intensity of the training sessions. After a 3-min warm-up period (20 W), charge increments of 15–20 $Wmin^{-1}$ were used, depending on the subject's weight and gender, in order that the exercise duration did not exceed 12 min. The blood pressure was measured using a sphygmomanometer (Boso-classico, Germany) every 2 minutes of incremental exercise test and 1 minute of recovery. The electrocardiogram was continuously recorded throughout and 5 minutes after the test, using a 12 lead stress electrocardiographic device (GE Medical System, Germany). Criteria for achieving a maximal effort test were a plateau in VO2 and/or plateau in ventilation together with a subjective judgment that the subject could not continue even after verbal encouragement. The CPET results were used for setting the proper effort intensity of the exercise programme, improve fat metabolism and increase the VO_2peak and endurance of each patient. For this, we divide the effort intensity according to HR at V' O2_AT and V'O2_RCP, into 4 training zones:

1. *Compensation Zone*: very low exercise intensity for warm up and cool down
2. *Extensive Endurance*: low intensity to start development of basic endurance
3. *Intensive Endurance* (in the anaerobic threshold range): medium intensity to maintain and develop basic endurance, and to increase aerobic performance
4. *Development Zone* (between anaerobic threshold and respiratory compensation point): high intensity within aerobic-anaerobic transition to increase aerobic capacity.

We used for the baseline exercise programmes both extensive and intensive endurance, and for intervals the development training zone.

Lifestyle intervention: General indications regarding healthy diet were set for each patient. On the entire period of study, all patients were supervised and encouraged to continue by a personal trainer (chosen from the master degree students from Physical Education and Sport Faculty, no more than 4 patients per trainer). The role of the personal trainer was to: teach the patient the correct running and breathing pattern, set the right workload for the fitness devices, analyze each training session using the Polar ProTrainer5 software and advise the patients (on each training session) regarding food choices and eating behaviour according to guidelines.

Exercise training: All subjects participated in a 6 months interval exercise training programme consisting in 3 times per week of 40 minutes at extensive and intensive endurance intensity zone, completed by 1 minute interval in development intensity zone for every 5 minutes of training. The programme took place mainly indoor using workload devices (cycle ergometer, cross-trainer, stepper, treadmill) which involves large muscle mass. Each training sessions was supervised, recorded, and computer analyzed using Polar RS800 heart rate monitors and a professional training software (Polar ProTrainer5 v.5.1, USA), in order to adjust the

intensity and duration of the exercise intervals.

Quality assurance: In order to ensure standardization of measurements taken, all equipment were calibrated and serviced as per the manufacturer's recommendations.

Ethical procedures: Our study obtained the approval of Local Research Ethics Committee. The study was conducted in accordance with the guidelines in the Declaration of Helsinki and was formally approved by the Ethical Committee of the west University of Timisoara. All participants in the research study received information about the protocol and written informed consent was acquired from all of them, by means of a signed declaration.

Statistics: Continuous variables are presented as mean and standard deviation. Change from baseline to follow-up within treatment groups were tested using paired t-test. The level of statistical significance was set at $p \leq 0.05$. The statistical analyses were performed with "GraphPad Prism v.5" for Windows.

RESULTS:

Using the paired t test to compare the data at baseline and at the end of the study, we noticed a significant improvement in mean weight, body mass index, waist circumference, systolic and diastolic blood pressure, fasting blood glucose, HDL cholesterol, LDL cholesterol and heart rate.

The cardiometabolic risk factors evolution after 6 months of intervenetion are presented in Table I and Figure1-6.

Table 1 Trend of cardiometabolic parameters after 6 months of lifestyle intervention.

Parameter	Baseline N: 53 patients (9 ♂)	After 6 months N: 53 patients (9 ♂)	P value
Weight (kg)	86±21	82.1±19.1	**<0.001**
BMI (kg/m²)	31.5±6.5	30.4±7.2	**0.022**
Waist (cm)	101±10.9	94±11.8	**<0.001**
SBP (mmHg)	131±10.9	120±9.5	**<0.001**
DBP (mmHg)	84.3±5.9	81.5±5.8	**0.002**
FBG (mg/dl)	90.1±14	77.6±9.4	**<0.001**
HDL (mg/dl)	30.1±10.9	36±12.5	**<0.001**
TG (mg/dl)	157± 2.5	140±53.3	0.123
LDL (cm²)	114 ± 9.6	103±28.4	**0.013**
HR (b/min)	77 ±10.9	68 ±18.6	**0.003**

Values are presented as mean with standard deviation.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL: HDL cholesterol; TG: triglycerides; LDL: LDL cholesterol; HR: heart rate

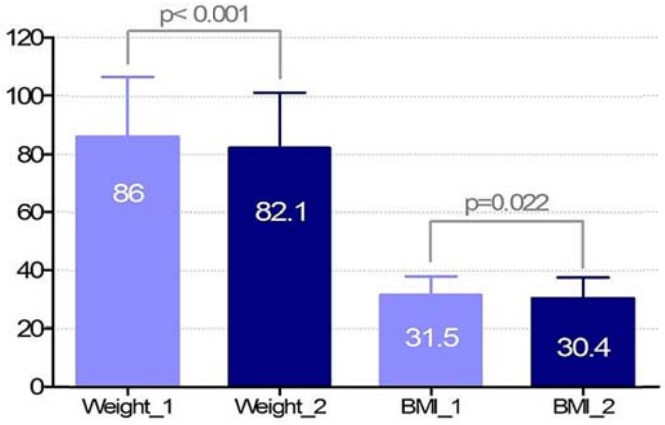

Fig.1 Trend of weight after 6 months of lifestyle intervention. Values are presented as mean with standard deviation. Weight_1: weight at baseline; Weight_2: weight after 6 months of lifestyle intervention; BMI_1: body mass index at baseline; BMI_2: body mass index after 6 months of lifestyle intervention.

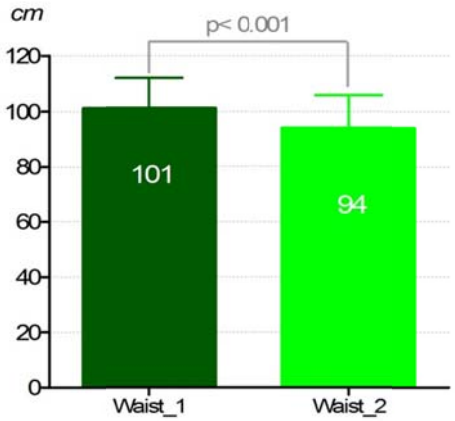

Fig.2 Trend of waist circumference after 6 months of lifestyle intervention. Values are presented as mean with standard deviation. Weight_1: waist circumference at baseline; Weight_2: waist circumference after 6 months of lifestyle intervention.

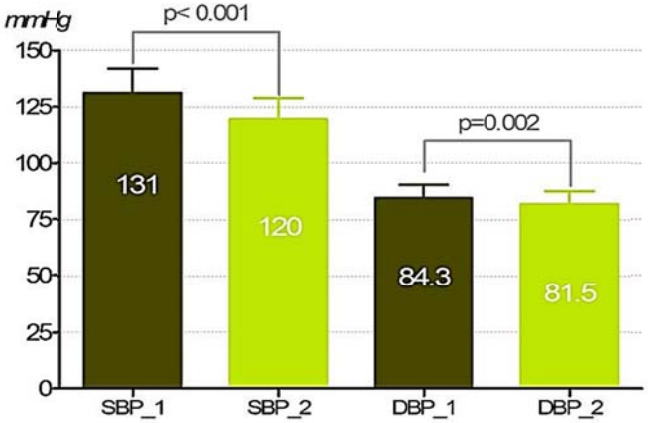

Fig.3 Trend of blood pressure after 6 months of lifestyle intervention. Values are presented as mean with standard deviation. SBP_1: systolic blood pressure at baseline; SBP_2: systolic blood pressure after 6 months of lifestyle intervention; DBP_1: diastolic blood pressure at baseline; DBP_2: diastolic blood pressure after 6 months of lifestyle intervention.

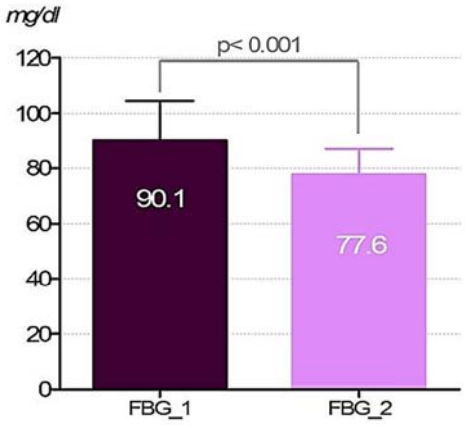

Fig.4 Trend of fasting blood glucose after 6 months of lifestyle intervention. Values are presented as mean with standard deviation. FBG_1: fasting blood glucose at baseline; FBG_2: fasting blood glucose after 6 months of lifestyle intervention.

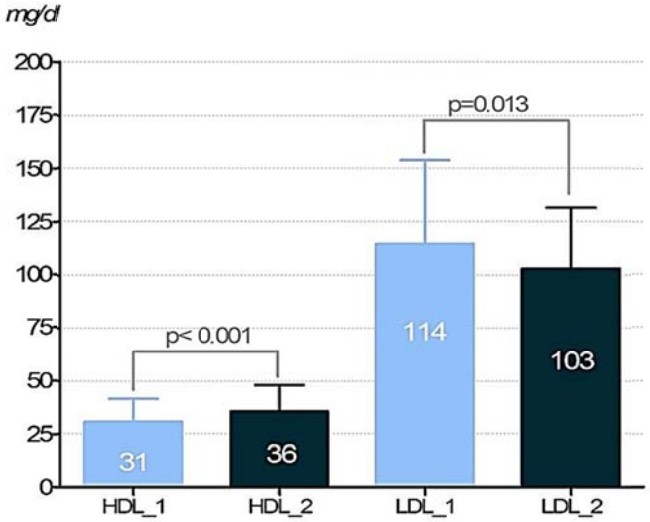

Fig.5 Trend of HDL cholesterol after 6 months of lifestyle intervention. Values are presented as mean with standard deviation. HDL_1: HDL cholesterol at baseline; HDL_2: HDL cholesterol after 6 months of lifestyle intervention; LDL_1: LDL cholesterol at baseline; LDL_2: LDL cholesterol after 6 months of lifestyle intervention.

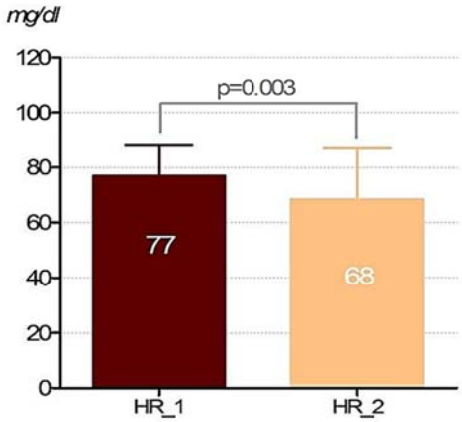

Fig.6 Trend of resting heart rate after 6 months of lifestyle intervention. Values are presented as mean with standard deviation. HR_1: resting heart rate at baseline; HR_2: resting heart rate after 6 months of lifestyle intervention.

DISCUSSIONS:

Recent data from a prospective study, describe a nearly 70% reduction in the number of young obese patients treated with an intensive lifestyle intervention for 1 year. The intervention included weekly 1-hour nutritional therapy, 60-minute training sessions, three times per week and weekly group counseling with a trained psychologist.[30]

Our study demonstrated a significant benefit in reduction of weight (almost 4 kg), body mass index (1.1 kg/m^2) and waist circumference (7 cm), which we consider to be important, especially because of the potential of maintaining the gained weight due to changes in bad dietary habits and increase in physical activity. This treatment is obviously not practical, but serves to show that it is successful if adopted. Previous studies demonstrated that for reducing modifiable cardiometabolic risk factors in patients with metabolic syndrome, a prescribed and supervised exercise programme, including both aerobic and resistance training, is more effective than conventional exercise counselling.[31]

A meta-analysis of randomized controlled trials concluded that dynamic aerobic endurance training reduces resting systolic blood pressure (SBP) and diastolic blood pressures (DBP) by 3.0 mmHg, and daytime ambulatory blood pressure by 3.3 mmHg.[32] A recent study reported a substantially decreased of heart rate and blood pressure, both at rest and during exercise in elderly men and women, after nine weeks of aerobic interval training (twice a week, 30 minutes sessions on cycle ergometer).[33]

In our study, lifestyle intervention focused on exercise training had a significant effect on the down regulation of SBP and resting heart rate. Our findings demonstrated that the benefit of lifestyle intervention is similar in younger sedentary patients with mild elevated blood pressure, especially regarding SBP (11 mmHg) and resting heart rate (9 b/min).

A recent study assessed the influence of dietary counseling and physical activity (three times a week), over a 24-week period on 64 obese young patients with metabolic syndrome. The study demonstrated a reduction in BMI and in waist circumference, with greater responses in males.

It was also noted in this study that, even in youth who did not lose weight, there was an improvement in insulin sensitivity through physical activity, probably resulting from metabolic conditioning.[11, 34]

Dyslipidemia in children and adolescents has become a frequent clinical condition, especially due to the increase in overweight and obesity prevalence in this age range.[35] The present study demonstrated also a rationale bases for the role of lifestyle intervention in the down regulation of blood lipids; we noticed an important increase in HDL cholesterol (with 6 mg/dl), without any contribution of medication (such rosuvastatin, knowing to produce an HDL cholesterol elevation after administration). We also noticed a moderate increase of LDL cholesterol (with 11 mg/dl), most probably due to diet changes following persistent advice provided during the intervention.

The alarming rise in the number of youth who are developing symptomatic diabetes and risk factors for cardiovascular disease calls for urgent action. In addition to increasing our knowledge of the causes, timing, and outcomes of adverse events that lead to cardiovascular disease in adulthood,

health care providers caring for youth must adopt effective screening tools, encourage healthy lifestyles for all children and their families while implementing the most timely and effective treatment for those at highest risk.[36]

CONCLUSIONS:

Intensive lifestyle intervention programmes can be the key for better results in metabolic syndrome management of young patients. The study is a clear demonstration that using close supervision of the lifestyle intervention programme, we can improve the cardiometabolic risk in young patients with metabolic syndrome.

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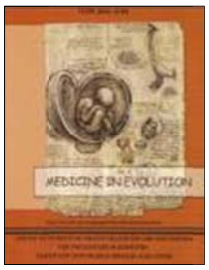
THE QUANTITATIVE ANALYSIS OF CORONARY INVOLVEMENT IN PATIENTS WITH AORTIC VALVE SCLEROSIS



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ABSTRACT

Aortic valve sclerosis and atherosclerosis were proven to be similar regarding their histo-pathological aspects, leading us to question if degenerative aortic lesion and atherosclerosis are different manifestations of the same disease.

Our aim was to investigate whether coronary artery disease is more severe in the presence of aortic sclerosis.

Means and method: *we investigated 123 patients with indication of angiographic evaluation that were also assessed echocardiographically, biologically and metabolically.*

Results: *In symptomatic coronary patients, aortic valve sclerosis is related with the severity of coronary artery disease. Echocardiography should be used for screening of degenerative valvular lesions, thus improving risk stratification among symptomatic patients for coronary artery disease.*

Key words: *aortic valve sclerosis, atherosclerosis, coronary artery disease, echocardiography.*

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INTRODUCTION

Aortic valve sclerosis and atherosclerosis have a strong correlation, emerging from the similarities regarding the histo-pathological aspects. Aortic valve sclerosis is a nonspecific degenerative process, characterized by the thickening/calcification of the aortic leaflets, without impairing the blood flow through the aortic orifice [1]. The initial lesion defining the aortic valve degeneration is endothelial dysfunction, followed by the remodeling of the valvular endothelium. Therefore, the degenerative lesions will be found on the aortic side of the leaflets, where blood flow is most turbulent [2].

AIM AND OBJECTIVES

An interesting question arises: could aortic valve sclerosis and atherosclerosis be different manifestations of the same disease and is aortic valve sclerosis a marker of the severity of coronary atherosclerotic lesions?

With this study we want to analyze the severity of coronary artery disease (quantitative measurement) in the presence of aortic degenerative lesions, i.e. aortic sclerosis.

MATERIAL AND METHODS:

The study population was retrospectively selected from the subjects referred to the Echocardiography laboratory at the Cardiovascular Disease Institute, Timisoara.

All the subjects had indications of invasive arterial evaluation, i.e. angiocoronarography, based on their symptoms (angina pectoris), on the electrocardiograms or the exercise stress testing. All patients were in sinus rhythm. We have excluded patients with acute coronary symptoms, congenital heart disease, renal failure (defined by a serum creatinine level above 2mg/dl) and patients with poor ecographic window. We have enrolled 123 patients; all the data were collected from the patients' medical charts and the confidentiality rules were followed. The blood pressure and heart rate were taken into consideration on admission. The blood tests were taken within 24 hours form admission. All the definitions and the classifications were made according to the European Society of Cardiology and the practical European and American guidelines.

Body mass index 25-29kg/m² = overweight; 30-34 kg/m²=grade I obesity; 35-39 kg/m²= grade II obesity, >40 kg/m²= grade III obesity. Hypertension: systolic blood pressure at rest > 140mmHg, diastolic blood pressure at rest > 90mmHg or patients undergoing antihypertensive treatment. Hypercholesterolemia: total cholesterol > 200mg /dl or patients undergoing statin treatment. Type II diabetes mellitus: fasting plasma glucose > 126mg/dl, patients known to be diabetic or undergoing oral/insulin therapy.

Echocardiography: all the patients were evaluated using the General Electrics Vingmed Ultrasound System, a Vivid E9 and Vivid 7 machines, MS5 and MS4 transducers.

The aortic valves were evaluated from several views: parasternal long axis, parasternal short axis-section at the level of the great vessels, apical 3 and 5 chambers. 2D and M-mode were

used to assess the aortic valve appearance, the aortic orifice aria and the aortic valve opening. Continuous and pulsed Doppler techniques were used to evaluate velocities through the aortic orifice, maximum and medium aortic transvalvular gradients. The severity of the aortic lesions was quantified according the ACC/AHA Guidelines 2006 [3] and EAE/ASE 2009 [4] as follows:

- ✓ *Aortic sclerosis*: thickening of at least one of the three aortic leaflets (high echogenity); normal transvalvular velocities and pressure gradients (<2,5m/sec) [5]
- ✓ *Mild aortic stenosis*: functional area > 1.5cm²; planimetric orifice > 0.85 cm² / m² body surface; Vmax 2.6-2.9 m/sec; Pmed < 20mmHg
- ✓ *Moderate aortic stenosis*: functional area 1- 1.5cm²; planimetric orifice 0.60-0.85 cm²/ m² body surface; V max 3-4 m/sec; Pmed 20-40mmHg;
- ✓ *Severe aortic stenosis*: functional area <1cm²; planimetric orifice < 0,60 cm²/m² body surface; Vmax >4 m / sec; Pmed >40mmHg.

Table 1 the Gensini Score the Score was multiplied by a factor, according to the coronary anatomy, as explained in table 2.

Severity Score	Narrowing of the coronary lumen (%)
1	25
2	50
4	75
8	90
16	99
32	100

Table 2 The multiplication of the Gensini Score

Left coronary artery:	Left main		X 5
	Proximal left coronary descendent		X 2.5
	Medial		X 1.5
	Distal		X 1
		First Diagonal	X 1
		2nd Diagonal	X 0.5
		Apical	X 1
Right coronary artery:	Proximal Circumflex artery		X 2.5
	Marginal obtuse		X 1
	Proximal segment		X 1
	Medial segment		X 1
	Segment distal		X 1
	Posterior descendent		X 1

The global ventricular systolic function was evaluated using the ejection fraction assessed using the end diastolic and end systolic volumes, calculated with the modified Simpson's formula [6, 7]. Mitral annulus calcification was assessed using 2D Echo, parasternal long axis view and apical 4 chamber view.

Angiocoronarography was performed using a standard angiograph, Siemens Coroskop, in order to detect atherosclerotic lesions of the coronary arteries.

Coronary artery disease was considered at a narrowing of more than 50% of one of the coronary arteries: right coronary artery, circumflex artery, left anterior descending (medial or distal), diagonal arteries, left posterior descending or marginal branches-monovascular disease. Bivascular disease was considered when 2 coronary arteries were involved or proximal left anterior descending. Trivascular disease

was considered when three of the coronary arteries were involved or the left main (stenosis > 50% of the left main). For the quantitative analysis of the coronary lesions we used the Gensini score [8], as seen in table 1.

Statistical analysis: The statistical analysis used the Epi Info program, the 6.0.2001 version and the SPSS program, the 18.2010 version. The statistically significant border was considered for a $p<0.05$, and $p<0.01$ was considered to be strongly significant.

For the parametric data we applied the t student test and for the non-parametric ones we used the Mann -Whitney test, Kruskal-Wallis test, and for the categorical data we applied the chi-square test.

RESULTS:

The baseline characteristics of our group are shown in table 3.

Patients with coronary artery disease had a higher prevalence of aortic valve sclerosis compared to that without coronary artery disease (75.8% vs. 24.2%; $p < 0,005$).

The percentage of coronary was 17.07% patients with tri-vessel disease, 27.64% with two-vessel disease, 27.74% with single-vessel disease, 27.64% without significant coronary artery disease and 10.57% patients had left main disease.

Table 3 the baseline characteristics of the analyzed group

Average age (years)	66,20 ± 8,11
Male sex (%)	67,50
Arterial hypertension (%)	85,40
Hypercholesterolemia (%)	36,40
Type II diabetes mellitus (%)	48,78
Body mass index (kg/mp)	28,48 ± 4,67
Coronary artery disease (%)	72,40

The Gensini score had a mean value of 35.47+/- 32.9, a median of 26 and a module of 7. Thus, 50% of the enrolled subjects had values less than 26 and 50% had a Gensini score higher than 26. The mean value of the Gensini score was different, according to the sub-group: no coronary artery disease (9.38+/-18.32), single-vessel disease (25.82+/-18.01), two-vessel disease (45.38+/-28.67) and trivessel disease (77.29+/29.52). We applied the Kruskall Wallis test in order to see if the Gensini score varies according to the severity of the coronary artery disease, and we obtained a positive result ($H(3)=74.92$; $p<0.001$): figure 2.

The Gensini Score was significantly higher in patients with left main stenosis versus those without left main atherosclerotic disease ($M=62.08$ vs. $M = 32.33$, $U = 291.5$; $p<0.001$): figure 3. We also analyzed the behavior of the particularities of the coronary artery disease in the presence of aortic valve sclerosis: in patients with degenerative aortic valves, the Gensini score was significantly higher ($M=44.66$) than in those without aortic valve sclerosis ($M=30.20$), $U=1486.5$, $z=-2.04$; $p<0.05$; $r=0.18$: figure 4.

The aortic valve sclerosis frequency in regard to the 3 subgroups of Gensini score was higher in patients with

high Gensini scores: 41.5% in the subgroup with Gensini score below 30, 58.3% in the subgroup with Gensini score between 31-60 and 63.6% in the sub group with Gensini score higher than 60: fig 5.

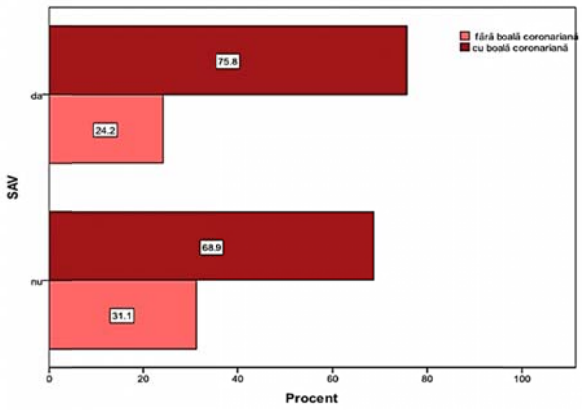

Fig.1 Prevalence of aortic valve sclerosis in relation with coronary artery disease.

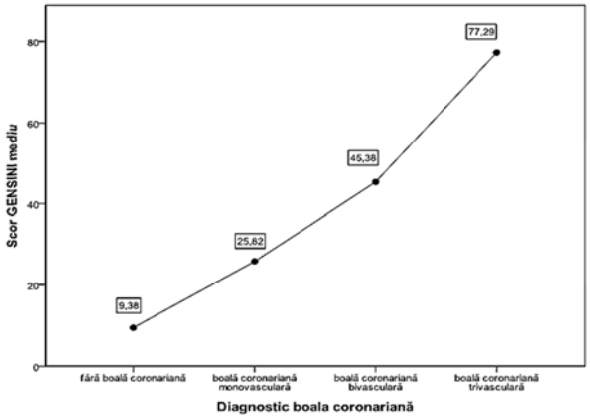

Fig.2 The mean Gensini score and the severity of the coronary artery disease.

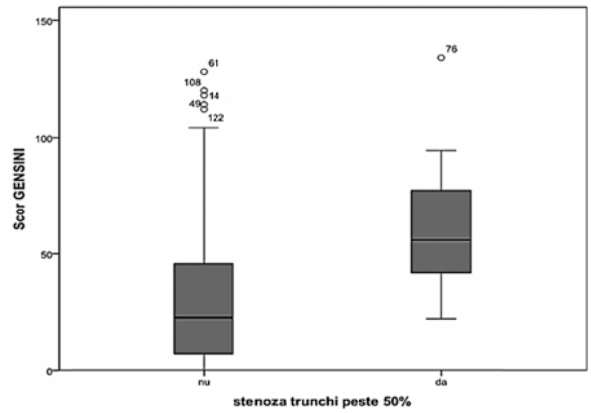

Fig.3 Left main atherosclerotic disease and the Gensini score.

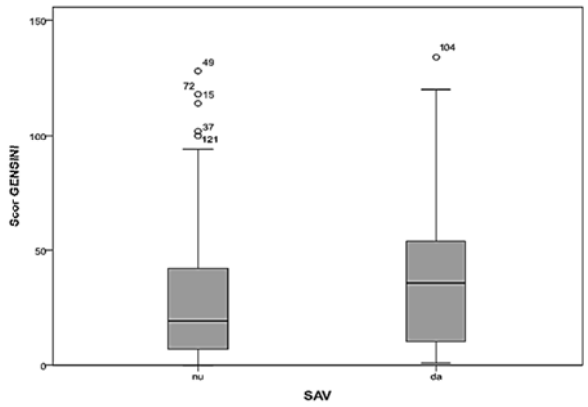

Fig.4 The Gensini score and coronary artery disease.

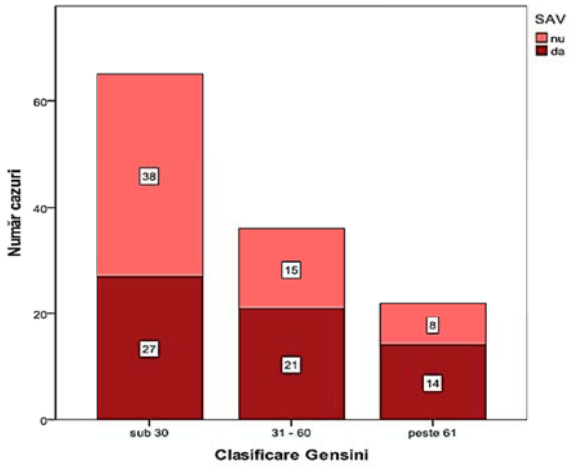

Fig.5 The frequency of aortic valve sclerosis in regards to the Gensini score severity.

DISCUSSIONS:

Is coronary artery disease associated with aortic valve sclerosis? So far, there is not enough data to relate the severity of coronary artery disease to aortic valve sclerosis. Our analysis has shown, as several studies done before, that in the presence of aortic valve sclerosis coronary lesions are more severe. The Gensini score remains a viable marker of the severity of coronary artery disease [9].

Our study stands proof that symptomatic coronary patients have higher prevalence of aortic degenerative lesions and, in the presence of aortic valve sclerosis, the Gensini score is higher. Therefore, our findings are consistent with those stating that aortic valve sclerosis could be a marker of vascular atherosclerotic disease that can be used for cardiovascular risk stratification.

Shu Jian et al [10] report that aortic valve sclerosis had sensitivity, specificity and positive and negative predictive value as follows: 63.8, -71.3, -61.7 and 73.1. Luca Conte et al [11] have analyzed 93 consecutive cases of patients with angina-like pain and indication of angiocoronarography and have found that aortic valve sclerosis is an independent predictor of coronary artery disease among subjects with thoracic pain.

Hiroto Utsunomya et al [12] report a prevalence of 38% of coronary lesions among patients with aortic valve sclerosis and suspicion of coronary artery disease, evaluated by using angio-CT imaging.

Our research has also shown that the Gensini score is significantly different according to the severity of the coronary lesions: single/ multi-vessel disease. Data for the CASS Study [13] identify 3 main indexes for evaluating the vascular prognostic: the number of coronaries affected by the atherosclerotic process, the number of proximal segments affected by atherosclerosis and the wall motion index of the left ventricle.

Peppes G et al [14] have underlined the impact of traditional cardiovascular risk factors (male gender, smoking, diabetes mellitus and hypertension) on the Gensini score, thus proving not only their ethyo-pathogenical involvement in coronary artery disease, but also their relation with the severity of the coronary lesion.

Our study, much to our surprise, showed no significant association between the Gensini score and the traditional cardiovascular risk factors, mitral and aortic annulus calcification. There are several possible hypotheses: most of the patients enrolled were high risk patients due to the cumulative effect of many traditional risk factors, regardless of aortic valve sclerosis; even though most of them were currently under medication according to the ESC Guidelines [15], only 1/5 of them have achieved a cardio-metabolic status offering vascular protection.

Study limitations:

Our study is an observational study, performed at one point of the vasculo-valvular degenerative process.

We have enrolled symptomatic patients with indication of coronarograhy, thus overestimating the prevalence of coronary artery disease among patients with aortic valve sclerosis.

Nevertheless, the echocardiographic screening for aortic sclerosis was not performed among asymptomatic subjects.

CONCLUSIONS:

In symptomatic coronary patients, aortic valve sclerosis is related with the Gensini score and the severity of coronary artery disease. Echocardiography should be used for screening of degenerative valvular lesions, thus improving risk stratification among symptomatic patients for coronary artery disease.

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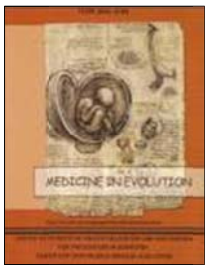
CLINICAL IMPLICATION OF AMBULATORY ARTERIAL STIFFNESS FOR PATIENTS WITH CORONARY ARTERY DISEASE



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ABSTRACT

The ambulatory arterial stifness index (AASI) has been proposed as a new measure derived from 24h-ambulatory blood pressure monitoring (ABPM) for the evaluation of arterial stiffness.

***Aim and objectives**: the present study aimed to investigate whether AASI reflects arterial stiffness in patients with coronary artery disease by comparing AASI and 24h-pulse pressure (PP) with carotid-radial puls wave velocity (PWV-CR), the proposed gold standard of arterial stiffness.*

***Material and methods**: we have analysed 214 consecutive symptomatic patients who underwent coronary angiography. Clinical, laboratory and echocardiographyc variables, 24h-ABPM and PWV-CR (Complior SP device) were obtained. AASI was calculated as 1-the regression slope of 24-h diastolic on systolic blood pressure.*

***Results**: in all subjects AASI correlated with PWV-CR (r=0, 925, p<0,001). This association was strongly significant in patients with single-vessel disease (r=0.942, p<0.001), two-vessel disease (r=0.90, p<0.001) and three-vessel disease (r=0.88, p<0.001). We found a positive correlation between AASI and both factors of arterial function: 24h-PP (r=0.79, p<0.001) and mean arterial pressure (r=0.49, p<0.001).*

***Conclusions**: AASI had a significant relationship with 24h-PP in the coronary artery disease patients. The correlation with 24h-PP was stronger for AASI than for PWV-CR. AASI may improve the risk stratification based on ambulatory blood pressure monitoring.*

***Key words:** ambulatory arterial stifness, atherosclerosis, coronary artery disease, echocardiography.*

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INTRODUCTION

The direct implication of arterial stiffness as an independent risk factor in cardiovascular pathology has already been well established [1]. The structural alterations of the arterial wall lead to arterial stiffness, which will trigger alterations of the arterial compliance, distensibility and elasticity.

During the past 10 years, many researchers have focused on finding surrogate markers of arterial function [2, 3]: a) markers of arterial stiffness: pulsed wave velocity (PWV), rigidity index; b) arterial compliance indexes: systemic arterial compliance, arterial distensibility; c) composite marker for the analysis of the reflected waves and systemic arterial stiffness: the systolic augmentation index (AIx).

The ambulatory arterial stiffness index (AASI) is an indirect measure of arterial stiffness, which reflects the dynamic relation between diastolic and systolic blood pressure throughout the day [4]. What do we know so far about this matter [5]?

Aortic pulse wave velocity is the gold standard for the assessment of arterial stiffness, but its measurement requires special equipment and trained observers;

The *AASI* is an indirect measure of arterial stiffness which can be easily determined from routine 24h-ambulatory blood pressure recordings,

Arterial *PWV* and *AASI* predict cardiovascular outcomes. AASI is especially predictive of stroke.

AIM AND OBJECTIVES

- To investigate whether AASI reflects arterial stiffness in patients with coronary artery disease by comparing AASI and 24h-pulse pressure (PP) with carotid-radial pulse wave velocity (PWV-CR), i.e. the proposed gold standard of arterial stiffness.

MATERIAL AND METHODS:

We enrolled 214 patients who underwent coronary angiography between 2008-2010 for the assessment of suspected coronary artery disease. The exclusion criteria were: previous myocardial infarction, previous percoutaneous coronary interventions, atrial fibrillation, conduction disturbances and known peripheral arterial disease. All patients were on anti-angina or antihypertensive medication before enrolling in this study. All vasodilatators such as nitrates or ACE inhibitors were withdrawn for at least 24 hours before the measurements were done. Antipleatlet agents, e.g. Aspirin, Clopidogrel were not withdrawn. All patients provided written informed consents before entering the study.

Angiographic protocol: the severity of coronary artery disease was assessed according to a vessel score: the number of coronary vessels with significant stenosis: more than 50% lumen narrowing. Left main stenosis was scored as a two-vessel disease.

Carotid-radial PWV was recorded using Complior SP [6]. Two sound probes were placed simultaneously over the right carotid and radial arteries. The probes were adjusted until good quality pulse waveforms were generated, 20 of which were captured for future analysis. The velocity (m/s) is gi-

ven by dividing the surface distance by the time between the 2 pulse upstrokes.

Ambulatory blood pressure monitoring: we programmed the recorders to obtain blood pressure readings every 30 minutes from 8:00 am until 10:00 pm and every 60 min from 10:00 pm until 08:00 am. From the 24-hours recordings we computed for each participant the regression slope of diastolic on systolic blood pressure. AASI was defined as 1 minus the regression slope. The stiffer the arterial tree, the closer the regression slope and AASI are to 0 and 1, respectively.

Biochemical tests: all blood samples for the measurements of lipid profile and glucose levels were obtained immediately after clinical evaluation, in the fasting state. The cardio-metabolic risk was defined according to the European Society of Cardiology Guidelines [7]; the definition of the metabolic syndrome was made after The International Diabetes Federation among adults in the USA [8].

Statistical analysis

Data were stored using the Microsoft Excel 97-03 version and analyzed using the 18th version of PASW, 2010. The statistically significant border was considered for a $p<0.05$, and $p<0.01$ was considered to be strongly significant. We applied the following statistical tests: the concordance test, Mann-Whitney test, t student test, ANOVA test, Pearson correlations, Kendall correlations, ROC curve and the multiple regression test.

RESULTS:

The prevalence of coronary artery disease defined by the angiographic criteria was 39.25%.

The demographic characteristics of the 84 coronary patients are presented in table 1. Mean age was 65.90+/-7.41 years and 69% of the subjects were males. The metabolic profile was characterized by the pro-atherogenic components, i.e. LDL-cholesterol and fasting plasma glucose (table 2). Metabolic syndrome-IDF was encountered in 54. 80% of the subjects.

Hemodynamic behavior was individualized by the presence of the 2 components that define arterial stiffness: mean value for 24 hours systolic blood pressure was 150.93+/-24.01 mmHg; mean value of pulsed pressure was 67.49+/-15.88mmHg (table 3).

Table 1 Demographic characteristics

Age (years)		**65.90±7,41**
Males		69
Hypertension		81
Type II diabetes mellitus		52.40
Hypercholesterolemia		64.30
Metabolic Syndrome-IDF		54.80
Smokers		58.30
Coronary artery disease	single vessel disease	51.19
	two vessel disease	32.14
	three vessel disease	16.66

Mean ±SD, % group

Table 2 Metabolic risk profile

		Fasting plasma glucose	TC	TG	HDL	LDL	TG/HDL
N	Valid	214	214	214	214	214	214
	Missing data	0	0	0	0	0	0
Mean		144.62	187.58	127.78	39.735	121.259	3.4456
Median		111.00	181.50	108.50	39.000	118.590	2.9300
Mode		98	150	80	33.0	125.0	2,10[a]
Std. Deviation		73.246	50.043	59.027	8.5115	45.8537	2.06743
Minimum		73	98	50	22.0	43.0	1.13
Maximum		376	311	369	67.0	240.3	12.60

Table 3 Hemodynamic behavior

		24h-Systolic blood pressure	24h-diastolic blood pressure	24h-PP
N	Valid	214	214	214
	Missing data	0	0	0
Media		150.93	83.50	67.49
Median		150.00	80.00	65.00
Mode		120	80	60
Std. Deviation		24.015	13.271	15.888
Minimum		110	60	40
Maximum		200	110	105

AASI and PWV - the gold standard of evaluating arterial stiffness:

In all of subjects AASI closely correlated with PWV-CR: r = 0.925, p < 0.001 (fig.1). This association was strongly statistically significant for single-vessel disease (r=0.942, p<0.001), two-vessel disease (r=0.90, p<0.001) and three-vessel disease (r=0.88, p < 0.001). AASI and the components of arterial dysfunction: 24h-PP and 24h-TAM: we found a statistically significant correlation between AASI values and 24h-PP(r=0.79, p<0.001); the association was very strong (fig. 2).

When we analyzed the relation between AASI and 24h medium systolic blood pressure, we found a positive significant correlation among coronary patients, r=0.49, p<0.001, the size of the correlation was r^2 =0.24, meaning a weak correlation (fig. 3).

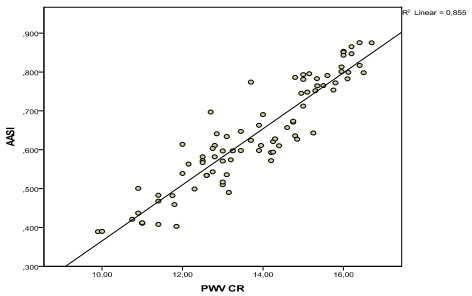

Fig.1 Relation between PWV-CR and AASI

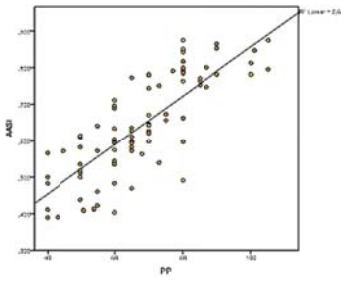

Fig.2 The relation between PP and AASI

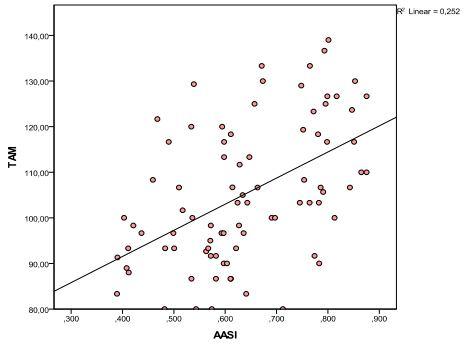

Fig.3 Relation between AASI and 24hMBP

Cardio-metabolic risk factors: we found no significant corelation between medium PWC-CR and diabetes mellitus, metabolic syndrome-IDF (p>0.05). Among diabetic patients with coronary artery disease, there was no corelation between PWV-CTR and HbA1c (p>0.05).

DISCUSSIONS:

AASI, a measure of the dynamic relation between diastolic and systolic blood pressure throughout the day reflects the arterial stiffness. Our study demonstrates a strong correlation between AASI and the two components of the blood pressure: the static component, mean arterial pressure and the pulsated component, pulse pressure.

Increased collagen/elastin ratio that characterizes vascular pathology may lead to increase in both stiffness and stiffening. This pressure-independent structural aspect may explain why AASI positively correlates with PWV and express arterial stiffening but not stiffness. Several investigators built part of their argument on the correlation of AASI with pulse pressure [9, 11]. In different clinical settings AASI was found to be an independent predictor of stroke [12]. The population-based Rotterdam study [13] was strongly associated with atherosclerosis at a variaty of sites on the vascular tree. However, there is little data on the relationship between PWV and the extent of coronary artery disease as determined by angiography.

We observed a strong and independent association between the manifestations of increased arterial stiffness, as derived from the noninvasive carotid-radial PWV and the extent of the coronary artery disease, as assessed by invasive coronary angiography. Arterial stiffness identified by carotid-radial PWV may predict the severity of coronary artery disease after adjusting for other cardiovascular risk factors [14]. Syeda et.al [15] has reported that patients with multivessel disease had a significant reduction in small arterial elasticity. We also found that the PWV-CR was higher in patients with multivessel coronary disease than in patients with single vessel coronary disease.

Increased arterial stiffness is associated with several risk factors, including age, hypertension and diabetes mellitus [16]. Cameron J.D et al. have reported that increased LDL cholesterol levels are associated with aortic PWV [17]. Conversely, Benetos et. al has found no significant correlation between total

plasma cholesterol level and the aortic PWV [18]. Our findings showed similar results: in the extent of the coronary artery disease the cardiometabolic risk doesn't have a bigger influence on the PWV-CR and AASI relationship. One potential limitation of our study was that the study group consisted of only symptomatic patients who reffered for coronary angiography.

CONCLUSIONS:

The developpment of AASI represents a theoretically attractive mean of easily exploring arterial stiffness without the use of dedicated, operator-dependent equipment. AASI had a significant relationship with 24h-PP in the coronary artery disease patients. The correlation with 24h-PP was stronger for AASI than for PWV-CR. AASI may improve the risk stratification based on ambulatory blood pressure monitoring.

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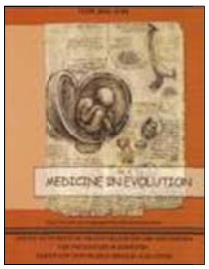
NEW METHODS OF LABORATORY TESTING OF PLATELET AGGREGATION TO DETECT THE ASPIRIN AND CLOPIDOGREL RESPONDER STATUS



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ABSTRACT

In the last decades, the issue of "aspirin and clopidogrel resistance" was a provocative theme in the medical literature [1, 4]. So far, there are a lot of studies published in this area, but its definition, diagnosis, ethiology and clinical implications remain uncertain. [1, 5]

Key words: *antiplatelet treatment, aspirine, clopidogrel, thrombosis.*

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Definition of ANTIPLATELET RESPONSE VARIABILITY or "*RESISTANCE*"

The term of "resistance" to a drug should be used when the drug is unable to hit its pharmacological target, due to inability to reach it (consequence of different factors: reduced bioavailability, negative interaction with other drugs, *in vivo* inactivation) or to alteration of the target [1, 5]. Based of this definition, the term of resistance to aspirin should be limited to situations in which aspirin is unable to inhibit COX-1-dependent thromboxane A_2 (Tx A_2) production and, consequently, TxA_2-dependent platelet functions [5]. Multiple signaling pathways mediate platelet activation and the occurrence of thrombotic events.

In consequence, a treatment strategy directed against a single pathway cannot be expected to prevent the occurrence of all events [6]. But thrombosis results from multiple signaling pathways, and therefore treatment failure alone is not sufficient evidence of drug "resistance".

The optimal definition of "resistance" or nonresponsiveness to an antiplatelet agent might be evidence of persistent activity of the specific target of the antiplatelet drug [7, 8].

Aspirin:

Aspirin acetylates a serine moiety present in cyclooxygenase-1 (COX-1). It irreversibley inhibits the COX-1- dependent synthesis of thromboxane A2 (T x A2), which is essential for the full aggregation response of platelets [9]. Aspirin resistance is infrequent among patients undergoing elective PCI who are treated with 325 mg daily as assessed by arachidonic acid-induced platelet aggregation with LTA [10, 11]. The incidence of aspirin resistance seems to be highly assay-dependent and is rare when determined by methods that directly indicate the activity of COX-1 [12, 13]. Treatment non-compliance can also affect the identification of aspirin "resistance" [10, 11].

Aspirin resistance also might to be associated with concomitant clopidogrel "resistance" [13, 14].

Patients identified as aspirin and clopidogrel resistant have exhibited high platelet reactivity to collagen in addition toADP and arachidonic acid stimulation [13, 15].

Recent studies suggest a generalized high-platelet-reactivity phenotype that might be associated with an increased risk for ischemic events.

Clopidogrel:

The active metabolite of Clopidogrel is responsive of irreversibly inhibition of $P2Y_{12}$ receptor, because of the new covalent disulfide bond; in cases of non-responder patients there are evidence of posttreatment $P2Y_{12}$ reactivity. For aspirin, the diagnosis of resistance would use a laboratory technique that detects residual activity of cyclooxigenase COX-1. The proposed mechanisms of antiplatelet response variability / resistance were described in a large number of publications [1-5, 7].

The status of "clopidogrel non-responder" was mainly detected using LTA in a large number of studies and using ADP as an agonist [6, 8-24, 26, 36]. Also different methods were used to identify the clopidogrel nonresponsiveness: point-of-care assays, VASP phosphory-

lation, flow-cytometric measurement of activation-dependent receptor expression after ADP stimulation [16, 17-20, 21-25].

The therapeutic response to clopidogrel has been most studied in patients undergoing PCI, and numerous studies have reported wide variations in response to therapy and rates of nonresponders of 5% to 44% [6-19]. Determination of VASP phosphorylation has also shown high residual reactivity of the $P2Y_{12}$ receptor in selected patients treated with clopidogrel [26]. Differences in the prevalence of non-responder status in different studies might be related to differences in definitions (relative versus absolute change in aggregation, maximum versus late aggregation), laboratory methods, and different dosages. Clopidogrel response variability has multiple proposed etiologies.

Laboratory assessment of platelet responsiveness to aspirin can be divided in COX-1–specific and COX-1-nonspecific. Arachidonic acid (AA) stimulation of platelet aggregation depends directly on COX-1 activity.

In vivo production of TxA_2 is assessed by measurement of stable metabolites via enzyme-linked immunoassays.

Adenosine diphosphate (ADP)- and collagen-stimulated aggregation are COX-1- nonspecific methods. Aggregation occurs through COX-1-independent and-dependent pathways after stimulation using latter agonists [6]. (Table 1.)

Table 1 Laboratory assessment of platelet responsiveness to aspirin

COX-1 specific methods	**COX-1 Non-Specific methods**
1.AA- Induced Platelet Aggregation -LTA (PRP,whole blood) -TEG (whole blood) -VerifyNow (whole blood) - Multiplate	1.ADP and Collagen-Induced Platelet Aggregation -LTA
2.Thromboxane Metabolite - Serum - Urine	2. Shear, Collagen/epinephrine-induced Platelet Aggregation -PFA-100

Table 2 Laboratory assessment of Clopidogrel responsiveness

1.	Receptor reactivity- intracellular signaling downstream from the $P2Y_{12}$	- Flow cytometry - VASP
2.	Receptor expression	- Flow cytometry - P-selectin
3.	Aggregation	- LTA - MEA - VerifyNow - Thrombelastography

Laboratory assessment of Clopidogrel responsiveness comprises different methods. ADP stimulates distinct receptors ($P2Y_1$ and $P2Y_{12}$) that are linked to specific signaling pathways. Response can be measured by:

1. Receptor reactivity; intracellular signaling downstream from the $P2Y_{12}$ receptor is measured by flow cytometry that assesses phosphorylation of vasodilator-stimulated phosphoprotein (VASP) with monoclenal antibodies; the $P2Y_{12}$ is coupled by a Gi protein to adenylyl cyclase which activates protein kinaseA (PKA).

2. Activation – dependent receptor expression (active glycoprotein GP IIb / IIIa and P-selectin) identified by monoclonal antibodies (Y) with flow cytometry.
3. Aggregation determined by light transmittance aggregometry (LTA), multiple electrodes aggregometry (MEA- whole blood platelet aggregation assessed with the Multiplate analyzer), aggregation of platelets with fibrinogen-coated beads (VerifiNow), or measuring the contribution of platelet aggregation to total platelet fibrin clot strength by thrombelastography. (Table 2)

Methods used to measure platelet function during antiplatelet treatment

In vitro platelet function was measured in aspirin-treated patients' using a number of functional assays, which were criticized because they do not reproduce the physiological conditions that determine the platelet aggregates development *in vivo*. None of these tests displays sufficient specificity for measuring the effects of aspirin on platelet function. In case of light- transmission aggregometry (LTA), despite of using the arachidonic acid, the precursor of TxA_2, as agonist of platelet aggregation, the results obtained with this technique may overestimate the prevalence of aspirin resistance [1].

Platelet-released factors

Methods that measure directly the capacity of platelets to synthesize TxA_2 are preferable. The urinary levels of the TxB_2 metabolite, 11-dehydrothromboxane B_2, represent a time-integrated index of TxA_2 biosynthesis *in vivo* [5]. The urinary level of this metabolite reflects systemic TxA2 formation, which largely occurs in the platelets. It has been calculated that about 30% of the urinary metabolite derives from extra-platelets sources and this percent may be increased in particular cases (inflammatory diseases) [6].

In contrast, tromboxane B2 (TxB_2) reflects the total capacity of platelet to synthesize TxA_2, of which it is a stable metabolite; therefore **serum TxB_2** is the most specific test to measure the aspirin effect on platelets [11]. Soluble CD40 ligand and P-selectin has been also observed in ACS in elevated levels [27]. The soluble markers are assessed using immunoassays; limitations in their utility include their presence in extraplatelet sources.

Light transmittance aggregometry (turbidimetric) (LTA) is the historical "gold standard" test, which is based on the stimulation of platelet-platelet aggregation in platelet-rich plasma after stimulation with various agonists. LTA has been the most widely used technique to monitor the effect of antiplatelet drugs, including aspirin, clopidogrel, other P2Y12 inhibitors, and platelet glycoprotein (GP) IIb/IIIa inhibitors [28].

Potential disadvantages include the immediate processing, variable reproducibility, large required sample volumes, lengthy processing time, and expenses of the aggregometer and trained operators. LTA has also been the most widely investigated method to predict clinical outcomes [29].

Platelet Function analysis using Multiple Electrode Aggregometry (Multiplate®)-Dynabyte, Munich.

Impedance aggregometry is conceptually similar to LTA, but it uses whole blood instead of platelet-rich plasma and platelet aggregation is measured by impedance, not light transmittance [30]. This recent method allows an easy and fast assessment of platelet function, with the possibility to decide

on treatment regimens when the patient is still in the CathLab (results in 10 minutes). In present, Multiplate is used in many expert centers and pharmaceutical companies throughout Europe.

Receptor expression

The resting and stimulated expression of activation-dependent receptors can be assessed by flow cytometry with monoclonal antibodies [28]. This technique was useful to assess pharmacologic effects. The most widely studied receptor includes P-selectin and GPIIb/IIIa. Platelet–leucocytes aggregates also have been easured as a marker of platelet activation, and they have been proposed as a more stable measure of acute coronary syndromes compared with P-selectin [30]. Major disadvantages are the complexity of the technique, which requires a high experienced laboratory staff and high costs.

Intracellular Signaling

The coupling of $P2Y_{12}$ to the inhibition of adenylate cyclase by an inhibitory G protein has been used to measure reactivity of the receptor in the presence of $P2Y_{12}$ inhibitors [31].

Vasodilator-stimulated phosphoprotein (VASP) is phosphorylated by protein kinases that are activeted by cyclic adenosine monophosphate. With flow cytometry and methods to make the platelet membrane permeable, it is possible to quantify the amount of phosphorylated VASPby monoclonal antibodies as a measure of unblocked $P2Y_{12}$ [21]. Advantages include the specificity for the $P2Y_{12}$ signaling pathway and the stability of the method in comparison with aggregometry.

Point-of-care Assays

The VerifyNow method (Accumetrics, San Diego, California) uses arachidonic acid, adenosine diphosphate (ADP), or thrombin receptor-activating peptide (TRAP) to assess platelet responsiveness to aspirin, $P2Y_{12}$ inhibitors, or GP IIb/IIIa inhibitors, respectively [22]. The techique measures platelet aggregation with fibrinogen-coated beads and has been used to predict outcomes in patients undergoing percutaneous coronary intervention (PCI). Advantages of the VerfyNow include its ease of use and correlation with turbidimetric aggregometry.

In the *thromboelastogram (TEG) Platelet Mapping technique* (Haemoscope Corporation, Niles, Illinois), the contribution of arachidonic acid-induced platelet aggregation and ADP-induced aggregation to the overall tensile strength of a platelet-fibrin clot can be quantified and correlated with turbidimetric aggregometry [23]. The preparation of samples for thromboelastography is more complex than that for VerifyNow, but thrombelastography can provide coagulation measurements not possible with VerifyNow.

Rotational thromboelastometry ROTEM is available as point-of-care coagulation monitoring in an increasing number of European operating theatres and emergency rooms.

The Platelet Mapping Assay has been described as a platelet aggregation assay for thromboelastography TEG.

The aim of this experimental trial was to evaluate feasibility of the Platelet Mapping Assay on the ROTEM test system. Whole blood was drawn from 22 adult volunteers and patients with and wit-hout antiplatelet medication.

Platelet aggregability was determined in three whole blood assays: the Platelet Mapping Assay using both activators arachidonic acid (AA) and adenosine diphosphate (ADP) on TEG, its adapted version on ROTEM, and the multiple electrode impedance aggregometer Multiplate.

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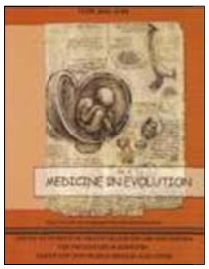
INFANTILE SPASMS WITH BODY EXTANSION. A CASE PRESENTATION



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ABSTRACT

Infantile spasms represent a form of the generalized myoclonic seizures which manifest in newborns, associated with a characteristic EEG aspect and usually accompanying organic lesions of the CNS. The most frequent causes are: perinatal asphyxia, brain trauma, sequelae after meningitis, intrauterine infections, brain malformations (tuberous sclerosis, Aicardi syndrome, congenital hydrocephalus). Infantile spasms involve most frequently the flexion, but also the extension of the trunk and limbs. The diagnosis is established based on the EEG pattern that consists in a multi-focal activity, with irregular spikes and high amplitude waves, referred to as hypsarrhytmia.

The authors present the case of a newborn infant aged 2 months, admitted to the Clinic II Pediatrics from Timisoara, with tonico-clonic seizures. After the clinical and neurologic investigations, as well as the EEG, the diagnostic of infantile spasms with extension was applied.

Key words: *infantile spasms, tonico-clonic seizures, newborns.*

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INTRODUCTION

The infantile spasms are a kind of newborn characteristic epilepsy, which typically appear between the fourth and eighth month of life. Specialty literature admits that, in 10-20% of the cases, the disorder appears in previously healthy infants, which were not exposed to potentially trigger events at birth, with normal CT-scan and NMR-scan and a psychomotor development according to the age, until the moment the seizures appear. Yet, most of the cases develop in children with severe neurological impairment and are classifyed as symptomatic epilepsy [1, 2].

The most frequent causes are: perinatal asphyxia, brain trauma, sequelae after meningitis, intrauterine infections, brain malformations (tuberous sclerosis, Aicardi syndrome, congenital hydrocephalus).

Most frequently, infantile spasms involve the flexion, but also the extension of the trunk and limbs; they involve the muscles of the nape - the head is thrust backwards and it remains in this position for a few seconds [2, 3, 4].

Seizures frequently occur after children wake up and occasionally during sleep.

The diagnosis is established based on the EEG pattern that consists in a multi-focal activity, with irregular spikes and high amplitude waves, referred to as hypsarrhytmia [4, 5].

CASE PRESENTATION

We are presenting case of a newborn infant aged 2 months, male, from the urban area, admitted to the Clinic II Pediatrics from Timisoara for additionnal investigations and diagnosis, after the manifestation of tonico-clonic seizures.

Patient history: The infant resulted from a monitored pregnancy; the mother was done all the compulsory and additional investigations required by the gynecologist, including the blood tests for CMV and toxoplasmasis; the healthy infant presents tonico-clonic seizures, with fixed gaze, just a few hours before being admitted to hospital.

The heredocolateral antecedents are not significant.

Physiologic personal antecedents: single child, born on term, Gn = 3850 g, T = 54 cm, APGAR score = 10, physiologic jaundice = 3 days, naturally fed. Pathologic personal antecedents: Suppurative left otitis.

The clinical examination upon admission to hospital revealed the following: - disturbed general state, psychomotor agitation, afebrile (T = 36.5^{o}C), pale teguments, well hydrated. Normal cardio-pulmonary values. Soft, elastic abdomen, expanding with breathing; liver and spleen within normal limits.

During the physical examination, the patient presents: an episode of muscle contraction, with the sudden extension of the head on the median line, the extension and external rotation of the upper and lower right limbs, fixed gaze, perioronasal cyanosis. After a few seconds, the symptoms resolved spontaneously.

Following the peak symptoms, the patient presented psycho-motor agitation and normal blood pressure. On investigation, hemoglobin was 10, 9, other parameters were within normal limit. Liver function tests and renal function tests were normal.

Neurological examination: repeated seizures with extension, followed by crying. Particular position, with the hyper-extension of the head. Absent cervical tonic reflexes. Spontaneous bilateral fan sign (Babinski + spontaneous sign) during the examination.

Fontanelle ultrasound investigation: average coronarz section: moderate hyperecogenous contour of the front lobes, lateral ventricles – physiologic aspect.

Ventricular system and cerebral parenchyma with normal aspect.

Electroencephalography (EEG): High-voltage polymorphic delta waves, with superimposed multifocal spike discharges (fig.1).

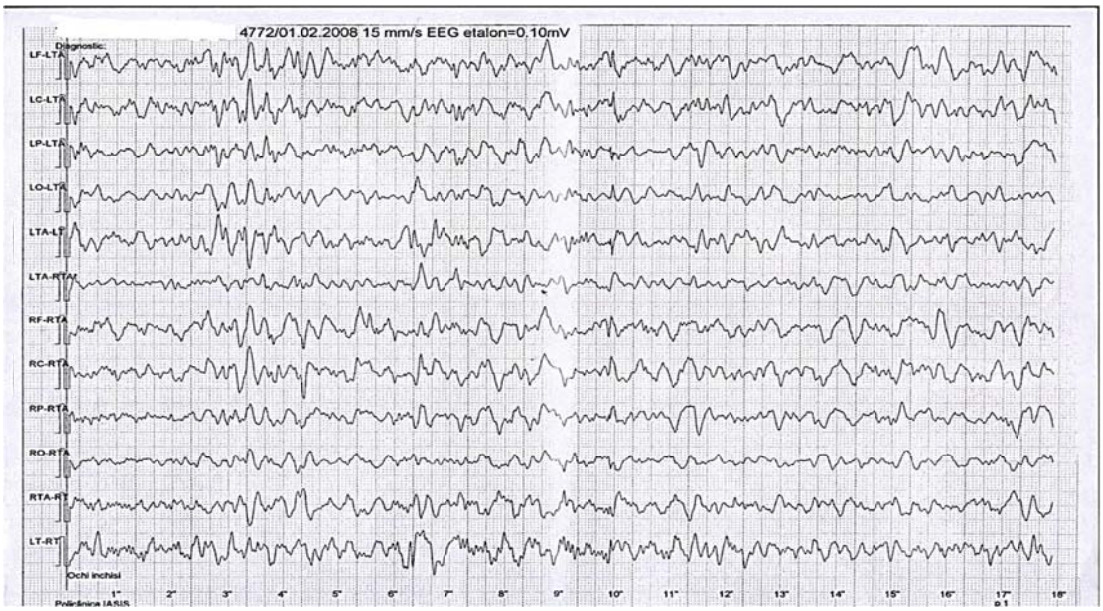

Fig.1 electroencephalography procedure.

Considering the clinical data and the EEG pattern modifications, the patient is diagnosed with epilepsy and seizures with extension.

As a consequence, the treatment administered during hospitalization is as follows: Desitin 3.5 mg (intrarectal administration – *during seizures*, followed by: Fenobarbital (intramuscular injection) – 10mg/ kg bodyweight/ day: 2 x 0.2 ml/ day, 48 hours, Manitol solution 20% - 10ml/ kg bodyweight/ day: 50ml/ 24h in perfusion – 48 hours; HSH 15mg/ kg bodyweight/ day: 3x0.025 mg/day – 72 hours.

At the indication of the Pediatric Neurology specialist, the Fenobarbital was replaced with Depakine (75mg/ ml) 3 x 0.8 ml/ day + Vit. B complex 2.5ml).

Upon release from hospital, the patient is prescribed a treatment with Depakine (75mg/ml) 3x0.8ml/ day + Vit. B complex 2.5 ml, Rivotril tablets, 0.5 mg. 1 tablet/ day, in the evening.

The immediate evolution under treatment was positive, yet the evolution in time depends on the type of epilepsy: Pediatric Neurology investigation, 7 days from the admission to hospital: improved clinical state; brief tremor of the right lower limb; incomplete tonic cervical reflexes; absent plantar cutaneous reflex (Babinski).

Incomplete Moro reflex. Periorbicular myoclonus.

DISCUSSIONS

The typical occurrence of these seizures is the sudden flexion and stiffening of the arms, legs and trunk. Sometimes, infantile spasms involve extension episodes. Usually, they are symmetrical, but sometimes a part of the body is more affected than the other. Each spasm lasts for several seconds and is followed by another spasm, after a pause lasting several seconds. Although there can also be individual spasms, infantile spasms occur in "clusters" of several spasms, in close succession. Usually, infants with infantile spasms become ill-tempered and their development is slower, even regressing, until the spasms are controlled. Some children with infantile spasms respond quickly to the medication, while others develop a resistance to the treatment. Unfortunately, in our case, the infant suffered convulsions of the same type at approximately one month after the treatment was started, in an afebrile state. In this case, a MRI investigation needs to be performed, in order to identify any possible associated malformations.

If, after the MRI investigation is performed, it is proved that the patient has no brain damage, the evolution of the disorder and the outcome are favourable – the seizures will disappear completely before the patient is one year old.

In case an organic lesion is identified, the evolution of the disorder and the outcome are unfavourable, as such forms of epilepsy are frequently non-responsive to treatment.

CONCLUSIONS:

The repeated epileptic crises may induce lasting morphologic changes which will increase the brain sensitivety, thus contributing to the persistence of the disorder and possibly changing its manifestations.

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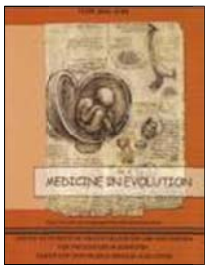
COMPARISON BETWEEN FASCIA TEMPORALIS AND CARTILAGE TYPE I TYMPANOPLASTY



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ABSTRACT

The tympanoplasty is the surgical procedure to reconstruct the tympanic membrane and/or the ossicular chain.

In this article there are analysed the surgical and audiometric results after type I tympanoplasty using fascia, cartilage island or cartilage pallisades.

The graft succes rate was of 91.8%. 7 perforations occurred in the fascia temporalis group (10.76%) and only one in the cartilage island group (5%) and 2 (5.4%) in the cartilage palissades group ($p<0.05$). The preoperative PTA calculated on 4 frequencies was of 26.7 dB and the postoperative average was of 17.2 dB ($p<0.05$). The differencies between the postoperative PTA in the three groups was of no statistical significance ($p>0.05$). The preoperative ABG was of 22.9 dB and the postoperative average of 12.8 dB ($p<0.05$). There were no statistically significant differences between the pre- and postoperative ABG in the three groups.

Cartilage appears to be a graft material that offers many advantages over perichondrium and fascia for the reconstruction of the tympanic membrane (TM).

***Key words**: type I tympanoplasty, fascia temporalis, cartilage island, cartilage palissades.*

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INTRODUCTION

The tympanoplasty, or repair of the tympanic membrane, was first introduced by Zoellner and Wullstein in 1952. Since that time, numerous graft materials and methods of placement have been described to reconstruct the tympanic membrane. Skin, fascia, vein, cartlage, pericondrium and dura mater have all been described as grafting materials for the tympanic membrane.

Thew temporalis fascia and the cartilage remain the most commonly employed materials for closure of TM perforations, and successful reconstruction is anticipated in approximately 90% of primary tympanoplasties.

Generally speaking, there are two distinct techniques utilized for cartilage reconstruction of the tympanic membrane: the perichondrium/cartilage island flap, which uses tragal cartilage, and the palisade technique, which uses cartilage from the tragus or cymba, depending on the surgical approach. Either technique can be used to reconstruct the TM; however, the choice of technique is typically dictated by the specific middle ear pathology or, in cases where the TM reconstruction is in conjunction with ossiculoplasty, the status of the ossicular chain. The palisade technique is preferred in cases of cholesteatoma and when ossicular reconstruction is needed in the malleus-present situation. The perichondrium/ cartilage island flap is preferred for management of the atelectatic ear and the high risk perforation.

MATERIAL AND METHODS:

A prospective study was undertaken in the ENT Clinic Timisoara, between 2006- 2009 on 122 patients.

The aim of the study was to compare the results of type I tympanoplasty according the type of the graft used: temporalis fascia, cartilage island or palisade soft cartilage.

The inclusion criteria in the study were: patients with small and subtotal perforations of the tympanic membrane, with no hystory of otologic interventions; intact ossicular chain; dry ear for at least one month; absence of lesions of the middle ear mucosa; absence of lesions of the mastoid, good cohlear reserve, permeability of the Eustachian tube.

The exclusion criteria were: hystory of otologic interventions; presence of cholesteatoma; concomitant mastoidectomy, ossiculoplasty or presence of atelectasis; syndromes that can affect the middle ear (e.g. Down syndrome, Kartagener syndrome, cleft palate); age under 18 years; patients with general diseases that contraindicate the surgical procedure.

Before the surgery the following steps were undertaken: complete ENT examination with otomicroscopy, evaluation of the Eustachian tube function; pure tone audiometry and calculation of the pure tone average (PTA) on 4 frequencies- 500 Hz, 1000 Hz, 2000 Hz and 3000 Hz, (according the indications of the Hearing and Equilibrium Committee of the American Academy of Otolaryngology Head and Neck Surgery) and of the air-bone gap (ABG); mastoid x-ray in Schuller incidence of both ears; laboratory analysis (blood cell count, blood sugar, creatinine, urea, GOT, GPT), cardiology consult, pulmonary x-ray and preanesthetic consult.

The surgical interventions were performed under general anesthesia with oro-tracheal intubation. The surgi-

cal approach was endaural or retroauricular, according the anatomical particularities of the patient, the localisation and the size of the tympanic perforateon and the experience and preferences of the surgeon. The temporalis fascia was harvested from the ipsilateral temporalis muscle. The cartilage- perycondrium island was harvested from the tragus and the catilage for the palissades fron the tragus or the cymba.

In all cases there was performed type I tympanoplasty under-overlay procedure. During the surgery there was checked the mobility of the ossicular chain and the status of the middle ear mucosa. There were analysed the graft succes rate and the change between the pre- and postoperative PTA and ABG. Succesful graft take was defined as full, intact healing of the graft without perforation, retraction or lateralization for at least 12 months postoperatively.

The audiometric evaluation was performed every 3 months after the surgery.

The functional auditive results were considered succesful for an ABG closure within 20 dB or a PTA of 30 dB or better. The data were analysed using the Excel program (Microsoft Office 2007 package). The statistical tests used were the t student and the chi square. Statistical significance was accepted for p values of <0.05.

RESULTS:

A total of 122 patients were included in the study, aged between 18 and 52 (median age 31.8±12.89). 60 of them were female and 62 were male. 116 of patients were diagnosed with safe otitis media and in 6 cases the perforations were posttraumatic. 91 of the perforateons (74.59%) were subtotal and the rest were smaller, all central and localised in the pars tensa.

The temporalis fascia was used in 65 cases (53.27%) and the cartilage in 57 (46.72%).

In 37 cases (30.32%) there were used the cartilage palissades and in 20 cases (16.39%) the cartilage perichondrium island.

The surgical approach was retroauricular in 103 cases (84.42%) and endaural in 18 (14.75%).

The graft succes rate was of 91. 8%. 7 perforations occurred in the fascia temporalis group (10.76%) and only one in the cartilage island group (5%) and 2 (5.4%) in the cartilage palissades group (p<0.05) (table 1).

Table 1 graft intake rates of the cases upon graft materials

	Fascia temporalis	Cartilage island	Cartilage palissades	p
Intact	58 (89.23%)	19 (95%)	35 (94.59%)	<0.05
Perforation	7 (10.76%)	1(5%)	2 (5.4%)	<0.05

The preoperative PTA calculated on 4 frequencies was of 26.7 dB and the postoperative average was of 17.2 dB (p<0.05) (table 2). The differencies between the postoperative PTA in the three groups was of no statistical significance (p>0.05). The preoperative ABG was of 22.9 dB and the postoperative average of 12.8 dB (p<0.05). There were no statistically significant differences between the pre- and postoperative ABG in the three groups (table 3).

The preoperative ABG was less than 20 dB in 51 patients (49.59%) and

less than 10 dB in 45 patients (36.88%) and the postoperative ABG was less than 10 dB in 109 patients (89.34%), with significant statistical differences ($p<0.05$).

Two retractions were observed (1.63%).

The two pouches were localised in the posterosuperior quadrant, they were first degree and they needed only postoperative follow-up, at least until the end of the study.

Table 2 preoperative and postoperative PTA of the cases upon graft materials

	Fascia temporalis	Cartilage island	Cartilage palissades	p
Preop. PTA	26.12 dB	26.34 dB	28.34 dB	>0.05
Postop. PTA	17.32 dB	17.4 dB	16.97 dB	>0.05

Table 3 preoperative and postoperative ABG of the cases upon graft materials

	Fascia temporalis	Cartilage island	Cartilage palissades	p
Preop. ABG	20.41 dB	22.12 dB	23.34 dB	>0.05
Postop. ABG	11.92 dB	12.31 dB	14.53 dB	>0.05

DISCUSSIONS:

The goals of surgery for chronic otitis media have not changed over the last 50 years, however new techniques have evolved to improve the outcome. Eradication of the disease, achieving a dry and self-cleaning ear and presserving or restoring hearing is the three most important principles of tympanoplasty.

Myringoplasty is the technique for reconstruction of a vibrating tympanic membrane and as such an integral part of any tympanoplasty. As a general surgical principle, maximum exposure is of utmost importance in order to stabilize the graft. An endaural or preferably retroauricular approach may be used. Visualizing the tympanic annulus almost always requires a canalplasty defined as partial or total widening of the bony external auditory canal. A narrow ear canal entrance within the cartilagineous portion may limit the postoperative care and proper ventilation of the ear canal, asking for a meatoplasty to enlarge the opening.

Not every perforation within the tympanic membrane is thought to be closed. A careful diagnosis is necessary and the surgeon's experience dictates the timing of the surgery. In rare instances a specific infection, such as a middle ear tuberculosis[1] or Wegener's disease may present with a running ear through one or multiple perforations. This is one of the reasons that determined us the exclude these patients from the study.

A chronic perforation may act as a "natural" ventilation tube and closing the hole may induce a middle ear atelectasis or an early reperforation. A very small perforation may be more prone for a graft failure than a kidney-shaped central lesion. The ventilation of the middle ear and mastoid finally dictates the position of the reconstructed tympanic membrane and limits the e-

ffectiveness of the myringoplasty. James Sheehy was quoted as "sometimes the best test of Eustachian tube function is a tympanoplasty". However, the condition of the middle ear mucosa, the degree of pneumatisation of the temporal bone on CT scan, the amount of pneumatised cells being obstructed with granulation tissue and/or fluid, the state of the contralateral ear and the presence or absence of a Valsalva maneuver help to identify possible increased risk factors determining a good or poor outcome of the myringoplasty[2].

Once the patient is scheduled for surgery, preoperative treatment should aim at drying the ear with local cleansing and topical antibiotics avoiding its permeation into the middle ear. The size and location of the tympanic membrane perforation dictate the surgical access route.

A transcanal approach through the speculum may be used in very wide external ear canal is with a posterior central perforation. An endaural approach is possible in small posterior perforations not necessitating a wide canalplasty. Since the rims of the perforateons need to be excised and freshened before reconstruction, many initially small perforations finally extend to a larger size and to an anterior extension. Therefore a retroauricular approach is the preferred access, providing enough exposure for a partial or circumferential canalplasty and direct view on the entire rim of the tympanic sulcus.

We observed a better intake rate for the cartilage (island 95% or palissades 94.59%) than for the fascia temporalis (89.23%). Gerber et al.[3] compared temporalis fascia and cartilage tympanoplasty in patients undergoing primary surgery and found no significant difference.

Although cartilage is similar to fascia in that it is mesenchymal tissue, it is more rigid quality tends to resist resorption and retraction, even in the milieu of continuous Eustachian tube dysfunction. [3-7]

It has been shown in both experimental and clinical studies that cartilage is well tolerated by the middle ear, and longterm survival is the norm when used for TM reconstruction.

It appears that cartilage grafts are nourished largely by diffusion and become well incorporated in the TM.[8] Yamamoto et al.[9] examined cartilage removed at revision or second- stage surgery both macroscopically and histologically. Grossly, the cartilage appeared unchanged, with no evidence of erosion or foreign body reaction. Histologically, the matrix of the cartilage was unchanged, but chondrocytes showed degenerative changes. There was evidence of partial absorption and fibrous tissue replacement in some cases.

Temporalis fascia is widely used for the reconstruction of eardrum perforations. It is easily accessible, available in sufficient size also during first time revision surgeries, can be effectively thinned and trimmed to the desired proportions and welded onto the tympanic annulus or over bony edges. Primary or staged ossiculoplasties are not restricted by the use of fascia. Recurrent or residual cholesteatomas can easily be seen as a white, bulging mass behind the reconstructed membrane. Long-term results are very favourable (85%-90% closure rate). The donor site morbidity is very minimal. A disadvantage may be encountered in poorly ventilated middle ears. The limited stiffness may lead to retractions, atelectasis or retraction cholesteatoma formation over time. The hearing results showed no significant differences between the three groups. Cartilage grafts increase the mass and the stiffness of the tympanic membrane which subsequently result in raised acoustic impedance[10]. But in vitro studies demonstrated the

acoustic behaviour of cartilage slices smaller than 0.5 mm was almost the same as that of the normal tympanic membrane[11].

CONCLUSIONS:

Cartilage appears to be a graft material that offers many advantages over perichondrium and fascia for the reconstruction of the TM in cases of severe middle ear pathology. It is more enduring against infection and it has low re-perforation rates on long term follow-up.

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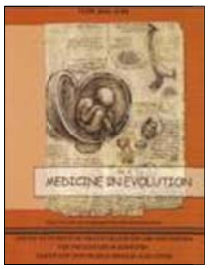
Cystatin C – A SEROLOGICAL MARKER with PREDICTIVE VALUE FOR DEVELOPMENT of CARDIO-VASCULAR and RENAL DISEASE



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ABSTRACT

Background *- We have formulated the hypothesis that serum cystatin C levels have a more pronounced linear association with cardiovascular functional status of patients with established coronary heart disease than serum creatinine based measurements. This study has investigated the corelation between maximum exercise capacity and heart recovery rate, which are two parametres of the exercise stress test, with serum cystatin C levels at patients with established coronary heart disease.*

Methods and Results *– Cystatin C was measured from fasting serum samples using a nephelometer with a particle-enhanced immunonephelo-metric assay. Serum creatinine was determined from venous samples obtained during the study visit, using the Jaffé reaction. We have used the following equation to calculate eGFR: eGFR = (186 × [serum creatinine/88.4] − 1.154) × (age) − 0.203 × (0.742 if female). Each patient underwent a symptom-limited graded exercise treadmill test according to a standard Bruce protocol. Continuous 12-lead electrocardiographic monitoring was performed throughout the testing. HRR was calculated as the difference between maximal heart rate during exercise and heart rate 1 minute into recovery. Systolic and diastolic blood pressures were measured with the patient at rest, using a calibrated sphygmomanometer. A rest echocardiogram, including all standard views, was used to determine left ventricular ejection fraction. In linear regression analyses, increasing value of cystatin C levels were associated with progressively worse exercise capacity. After multivariate analysis, participants with cystatin C concentrations between 1,07-1,28 mg/l and higher 1,29 mg/l had 1.0 and 1.7 METs lower exercise capacity than those with cystatin C concentrations lower than 1,06 mg/l. Quartiles II and III of eGFR and creatinine were associated with less substantial decreases in exercise capacity, and only the fourth quartile of eGFR was significantly different from the first quartile in multivariate analysis.*

Conclusions *- We have observed that elevated cystatin C levels have a linear evolution with the deterioration of exercise capacity and heart rate recovery at patients with CHD. The results of this study suggest that at patients with established CHD, the preclinical and clinic renal function deterioration is associated with bad cardiovascular functional capacity. Deterioration of cardiovascular functional capacity contributes to the elevation of risk for development of CV events, which are associated with elevated serum cystatin C levels and with preclinical renal function deterioration.*

Key words: exercise capacity, cystatin C, cardiovascular, kidney, renal.

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INTRODUCTION

Cystatin C, an alternative of serologic evaluation of renal function, has a greater predictive value for future development of cardiovascular events than serum creatinine or estimated glomerular filtration rate. We have measured the values of cystatin C, seric creatinine and e GFR at a group of 90 patients with coronary heart disease. The study has examined the association of these three estimative parameters of renal function with treadmill exercise capacity and heart rate recovery at 1 minute after test completion, using the method of linear and logistic regression.

Raised values of cystatin C have proved a linear association with deterioration of treadmill exercise capacity and heart rate recovery. The proportion of participants which have demonstrated a low exercise capacity (METS<5) was 45% (10 of 22 participants), for cystatin C values greater than 1,30 mg /L, compared with 12% (3 of 24 participants), for cystatin C values less than 0,92 mg/L; (adjusted odds ratio, 3.2; 95% confidence interval, 1.6 to 6.5; P = 0.001).

The proportion of participants with low heart recovery rate (HRR<16 b/min) was 42% (9 of 21 participants) for those with cystatin C values situated in the superior quartile compared with 16% (a of b participants) for those with cystatin C values situated in the inferior quartile (adjusted odds ratio, 2.2; 95% confidence interval, 1.2 to 4.0; P = 0.01).

For the patients with coronary heart disease, the cystatin C concentration shows a linear association with low treadmill exercise capacity and heart rate recovery. Cystatin C measuring allows a better detection of the association between affected renal function, low exercise capacity and decrease heart rate recovery than serum creatinine.

Cystatin C is a low molecular weight protein synthesized in most nucleated cells, freely filtered by the glomerular membrane and metabolized in the proximal tube. Elevated seric values of cystatin C have predictive value for development of cardiovascular events at patients with or without established coronary heart disease and for patients with acute coronary syndromes.

Cystatin C values demonstrate a more linear correlation with mortality due to cardiovascular events compared with serum creatinine based measurements.

Maximum exercise capacity and heart rate recovery are well validated and objective parameters of the cardiac functional status and are also independent prediction factors for cardiovascular and general mortality.

Heart rate recovery after exercise test is considered a function of vagal reactivity.

A delay in the decrease of heart rate along the first minute after exercise test completion reflects a diminished vagal activity and is a strong predictor for general mortality. We have generated the hypothesis that cystatin C serum level has a significant linear association with maximum exercise capacity and heart rate recovery being a more accurate indicator than creatinine level based measurements.

In order to investigate the correlation between cystatin C values and cardiovascular functional status, we have measured the serum levels of cystatin C and creatinine, treadmill exercise capacity and heart rate recovery for 90 patients with established CHD, enrolled in this study.

MATERIAL AND METHODS:

Admission criteria

Patients have been included in the study group if they have on of the following criteria:

- prior acute myocardial infarction ;
- angiographic evidence of >50% stenosis on one ore more coronary arteries ;
- ischemic manifestations on exercise test ;
- prior coronary revascularisation.

Between September 2007 and march 2010, a total of 102 participants were examined for admission in the study based upon an anamnestic interview, physical examination and a detailed questionnaire regarding health status at that moment. Out of these patients, 8 participants have not been able to complete the exercise test and 3 participants have not submitted the blood sample for the laboratory. The remaining 90 participants form the final study group. Cystatin C was measured from fasting serum samples using a nephelo-meter with a particle-enhanced immunonephelometric assay.

The detection limit of the assay is 0.05 mg /L, analytical sensitivity is 0.005 mg /L, and the reference range for healthy persons is 0.53 to 0.95 mg /L. Serum creatinine was determined from venous samples obtained during the study visit, using the Jaffé reaction.

We have used the following equation to calculate eGFR: eGFR = (186 × [serum creatinine/88.4] − 1.154) × (age) − 0.203 × (0.742 if female).

Kidney function was categorized into four groups by using cystatin C, eGFR, or serum creatinine. We also used both eGFR and cystatin C level to categorize participants as having CKD (eGFR < 60 mL/min [<1.00 mL/s]), preclinical kidney disease (pre-CKD; eGFR > 60 mL/min [>1.00 mL/s] and cystatin C ≥ 1.0 mg/L), or normal kidney function (eGFR > 60 mL/min [>1.00 mL/s] and cystatin C < 1.0 mg/L).

Each patient underwent a symptom-limited graded exercise treadmill test according to a standard Bruce protocol. Continuous 12-lead electrocardiographic monitoring was performed throughout the testing, and exercise capacity was calculated as total metabolic equivalent task (METs) achieved at peak exercise (1 MET = 3.5 mL of oxygen uptake per kilogram of body weight per minute). We defined poor (<5 METs) exercise capacity according to previously published criteria.

After achieving maximal workload, subjects were immediately placed supine. Heart rate was measured exactly 1 minute after termination of exercise to compensate for the effects of physiological venous blood redistribution in the immediately after exercise period. HRR was calculated as the difference between maximal heart rate during exercise and heart rate 1 minute into recovery. For purposes of analysis, we categorized poor HRR as the lowest group compared with the upper 3 groups of HRR.

Age, education, income, marital status, smoking, alcohol use, angina frequency and physical activity were determined by means of questionnaire. Medical history was determined by self-report. Resting heart rate was obtained as part of the intake physical examination, and body mass index was calculated as weight in kilograms divided by the square of height in meters. Participants were instructed to bring their medication bottle to the study appointment, and study personnel recorded all current medications.

Systolic and diastolic blood pressures were measured with the patient

at rest, using a calibrated sphygmomanometer. A rest echocardiogram, including all standard views, was used to determine left ventricular ejection fraction. We calculated wall motion score index immediately after exercise as a measure of ischemia. The wall motion score index represents the sum of wall motion scores from 16 wall segments, divided by the number of segments visualized. A normally contracting left ventricle received a wall motion score index of 1 (16/16 = 1), and higher scores indicated a worse contractility.

RESULTS

Of 90 participants, 22 (24%) had poor exercise capacity (METs<5). Compared with participants who achieved 5 METs or greater, those with poor exercise capacity were older and less likely to have attained a high school education and had lower income. (Table1.)

Table 1

Variables	**Low exercise capacity METs<5**		**Normal exercise capacity METs ≥5**		
	nr	***%***	***nr***	***%***	***p***
Number of patients	22	24%	68	76%	
Demographic					
Age (y)	71 ± 11		65 ± 10		0.0001
Females	5	23%	11	16%	
Males	17	77%	57	84%	0.12
Medical history					
Hypertension	17	77%	46	68%	0.01
Myocardial infarction	12	53%	37	54%	0.8
Coronary revascularization	4	20%	42	62%	0.007
Congestive heart failure	5	24%	10	14%	0.0005
Stroke	4	20%	7	11%	0.0003
Diabetes mellitus	7	33%	16	23%	0.002
Chronic pulmonary disease	2	7%	1	2%	0.0003
Peripheral vascular disease	3	14%	5	8%	0.03
Current angina (any v none)	5	24%	12	17%	0.14
Kidney function					
Cystatin C (mg/L)	1.4 ± 0.75		1.1 ± 0.39		0.0001
Estimated glomerular filtration rate eGFR (mL/min)	69.6 ± 23.8		78.9 ± 21.6		0.0001
Serum creatinine (mg/dL)	1.3 ± 0.83		1.1 ± 0.42		0.0001
Other characteristics					
Regular alcohol use	6	27%	21	31%	0.22
Current smoking	5	24%	13	19%	0.26
Body mass index (kg/m2)	29 ± 6		28 ± 5		0.0003
Hemoglobin (g/dL)	13.5 ± 1.5		14 ± 1.3		0.0001
Albumin (g/dL)	3.8 ± 0.4		3.9 ± 0.3		0.0001
Cardiac function					
Resting heart rate (beats/min)	69 ± 12		67 ± 12		0.1
Systolic blood pressure (mm Hg)	134 ± 19		131 ± 19		0.05
Diastolic blood pressure (mm Hg)	72 ± 11		75 ± 10		0.003
Ejection fraction (%)	61 ± 1		62 ± 1		0.02
Wall motion score index	1.2 ± 0.4		1.2 ± 0.4		0.12
Medication use					
b-Blocker	13	60%	39	57%	0.4
Statin	12	53%	46	68%	0.0008
Renin-angiotensin inhibitor	13	60%	33	49%	0.009
Aspirin	16	73%	54	80%	0.02

Patients with exercise capacity under 5 METs were more likely to have hypertension, congestive heart failure, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, and a history of stroke, but less likely to have undergone prior revascularization. Participants with poor exercise capacity had greater body mass index, but lower ejection fraction, albumin level, hemoglobin level, and diastolic blood pressure. Participants with poor exercise capacity also were more likely to be using a renin-angiotensin inhibitor and less likely to be using aspirin or a statin.

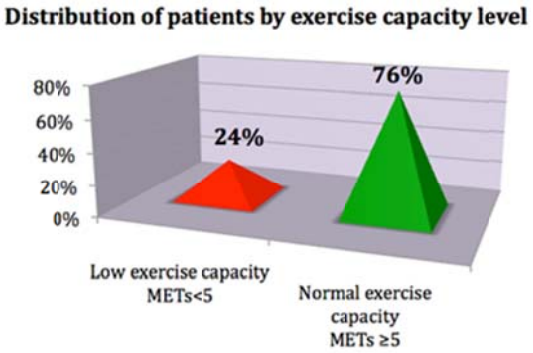

Fig. 1. Distribution of patients according to maximal exercise capacity.

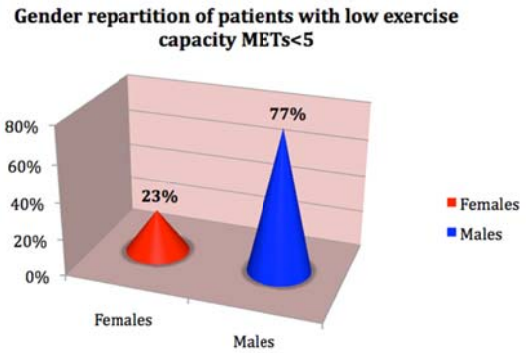

Fig. 2. Gender repartition of patients with low exercise capacity

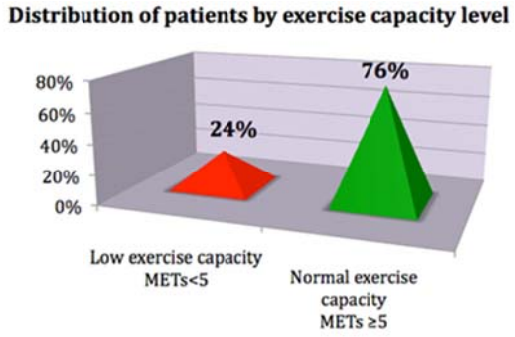

Fig. 3. Distribution of patients by exercise capacity level

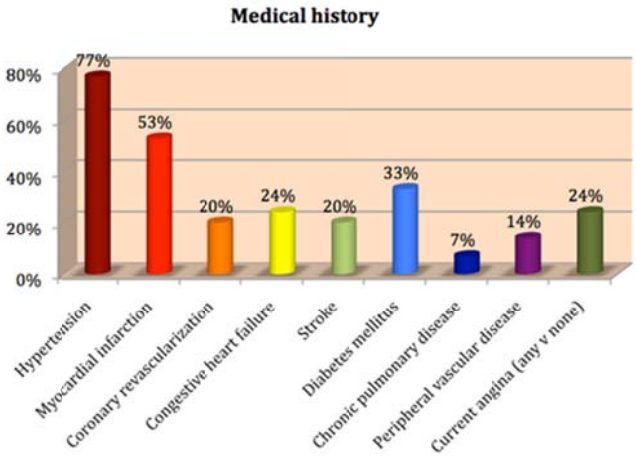

Fig. 4. Medical history

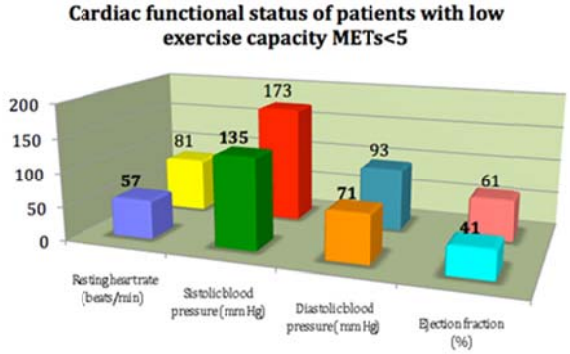

Fig. 5. Cardiac functional status of patients with low exercise capacity

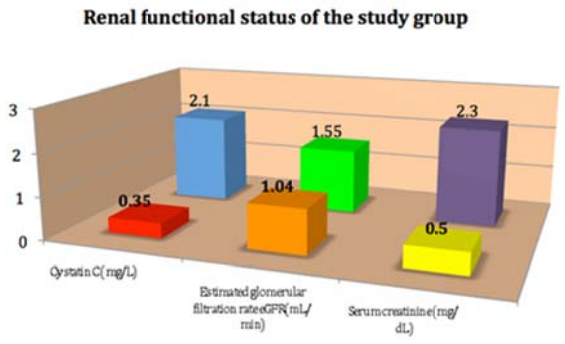

Fig. 6. Renal functional status of the study group

In linear regression analyses, increasing values of cystatin C levels were associated with progressively worse exercise capacity. After multivariate analysis, participants with cystatin C concentrations between 1.07-1.28 mg/l and higher 1,29 mg/l had 1.0 and 1.7 METs lower exercise capacity than those with cystatin C concentrations lower than 1,06 mg/I (Table 2).

Quartiles II and III of eGFR and creatinine were associated with less substantial decreases in exercise capacity, and only the fourth quartile of eGFR was significantly different from the first quartile in multivariate analysis.

Multivariate analisys

When entered as continuous variables, areas under the ROC curve for predicting poor exercise capacity (METs < 5) were 0.71 (95% CI, 0.67 to 0.75) for cystatin C level, 0.59 (95% CI, 0.54 to 0.63) for serum creatinine level, and 0.62 (95% CI, 0.58 to 0.66) for eGFR.

Table 2 Renal status for patients with low exercise capacity

	Subgroups			
	I	II	III	IV
Cystatin C(mg/l)	0,35-0,92	0,93-1,06	1,07-1,28	>1,29
eRFG (ml/min.)	>90	89,9-76,2	76,1-62,5	62,4-8,1
Serum creatinine(mg/dl)	0.5-0.9	0,9-1,0	1,1-1,2	>1,3

Results were similar for HRR. In adjusted analyses, the third and fourth quartiles of cystatin C were associated with slower HRR (P = 0.06 and 0.001); whereas only the fourth quartiles of creatinine level and eGFR were statistically significant (Table 3).

Areas under the ROC curves for predicting poor HRR (<16 beats/min) were 0.66 (95% CI, 0.62 to 0.70) for cystatin C level, 0.59 (95% CI, 0.54 to 0.63) for serum creatinine level, and 0.62 (95% CI, 0.57 to 0.66) for eGFR.

Table 3 Renal status for patients with low exercise capacity

	Subgroups			
	I	II	III	IV
Cystatin C(mg/l)	0,35-0,92	0,93-1,06	1,07-1,28	>1,29
eRFG (ml/min)	>90	89,9-76,2	76,1-62,5	62,4-8,1
Serum creatinine (mg/dl)	0.5-0.9	0,9-1,0	1,1-1,2	>1,3

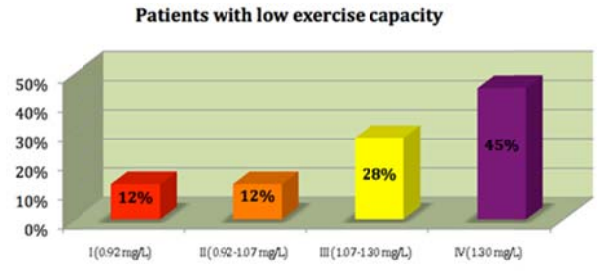

Fig. 7. Corelation between cystatin C values and low exercise capacity

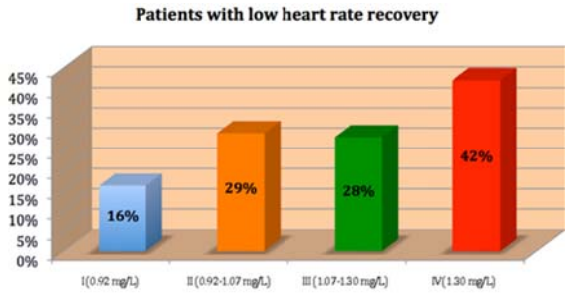

Fig. 8. Corelation between cystatin C values and low heart rate recovery

We have evaluated the association of cystatin C level with poor exercise capacity, defined as achieved MET_s < 15.

The prevalence of poor exercise capacity ranged from 12% in the lower 2 quartiles to 45% in the highest quartile (Table 4).

Table 4 Renal status for patients with low exercise capacity

Cystatin C	Patients with low exercise capacity (%)	Unadjusted Odds ratio (95% CI)	P	Adjusted Odds ratio (95% CI)	P
I (0.92 mg/L)	12%	1	–	1	–
II (0.92-1.07 mg/L)	12%	1.0 (0.6-1.8)	0.94	0.7 (0.3-1.5)	0.41
III (1.07-1.30 mg/L)	28%	2.8 (1.7-4.5)	0.0001	1.8 (0.9-3.6)	0.09
IV (1.30 mg/L)	45%	5.9 (3.7-9.4)	0.0001	3.2 (1.6-6.5)	0.001

Table 5 Association between serum cystatin C level quartile and low heart rate recovery

Cystatin C	Patients with low HRR (%)	Unadjusted Odds ratio (95% CI)	P	Adjusted Odds ratio (95% CI)	P
I (0.92 mg/L)	16%	1	–	1	–
II (0.92-1.07 mg/L)	29%	1.2 (0.8-2.0)	0.4	0.9 (0.5-1.6)	0.6
III (1.07-1.30 mg/L)	28%	2.1 (1.4-3.4)	0.001	1.5 (0.9-2.8)	0.14
IV (1.30 mg/L)	42%	3.9 (2.5-6.1)	0.0001	2.2 (1.2-4.0)	0.01

Table 6 Association between low exercise capacity, low heart rate recovery and renal disease in preclinic and clinic stages

	Renal disease in preclinic stage	Renal disease in clinic stage
Low exercise capacity	2,2 (1,3-3,9)	2,8 (1,5-5,3)
Low heart rate recovery	1,7 (1,0-2,7)	2,2 (1,3-3,9)

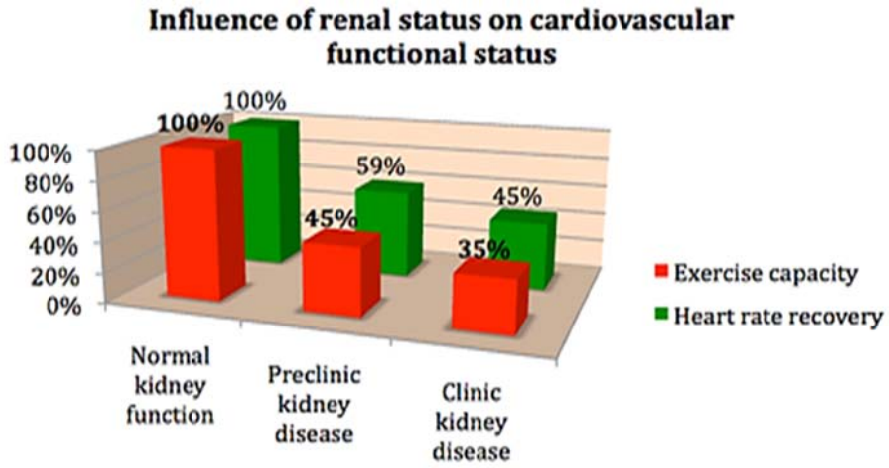

Fig. 9. Influence of renal status on cardiovascular functional status.

After a multivariate adjustment, the fourth quartile retained a 3-fold odds of poor exercise capacity compared with the first quartile. The preva-

lence of poor HRR increased across quartiles of cystatin C levels from 16% to 42%. In adjusted analysis, the highest quartile had 2-fold odds of poor HRR compared with the lowest quartile. We repeated these logistic regression analyses using kidney function categories that incorporated both eGFR and cystatin C level (Table 6.).

Compared with participants who had normal kidney function, those with pre-CKD had 2.2-fold odds of poor exercise capacity and 1.7-fold odds of poor HRR in adjusted analyses. Participants with CKD had 2.8-fold odds of poor exercise capacity and 2.2-fold odds of poor HRR in multivariate analyses.

DISCUSSIONS:

Cystatin C serum level has proved to be a superior indicator for prediction of risk regarding the development of cardiovascular disease, cardiac insufficiency and related mortality than creatinine. The difference of the predictive value between the two markers of glomerular filtration is pronounced for patients with eGFR>60mL/min (>1.00 mL/s). Cystatin C level shows a significant association with cardiovascular risk at persons with eGFR>60mL/min (>1.00mL/s) while creatinine level and eGFR do not demonstrate this kind of association.

Renal affection in clinical stage, defined by creatinine clearance <60mL /min (<1.00mL/s), has been associated with six times greater probability of exercise capacity deterioration compared with the group of patients with raised values for creatinine level.

The present study extends these observations detecting a more important association of cystatin C levels with the deterioration of exercise capacity and heart rate recovery, which can be found also at persons with preclinical renal disease. Because previously discussed data suggest that cystatin C level reflects more accurately the diminution of glomerular filtration capacity compared with creatinine level measurements, the results of the present study also suggest that even a moderate deterioration of renal function is associated with a rise in the severity of cardiovascular pathology.

These conclusions have certain limitations, determined by the elderly study group; therefore statistical validation for extending these findings to other groups of patients requires supplementary research.

CONCLUSIONS:

a. The combined therapy in patients with skeletal anomalies and bone maturity is becoming more and more popular among the modern contemporary techniques. The motives are esthetic, functional and increase the self esteem.
b. Although the results are spectacular, they present no stability if the exact steps described above are not followed. Highly important are the cephalometrical measurements in diagnosing these anomalies.
c. Keeping in mind that the functional comes before the esthetics leads us to the idea of the conjunction of these two desiderates.

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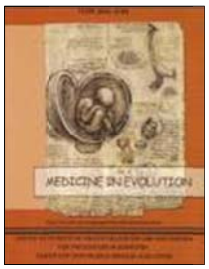
CORRELATION BETWEEN URO- AND ODONTOLITHIASIS



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ABSTRACT

There is no unique lithogenesis mechanism but a complex of multifactorial mechanisms, usually acting in combination. If each case is not investigated with regard to the intimate lithogenesis mechanism, and if therapeutic correction is not applied, this will sooner or later lead to lithiasis rebounds. The consequences of not correcting lithiasic rebounds and respective treatments will lead in time to the progressive, potentially severe, disturbance of the impacted organ with consequences upon the entire organism. In search of new investigation and treatment methods we approached the lithiasic phenomenon both in the urinary apparatus (urolithiasis) and in the dental organ (odontolithiasis).

The study was performed in 30 urinary lithiasis cases in the Timisoara Clinical Emergency County Hospital, during the period 2009-2010. Patients were subjected to a standard general clinical and biological examination of the urinary apparatus and a dental examination with diagnostic purposes. In two of the patients the nature of the collected lithiasic concrement (urinary calculus, dental tartar) as well as of the amino acid content of the protein residue of dental tartar as compared to those specific for the oral mucosa collagen were determined. Determining the composition of lithiasic concrements was attempted in order to establish the uro-odontolithiasis correlation as (general and local) favoring factors in generating periodontal pathology. Information regarding the physical-chemical characteristics of uro- and odontolithiasic concrements may be important in the investigation, prophylaxis and treatment management for both uroligist and dentist. The observation of the rhythm of formation and accumulation of the tartar deposit and of the mineralization degree achieved in a certain time interval under certain conditions may represent an indicator of the mineralization degree occuring in the urinary apparatus and may thus represent a noninvasive, predictive diagnostic method.

***Key words**: urolithiasis, odontolithiasis, periodontal pathology*

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INTRODUCTION

There is no unique mechanism for lithogenesis but a complex of multifactorial mechanisms usually acting in combination. Not thoroughly investigating the lithogenesis mechanism in every case, and not correcting it by therapy, will, sooner or later, cause lithiasic rebound. The consequences of uncorrected lithiasic rebounds and of targeted treatments will in time lead to a progressive and potrentially severe damage of the impacted organ with consequences over the entire organism. In search of novel investigation and treatment methods we approached the lithiasic phenomenon both in the urinary apparatus (urolithiasis) and in the dental organ (odontolithiasis).

MATERIAL AND METHODS:

The study was performed in 30 urinary lithiasis cases in the Timisoara Clinical Emergency County Hospital, during the period 2009-2010.

Patients were subjected to a standard general clinical and biological examination of the urinary apparatus and a dental examination with diagnostic purposes.

In two of the patients, the nature of the collected lithiasic concrement (urinary calculus, dental tartar) as well as of the amino acid content of the protein residue of the dental tartar as compared to those specific for the oral mucosa collagen were determined.

Determining the composition of lithiasic concrements was attempted in order to establish the uro-odontolithiasis correlation as (general and local) favoring factors in the generation of periodontal pathology.

RESULTS

FTIR spectra were obtained on a Perkin Elmer One spectrometer with accessories for attenuated total reflectance (ATR). Solid samples were placed on the diamond crystal surface and covered with the steel plate. An >100 Torr pressure was applied in order to achieve a good contact between solid and crystal. The spectra analysis was performed with the Perkin Elmer soft. The spectrograms of lithiasic concrements (urinary calculus and dental tartar) collected from the two patients are comparatively presented (Fig.1a, 1b).

The FTIR spectrogram of the first patient (Fig.1a) shows that dental tartar has a phosphate nature being an apatite (hydroxiapatite/carbone apatite), and the urinary calculus is a simple uric acid calculus (non-calcium group).

The FTIR spectra of uric acid ($C_5H_4N_4O_3$) are characterized by absorption bands of the purine ring (at 3138, 3020 and 2836 cm^{-1}), bands caused by expansion vibrations of the N-H bond, as well as additional bands with wave lengths of 1351, 1124, 1029 and 786 cm^{-1}. In the case of urinary calculus, bands occur at 3140, 3024, 2851 cm^{-1} and additional bands at 1352, 1125, 1030 and 788 cm^{-1}, thus confirming the presence of uric acid.

Uric acid calculi are formed when urine becomes oversaturated with non-dissociated uric acid, protonated in the N-9 position. In gout, idiopathic uric lithiasis and dehydration, the medium pH is usually under 5.4 and often under 5. This is why the non-dissociated uric acid which is urine-soluble only in

concentrations of 100 mg/l. is predominant. Higher concentrations represent an over-saturation causing crystals or calculi production. When hyperuricosuria is also present, it leads to an increase in oversaturation, but low pH urine may be oversaturated with non-dissociated uric acid even when the daily excretion rate is normal. Myeloproliferative syndromes, chemotherapy in malignant tumors and Lesch-Nyhan syndrome cause an increased production of uric acid with consecutive hyperuricosuria leading to the formation of uric calculi even at a normal level of urine pH.

The FTIR spectrogram of the second patient (Fig.1b) shows that dental tartar is of phosphate nature, being an apatite, and the urinary calculus has a complex nature (non-calcic and calcic) being composed of struvite and apatite.

Struvite (hexahydrated amonium-magnesium phosphate, $NH_4MgPO_4{\cdot}6H_2O$) presents a characteristic IR spectrum and may be easily recognized even in complex calculi due to the presence of a strong absorption band at 1008 cm^{-1} (caused by the absorption of the phosphate group) and by the presence of 2377, 1476, 1437, 872, 770 and 574 cm^{-1} bands. Bands at 1476 and 1437 cm^{-1} may be attributed to the amonium group (NH_4^+). When struvite is associated to apatite, the presence of the latter may be infered through the presence of the absorption band at 600 cm^{-1} and through the presence of a sharp high intenstity band around the value of 1015 cm^{-1}. In the case of urinary calculus the band is at 1018 cm^{-1}. Expansion frequencies of 567, 603, 985, 1038 with „shoulders" at 1105 cm^{-1} corespond to apatite – the mineral form of calcium phosphate.

The phosphate ion in apatite (hydroxiapatite – HAP / carbonate-apatite – CAP) has a strong absorption between 1100 and 1000 cm^{-1}. In order to determine the calcium carbonate, its specific absorption values at 1415 and 875 cm^{-1} must be taken into account.

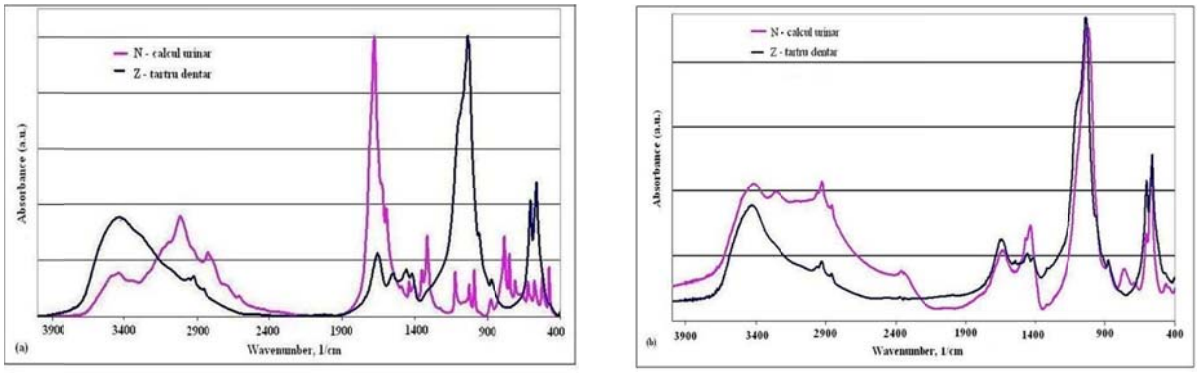

Fig.1 FTIR spectra for urinary calculi (N) and dental tartar (Z).

Struvite calculi do not form in urine in the absence of infection because the level of NH4+ is low in alkaline urine as a response to physiological stimuli. Chronic Proteus infection may occur due to alterations in the urinary drainage, ureteral catheterization, or surgical procedures and especially due to chronic antibiotic treatment which may lead to the predominance of Proteus species in the urinary tract. The phosphate-ammonium-magnesium lithiasis by successive appositions (salting out phenomenon) occurring during calculus formation and development is secondary impregnated with

calcium, thus increasing to 90% the global incidence of calcium in the structure of urinary calculi.

Carbonate apatite is characterized by IR bands with values of 1422 and 1652 cm^{-1}.

These bands, with wave-lengths approximately equal to those specified (i.e. 567, 603 985, 1038 cm^{-1}) as well as a strong absorption at 1042 cm^{-1} (Fig.1a) and 1040 cm^{-1} (Fig.1b) also occur in spectra of tartar samples collected from both patients, confirming their phosphate apatite nature (HAP/CAP).

SEM (Scanning Electron Microscopy): lithiasic triturated concrements were placed on the sample pad, gilt in order to avoid electrostatic charging and investigated in electron microscopy with a conventional HITACHI S-3000N microscope at an acceleration voltage of 15 kV. The obtained images are comparatively shown at 50 µm and 10µm magnification (Photo 1,2,3,4).

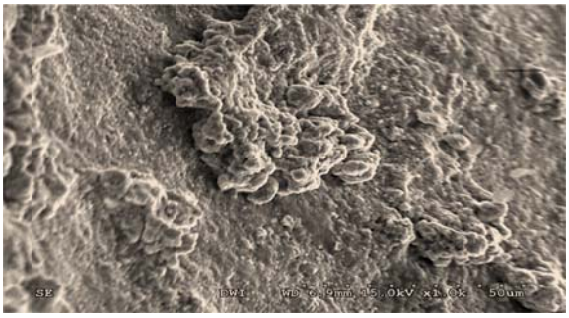

Photo 1 Urinary calculus

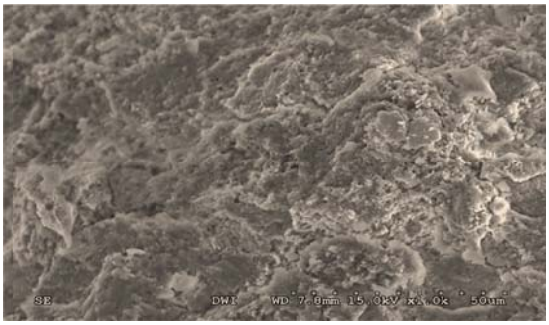

Photo 2 Dental tartar

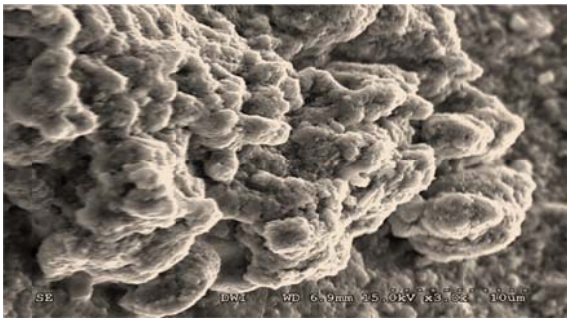

Photo 3 Urinary calculus

Photo 4 Dental tartar

The microscopic image of calcified bacterial aggregates in the studied lithiasic concrements may offer clues on their nature and allows us to infer the way deposits are formed by successive apposition.

On both types of samples (urinary calculus, dental tartar) areas with similar crystaline structures with predominance of apatite-like anorganic crystals and calcified microorganisms may be observed. When the magnification is increased the bacterial colonies resulted from co-aggregation of Gram positive and Gram negative species become visible. Mineralization in small foci which confluate through chelation of calcium by carbohydrate-protein complexes and sediment forming intracellular apatite crystals is also confirmed by the microscopic aspect of examined samples. The nutritional source of bacterial growth and multiplication in dental tartar is represented by salivary and/or serum proteins depending on the deposit site.

The analysis of the amino acid content in the tartar proteic residue was

performed using the Alpha-Plus II, Pharmacia analyzer by the Spackman, Stein and Moore method. Each sample was hydrolyzed in 3 ml of 6N HCl at 110 °C for 24 h. Hydrolyzed samples were heat dried in the rotative evaporator. The percent of amino acid content of dental tartar and of the collagen of the oral mucosa are shown in Fig.2.

The amino acid content analysis of the proteic residue following the hydrolysis of dental tartar samples compared to the amino acid content of the oral mucosa collagen – from the DWI data bank – show that dental tartar proteins have a different composition from that of collagen, thus excluding the assumption that they originate from the mucosa, or from aliments (e.g. meat which must also contain high quantities of hydroxiproline and glycine). The presence of high quantities of glutamic acid / glutamine, aspartic acid / asparagine and alanine, as well as leucine and lysine in the composition of dental tartar indicates a probable bacterial source.

The study of bacteria accumulated in the collected dental tartar may also offer clues on the infection source which lies at the origin of periodontal pathology and of their penetration into other organs carried by the blood or saliva flow. The detection of pathogene bacteria is essential but not sufficient for the diagnosis of periodontal disease as apparently non-inflammatory forms, juvenile periodontitis, "senescence" periodontopathies, are also based upon microbial aggression but with discrete clinical manifestations. In other cases, gingival lesions occur as a consequence of viral, fungal diseases or as a part of systemic diseases.

Only by a correct and simultaneous correlation of data on the nature of local factors contributing to periodontal disease, an acurate diagnosis may be obtained. Investigation on the nature of lithiasic concrements by determining the metal concentration (atomic absorption spectrometry AAS) with consecutive FTIR spectrometry might offer additional information in the oral pathology of patients with urinary lithiasis. Dental tartar accumulates on teeth as a result of a complex microbial community with over 10^{10} bacteria/mg. It is estimated that dental tartar contains around 400 distinct bacterial species together with epithelial cells, leukocytes and macrophages. Bacterial products and saliva form together the extracellular matrix which contains proteins, polysaccharides and lipids. [2] An important part of the dental tartar also contains anorganic products, mostly calcium phosphates. These anorganic compounds are involved in the calcification of the organic deposit and thus, in the end, the deposit is far more difficult to remove. Moreover, after cleaning off the calcified deposit, the surface remains rough and the area is easily colonized by new bacterial populations. From this standpoint FTIR results and the amino acid composition are concordant to known data on dental tartar.

The exact formation mechanism of dental tartar is a debated subject, although some connections to environmental factors are underlined. The same is true concerning urinary calculi. Even if there are hypothesis on possible relations to alimentation, the biochemistry of the process is still not elucidated.[3,9] One of the recent hypothesis [4] assumes that the renal calcium phosphate deposits are initiated by nanobacteria, 80-200 nm microorganisms identified at the beginning of the '90s [5]. These microorganisms are very small Gram negative bacteria. They belong to the Proteobacteria group and reach up to 1/20 of the dimension of most other bacteria of the group. They seem capable to play a pathogenic role

through the unique capacity to form a protective acicular crystallized calcium phosphate wall. Several research groups performed studies based upon this hypothesis [4] and managed to demonstrate that these nano-bacteria are the germs initiating the renal calcification process [6]. Moreover, new results suggest that calcification processes in other area of the organism – e.g. those connected to atherosclerosis – are also due to these nano-bacteria which, once they penetrate the body, are eliminated into the blood flow. [7]. Our data also support the hypothesis of nano-bacteria initiating the process of phosphate deposits.

The analysis or urinari calculi indicates, as previously stated, the existance of levels of calcium phosphate, upon which further deposits were formed by successive appositions (salting out phenomenon) occuring during calculus development. The dental tartar analysis shows, besides calcium phosphate, levels of proteins with a structure resembling that of bacterial proteins. Thus, the assumption that, in the case of dental tartar the germs of the calcification process are nano-bacteria which entered the organism appears as natural.

The oral penetration route is very likely in the studied cases, thus inducing the formation of dental tartar (calcium phosphate).

After penetrating the organism, nano-bacteria are released into the blood flow, as shown in the above mentioned studies performed in the 90s, and reach the kidney where they may initiate calcium phosphate deposits. These form the core for further deposits.

Augmenting this hypothesis the patients in question might also have coronary problems caused by atheroma forming in blood vessels following the action of the same nano-bacteria. [8].

We must emphasize that this hypothetic mechanism needs the presence of local conditions for each stage (pH of vital fluids, food, hormonal balance, etc.).

Nano-bacteria may act in the oral cavity without producing effects on the urinary apparatus and vice versa.

In other words, the formation of high quantities of tartar suggests a high probability of urological problems (and vice versa, urological problems indicate a high potential for tartar occurence), but it does not necessarily involve their existance.

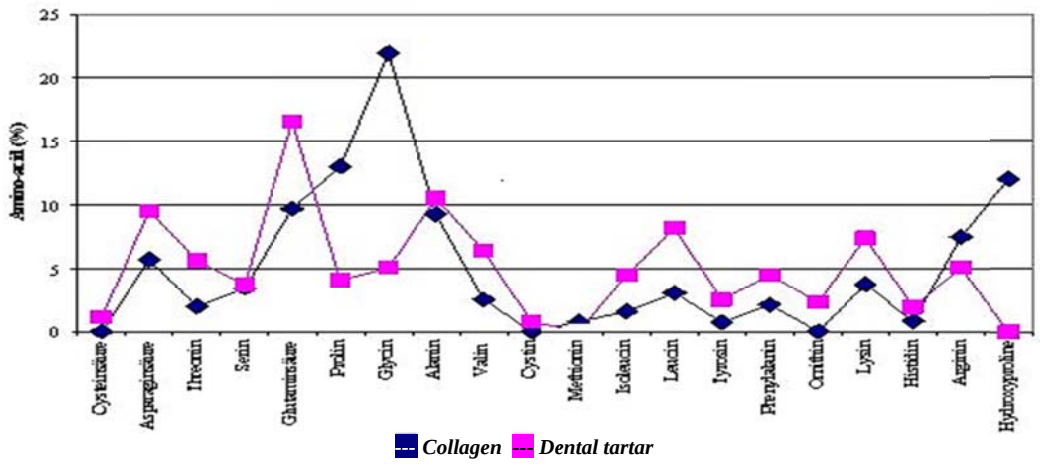

Fig.2 Amino acid content of dental tartar and of the collagen in the oral mucosa..

CONCLUSIONS:

Information regarding physical-chemical characteristics of uro- and odontolithiasic concrements may be important in investigating, preventing and managing the therapeutic approach for both urologist and dentist.

Observing the rhythm of tartar deposits formation and accumulation and of the mineralization degree achieved during a certain interval, under certain conditions, may represent an indicator of the mineralization degree occuring in the urinary apparatus and may thus represent a noninvasive, predictive diagnostic method.

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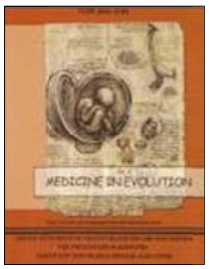
TEMPORO – MANDIBULAR DISORDERS IN ASYMMETRICAL CLASS III



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ABSTRACT

***Rationale**: Facial asymmetries, particularly the mandible ones, were considered in the literature as modified morphological features, potentially associated with temporomandibular joint (TMJ) pathology.*

***Objective**: our research is aimed to quantify the degree of mandible asymmetry on Class III patients and its implications on the onset of temporomandibular disorders (TMD).*

***Methods and results**: our research was performed on a selected group of 50 patients (ages 11-17 years). The subjects were divided into a control group of 25 Class I patients and a study group of 25 Class III patients. Each patient received full clinical examination and standard orthodontic records prior to orthodontic treatment. The mandible asymmetry was assessed through digital analysis of the orthopantomograph images, using the asymmetry indices described by Kjellberg et al (1994). TMD symptoms were present on 56% of the control group patients and on 48% of the study group patients.*

***Discussion**: 76% of Class I patients and all Class III cases presented different degrees of mandible asymmetry, and no gender-related differences were noticed. In some cases, the asymmetry value correlates with the gravity of the temporomandibular disorder. The routine evaluation of the orthopantomograph regarding the asymmetry indices of the vertical rami represents a valuable aid for proper diagnosis and appropriate treatment selection.*

***Key words:** temporomandibular disorder, mandible asymmetry, orthopantomograph, skeletal Class III.*

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INTRODUCTION

Facial and cranial asymmetry is a common naturally phenomenon, including on patients who seem to have perfectly aesthetic faces [1]. Concerning facial morphology, symmetry represents the correspondence of the figure's half sides regarding their shape, size and location of the anthropological landmarks relative to the median sagittal plane. The facial landmarks must be placed on the same vertical and horizontal levels, in order to create a balanced figure (fig. 1) [2]

The mandible asymmetry affects directly the attractiveness of patient's face, but it may also be the cause of some dysfunctions of the stomatognathic system. Many authors consider the two condylar areas responsible for the onset of a mandibular asymmetry [3]. Scientific studies demonstrate the increase of TMD incidence among patients with skeletal asymmetries accompanied by length differences between the two mandible vertical rami [4, 5].

Habets et al (1987) investigated the correlation between the degree of mandible asymmetry, assessed on orthopantomograph, and the presence of TMD [6].

They proposed an evaluation of the asymmetry indices, calculating the condylar and ramal heights and then using the left and the right sides values in a mathematical formula. Results higher than 3% indicated a mandibular ramal asymmetry. Xie et al (1997) demonstrated that inaccurate vertical measurements can result from incorrect positioning of the patient's head, measurement errors on the film, or discrepancies in the projection angle [7]. The calculated asymmetry indices can't be viewed as actual anatomical relationships [8].

Kjellberg et al (1994) published a method to be applied unilaterally on each mandibular side, in order to eliminate errors caused by magnification of the radiological technique [9].

Fig.1 Case B.C., ♂, 17 years old, skeletal Class III accompanied by facial asymmetry: clinical and photographic analysis of facial landmarks

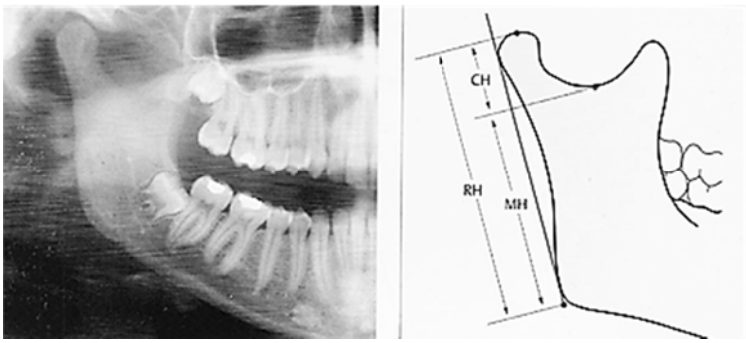

Fig.2 Kjellberg Asymmetry Index (Bumann & Lotzmann 2002); RH = total height of the mandible ramus; CH = condyle height; MH = height of the mandible ramus without the condyle.

OBJECTIVE:

The aim of our study is to investigate the prevalence of the mandible asymmetry among Class III patients and to evaluate possible correlations between the degree of asymmetry and the onset of TMD signs and symptoms.

MATERIAL AND METHODS:

The study was performed on a selected group of 50 patients (age ranged 11-17 years), investigated prior to orthodontic treatment. The patients' were fully informed on the objectives of the study and signed a written informed consent form.

Each patient received clinical examination and standard orthodontic records (plaster models, orthopantomograph, profile radiographs). The patients were assigned to 2 groups: a control group of 25 patients (13 females and 12 males) with Class I skeletal anomalies, and a study group, consisted of 25 patients (15 females and 10 males) with Class III skeletal anomalies. For each case, we established a complete diagnosis, based on clinical and radiological data, we calculated the Helkimo anamnestic and dysfunctional indices, and we analyzed the orthopantomograph according to the Kjellberg method.

During the anamnesis, we asked each patient to fill out a written questionnaire, regarding the existence of prior signs of TMD.

The questionnaire was based on previous models from the literature [10]:

1. Is it difficult to open your mouth?
2. Is it difficult to move your jaw sideways?
3. Do you have discomfort or pain on chewing?
4. Do you have a unilateral chewing pattern?
5. Do you prefer a harder or softer consistency of food?
6. Is your chewing rhythm slow, fast or normal?
7. Do you have frequent headaches?
8. Do you have pain in the neck and/or shoulders?
9. Do you have pain in the ear area?
10. Do you have facial pain on waking?
11. Did you notice any TMJ noise?
12. Do you consider your bite "normal"?

The answers were evaluated using the Anamnestic Helkimo Index (A_i) [11]:

- A_i = 0 – no TMD symptoms
- A_i = 1 – mild TMD symptoms (maxillary fatigue sensation, morning muscular pain, TMJ noises)
- A_i = 2 – severe TMD signs (opening difficulties, maxillary blocking, TMJ luxation/subluxation, muscular/articular pain).

The TMJ was examined by palpation of the lateral and posterior aspects; maximum opening, lateral and protrusion mandibular movements; and observation of the TMJ noises. The muscular exam consisted of the bilateral palpation of the masticator muscles. The clinical signs were quantified with the Helkimo Clinical Dysfunction Index (D_i) (tab. 1). D_i value is obtained by the addition of all points:

D_i = 0 – clinically healthy patient;
D_i = 1-4 – mild TMD;
D_i = 5-9 – moderate TMD;
D_i = 10-25 – severe TMD.

On orthopantomograph, Kjellberg asymmetry indices were calculated, as expression of symmetrical mandibular development. In order to determine those indices, the orthopantomographs were traced, digitized, and the following points were marked on the images: Co – Condylion (the most superior point on the condyle head), Inc – Incisura (the lowest point between condylar and coronoid processes of mandible), Go – Gonion (a constructed cross point of two lines: tangential to ramus and tangential to mandibular body). With these points, we delineated the following segments: Co – Inc

(condyle height = CH), Inc – Go (height of the mandible ramus without the condyle = MH), and Co – Go (total height of the mandible ramus = RH) [12]. Calculations were performed according to formulas: CH/RHx100% and MH/RHX 100% for the left (L) and right (R) sides (fig. 2, 3). The Kjellberg indices (K_i 1 and K_i 2) were then calculated, as indicators of asymmetrical relationships in the ascending rami.

K_i 1 = (CH_R/RH_R x 100) - (CH_L / RH_L x 100);

K_i 2 = (CH_R/MH_R x 100) - (CH_L / MH_L x 100)

All statistical analysis was performed using the SPSS software package. Descriptive statistics were computed.

The Spearman's rank correlation (a nonparametric test) was used as a measure of the variable's association.

Table 1 Helkimo's quantification of TMD signs.

Clinical signs/Evaluation criteria	**Points**
1. Amplitude of jaw movements	
Normal limits (motility index = 0)	0
Slightly reduced (motility index = 1-4)	1
Limited (motility index = 5-25)	5
2. Mandible opening movement	
No TMJ noises, horizontal deviation < 2 mm	0
TMJ noises, and/or horizontal deviation ≥ 2 mm	1
Blocking and/or luxation	5
3. Muscular palpation sensibility	
No sensibility	0
Palpation sensibility in 1-3 places	1
Palpation sensibility in 4 or more places	5
4. Articular palpation sensibility	
No sensibility	0
Lateral aspect sensibility	1
Posterior aspect sensibility	5
5. Pain during movements	
No pain	0
Pain during one mandible movement	1
Pain during 2 or more mandible movements	5

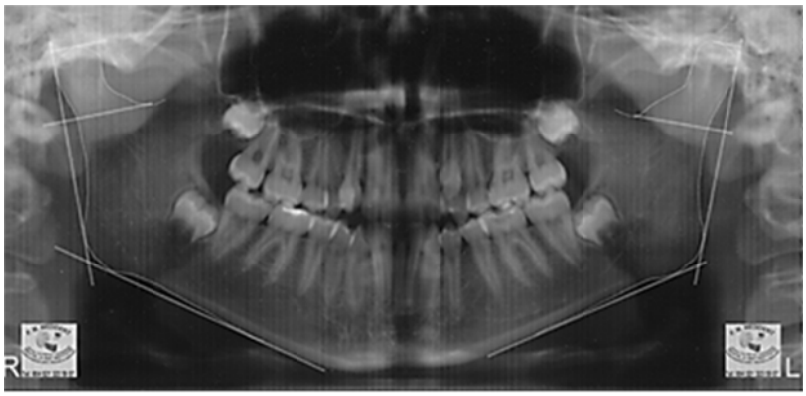

Fig.3 Case A.I., ♀, 14 years old, skeletal Cls. III: orthopantomograph analysis:
CH_R/RH_R = 32,53%; CH_L/RH_L = 39,48%; K_i 1 = 6,95%; CH_R/MH_R = 48,21%; CH_L/MH_L = 65,23%; K_i 2 = 17,02%

RESULTS

The study population presented a mean age of 13, 5 years. The control group (Class I patients) had a mean age of 13, 1 years, and the study group (Class III patients) had a mean age of 13, 6 years. Gender distribution in the sample was 52% (F) and 48% (M) in the control group, and 60% (F) and 40% (M) in the study group.

The Anamnestic Helkimo Index (Ai) was 0 for 56% of Class I patients and 48% of Class III patients, respectively 1, for 44% Class I patients and 52% Class III patients. The values of the Clinical Dysfunction Index (Di) ranged 0 - 4 (tab. 2). The figure 4 compares the values of Ai and Di indices in the studied groups. The measurements performed on the orthopantomograph revealed different degrees of mandible asymmetry (tab. 3). 48% of asymmetrical Class I patients and 76% of asymmetrical Class III cases exhibited moderate TMD signs (Di = 1-4) (fig. 5).

The results of the Spearman's rank correlation test showed that the values of Kjellberg indices correlated with those of Helkimo indices for Class III patients, in other words, the degree of mandible asymmetry correlated with the appearance of TMD signs and symptoms in the study group (tab. 4).

Table 2 The values of the Clinical Dysfunction Index (Di) in the study group.

	Di = 0	Di = 1	Di = 2	Di = 3	Di = 4
Cls. I patients	36%	36%	28%	-	-
Cls. III patients	24%	36%	12%	20%	8%

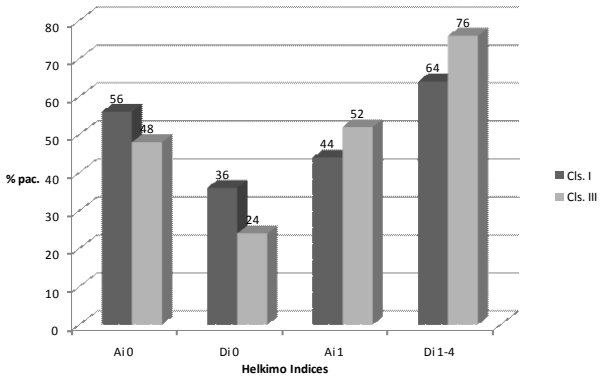

Fig.4 Distribution of the Helkimo Indices in the control group and in the two groups.

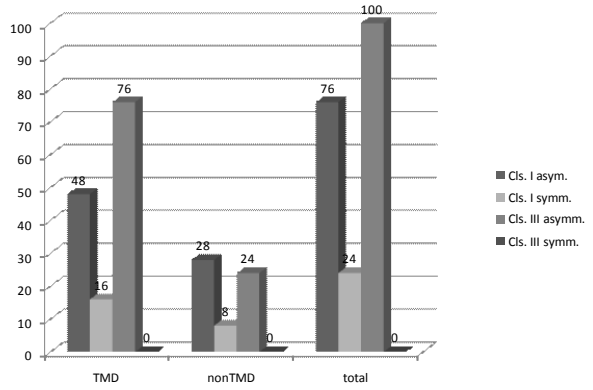

Fig.5 Distribution of TMD signs and symptoms among groups

Table 3 The calculated values of the Kjellberg Indices.

Groups	Kjellberg Indices	N	Minimum	Maximum	Mean	Std. Deviation
Cls. I	K_i 1	25	,00	4,90	2,2840	1,78575
	K_i 2	25	,00	13,30	5,4920	4,58357
Cls. III	K_i 1	25	,80	9,70	3,4800	2,82164
	K_i 2	25	1,90	21,40	8,3520	6,42976

DISCUSSIONS:

All components of the stomatognathic system and of the craniomandibular region are closely interrelated, so disturbances in one part to some extent affect other parts.

Mandible asymmetry influences normal TMJ functionality and structure, and vice versa. Our study' results plead for the existence of a relationship between mandible rami asymmetry and TMJ functionality, particularly in the presence of an orthodontic disorder. The idea of asymmetrical force loading of the two TMJ, in the presence of dental and skeletal discrepancies can be sustained. In time, such asymmetrical loads may influence intra-articular pressure and act as a trauma to the TMJ structures, inducing morphological and functional changes [13].

The present study focused on young patients, at the end of their growth period and analyzed the mandible development through comparative analysis of vertical mandible rami on orthopantomograph. In literature, the main question regarding the use of panoramic radiographs in evaluating mandibular asymmetries concerns the effect of magnification occurring at the vertical dimensions of the mandible on vertical measurements, but the orthopantomograph is well-suited as a screening tool for primary temporomandibular joint diseases, having a high sensitivity (0,81) and specificity (1,00) [14].

TMD diagnosis was based on the anamnestic and clinical data of each case. All the patients filled out a questionnaire and answered in a self-applicable manner.

The Ai Index was obtainned after the evaluation of the answers to this questionnaire.

Table 4 The results of the Spearman's rank correlation test.

Groups				Ai	Di	Ki 1	Ki2
CLS. I	Spearman's rho	Ai	Correlation Coefficient	1,000	,700(**)	-,148	-,148
			Sig. (2-tailed)	.	,000	,481	,481
			N	25	25	25	25
		Di	Correlation Coefficient	,700(**)	1,000	-,025	-,025
			Sig. (2-tailed)	,000	.	,906	,906
			N	25	25	25	25
		Ki1	Correlation Coefficient	-,148	-,025	1,000	1,000(**)
			Sig. (2-tailed)	,481	,906	.	.
			N	25	25	25	25
		Ki2	Correlation Coefficient	-,148	-,025	1,000(**)	1,000
			Sig. (2-tailed)	,481	,906	.	.
			N	25	25	25	25
CLS. III	Spearman's rho	Ai	Correlation Coefficient	1,000	,794(**)	,700(**)	,631(**)
			Sig. (2-tailed)	.	,000	,000	,001
			N	25	25	25	25
		Di	Correlation Coefficient	,794(**)	1,000	,581(**)	,524(**)
			Sig. (2-tailed)	,000	.	,002	,007
			N	25	25	25	25
		Ki1	Correlation Coefficient	,700(**)	,581(**)	1,000	,981(**)
			Sig. (2-tailed)	,000	,002	.	,000
			N	25	25	25	25
		Ki2	Correlation Coefficient	,631(**)	,524(**)	,981(**)	1,000
			Sig. (2-tailed)	,001	,007	,000	.
			N	25	25	25	25

** Correlation is significant at the 0.01 level (2-tailed).

Table 5 Results of previous studies regarding the prevalence of TMD signs and symptoms.

Author	No. of individuals	No. of women/men	Age (yrs)	Population	Prevalence (%)	
					At least one symptom	At least one clinical sign
Solberg et al, 1979	739	370/369	19-25	American university students	26	76
Swanljung and Rantanen, 1979	583	341/256	18-64	Finnish workers	58	86
Nilner and Lassig, 1981	440	218/222	7-14	Swedish children	36	72
Rieder et al, 1983	1040	653/387	13-86	American private practice	33	50
Gazit et al, 1984	369	181/188	10-18	Israeli children	56	44
Pullinger et al, 1988	222	102/120	19-40	Dental hygiene and dental students	39	48
Agerberg and Inkapool, 1990	637	323/314	18-64	Swedish adults	14	88
De Kanter et al, 1993	3468	1815/1653	15-74	Dutch nationals	22	45
Magnusson et al, 1993	293	164/129	17-25	Swedish young adults	43	-
Nourallah and Johansson, 1995	105	0/105	23	Saudi dental students	20	56
Hiltunen et al, 1995	342	243/99	76-86	Finnish older adults	80	-
Bencze et al, 2009	62	34/28	10-23	Romanian children and youth	-	64,5

Previous studies [15, 16] proved the reliability of data obtained by the anamnestic questionnaire, reporting a high correlation among the patients' answers and the clinical findings. Adding the anamnestic data provided by the charts to the physical exam's findings we can establish a correct TMJ assessment, indispensable before, during and after the orthodontic therapy.

The results of our study are comparable to those of similar surveys regarding the prevalence of TMD among different populations (tab. 5) [17, 18].

Clinical studies conducted by Ricken (2000) [19] demonstrated the onset of TMD signs and symptoms at very early ages (after 5 years old). The same author stated that 80% of orthodontically treated patients had different types of TMD before the beginning of the therapy.

These TMJ changes, undetected and ignored in the therapeutical plan, may worsen during the orthodontic treatment, which modifies the mandible-cranial position through regressive adaptation in the TMJ.

In daily practice, the evaluation of facial and mandible symmetry tends to be subjective and the inclusion of the asymmetry among treatment objectives depends on the severity of physiognomy and function alterations [20].

Asymmetry indices are objective tools aimed to estimate the mandible growth and symmetry according to radiographing images.

CONCLUSIONS:

The mandible asymmetry, constantly encountered among Class III patients in our study, correlates with the presence of TMD signs and symptoms.

Digital analysis of the orthopantomograph (routine investigations) provides important data related to mandible asymmetry and represents a value-

ble aid for proper diagnosis and treatment selection.

The results of our study revealed that 76% of Class I patients and all Class III patients presented different degrees of mandible asymmetry; we noticed higher Kjellberg Indices values among the second group.

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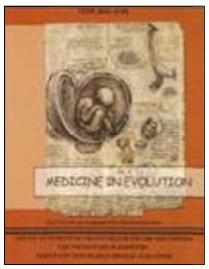
RELATIONS BETWEEN CERVICAL VERTEBRAL MATURATION AND CHRONOLOGICAL AGE



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ABSTRACT

Abstract: The aim of this study is to the establishment of the relationship between patients' chronological age and the degree of skeletal maturation in cervical vertebrae appreciated with the help of profile teleradiographies.

Material and method: we analyzed the side cephalograms of a child cohort of puberty and prepuberty age. The selected criteria applied to the subjects included were: age between 9-14, normal conditions regarding general growth and development, without severe affections in the antecedents. While the subjects' chronological age refers to the date of birth, the degree of skeletal maturation is determined through method CVM (Cervical Vertebral Maturation). In order to appreciate skeletal age 6 stages of CVM maturation are used.

Results: Stage 1 CVM of skeletal maturity or the prepubertary stage can be identified with the early stage of mixed dentition or the initial stage of permanent dentition. Stage 3 CVM or the puberty phase was identified with the last phase of mixed dentition or the initial stage of permanent dentition.

Conclusions: The early stage of mixed dentition is an excellent indicator for appreciating the degree of skeletal maturation in the growth period. The intermediate phase of mixed dentition is not a valid indicator in order to establish skeletal age.

Key words: *cervical vertebrae, skeletal maturation.*

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INTRODUCTION

The pubertary period has many advantages for doing various orthodontic treatments, and the planning of orthodontic treatment at the right time, through identifying the top of the growth period, significantly contributes to the correction of dental-maxillary anomalies.

Due to multiple changes that occur in this period; the chronological age cannot really be considered a guide regarding the child's development level. Moreover, other parameters proved to be more precise, like for example the growth speed, hormone changes, teeth development and eruption, skeleton maturation.

The standard method constantly used in the orthodontic practice for appreciating bone maturation is represented by the use of the radiography of carpal bones and hand joint that corresponds to certain stages of skeletal maturation (number of ossification centers) used as inter-laboratory standard and presented in the reference atlases.

OBJECTIVE:

The aim of our researches is to establish the relationship between the patients' chronological age and the degree of skeletal maturation in cervical membrane through up to date methods with a peculiar character that can represent suggestive indicators in establishing top periods regarding the body's growth and development.

MATERIAL AND METHODS:

We have searched the cervical vertebrae C2, C3, C4 visible on the routine teleradiographies used in the diagnosing and planning of the orthodontic treatment, in the aim of appreciating bone maturation. On the side teleradiography we can notice the form changes of cervical vertebrae upon growth. The appreciation method of the degree of skeletal maturation through examining the form of cervical vertebrae is known in the international and specialty literature as method CVM (Cervical Vertebral Maturation).

Method CVM takes into consideration the morphological changes in cervical vertebrae C2, C3 and C4 such as the concavity of the inferior margins, height and length, but also the form of these vertebrae. There are 6 stages of cervical vertebrae maturation and at each level of skeletal development, the form of these vertebrae modifies: in the first stage of cervical vertebrae maturation, the inferior margins of vertebrae C2, C3 and C4 are plate, and in the flat, and in the last stage their margins become concave.

The appreciation of the cervical vertebrae maturation degree with the help of side teleradiographies is an alternative to the classical method of evaluating the ossification degree at the level of the hand wrist HWM (Hand Wrist Method). The two radiological images, represented by the radiography of hand bones and side radiography, suggest this alternative.

We have analyzed the side cephalograms of a cohort of 24 children from all the phases of mixed and permanent initial dentition. The selection criteria applied to the subjects included in the study were: age between 9-14, normal

conditions regarding normal growth and development, without severe affections in antecedents. The subjects' exclusion criteria were: temporary dentition, permanent dentition of the adult type, craniofacial anomalies and anomalies at the level of hand bones. The subjects' chronological age refers to the date of birth, while the degree of skeletal maturation is determined through method CVM. We have emphasized the following aspects:

a. The presence or absence of the concavity of the inferior margin of the vertebrae body C2, C3 and C4

b. The form of vertebrae C2, C3 and C4 at different ages, taking into consideration 4 types of forms: trapezoidal (the superior margin of the vertebral body is elongated towards the top, from back to front, horizontally rectangular (the back and front sides have equal heights and the upper and lower sides are much larger than the front and back sides), the square form, the vertically rectangular form (the back and front sides are larger than the upper and lower sides).

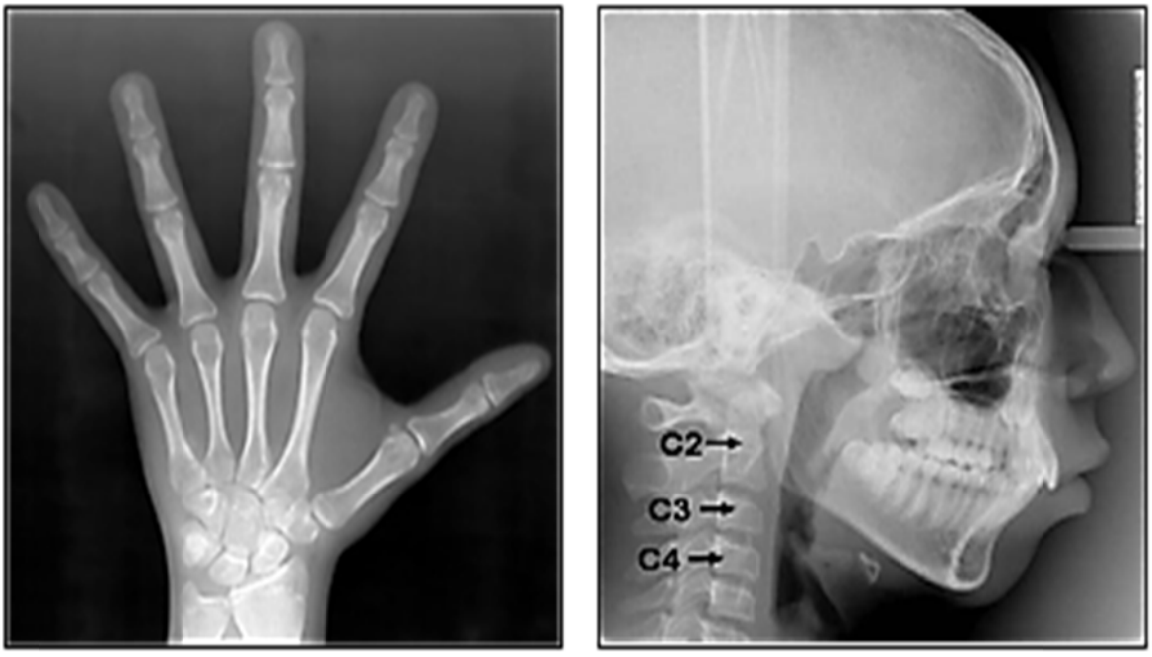

Fig.1 The radiography of hand bones and the side radiography

These characteristics are subclassified in 6 stages of CVM maturation:

Stage CVM 1. The inferior margins of vertebra 3 are flat. The body of vertebrae C3 and C4 has a trapezoidal form. The top moment in the mandibular development will not be reached sooner than 2 years from this stage.

Stage CVM 2. The inferior margin of vertebra C2 is concave. The body of vertebrae C3 and C4 is still trapezoidal. The top moment in the mandibular development will not be reached sooner than one year from this stage.

Stage CVM 3. We can notice concavities at the level of inferior margins of C2 and C3. The body of vertebrae C3 and C4 is trapezoidal or rectangularly horizontal shape. The top moment in the mandibular development will be reached in less than one year.

Stage CVM 4. We can notice concavities at the level of the inferior margins of C2, C3 and C4. The body of ver-

tebrae C3 and C4 is rectangularly horizontal. The top moment in the mandibular development took place one or two years before this stage.

Stage CVM 5. Further on we can notice concavities at the level of the inferior margins of C2, C3 and C4. The body of at least one of the C3 or C4 vertebrae has a square form, and the other is further on horizontally rectangular. The top moment in the mandibular development took place a year before this study.

Stage CVM 6. The concavities at the level of inferior margins of C2, C3 and C4 are still obvious. The body of at least one of the C3 or C4 vertebrae is rectangularly vertical, and the body of the other vertebra is square. The top moment in mandibular development took place approximately two years before.

RESULTS AND DISCUSSIONS

Method CVM supposes the emphasis of 6 stages of skeletal maturation, with the top moment of mandibular development taking place between stages 3 and 4. The pubertal top is not reached without undergoing stages 1 and 2 of bone maturation. The detection of stage 2 indicates the fact that the top moment of growth is approaching, and it will be produced in stage 3 CVM, at approximately one year from stage 2 of maturation. The active growth and development are finalized the moment when the changes of vertebrae C2, C3 and C4 correspond to stage 6 of maturation.

Stage 1 CVM of skeletal maturation or the prepuberty stage was identified with the early stage of mixed dentition or its intermediate phase.

Stage 3 CVM or the puberty phase was identified with the last phase of mixed dentition or the initial stage of permanent dentition. In the case of subjects from the intermediate stage of mixed dentition we can identify the prepuberty stage of skeletal maturation: around 60 % were diagnosed with stage 1 CVM and around 40 % with stage 2 CVM. Around 30n % of subjects with permanent dentition examined presented stage 3 CVM and only 15 % presented stages 5 and 6 CVM.

The moment when we can diagnose stages 1 and 2 of skeletal maturation in a child with mandibular deficiency, the orthodontist physician and the radiologist may wait for at least a year until a reexamination of vertebrae C2, C3 and C4 in view of starting the treatment. The appearance of a definite concavity at the level of the inferior margin of C2 vertebra indicates that the top moment of growth is approaching, at approximately one year from this stage. Stage 3 of skeletal maturation represents the ideal time span for the start of functional orthopedics, as the top moment in mandibular development will take place in less than one year from this stage.

The treatment of class II anomalies has the highest efficiency level when it includes the top moment in the mandibular development (stage CVM 3). The treatments of class III anomalies with maxillary expansion is efficient for the maxillary only if it is done before the top moment of growth (in stages 1 and 2 CVM), while for the mandible it is efficient both in the puberty and prepuberty stage. The effects of maxillary expansion in view of correcting the transversal deficiency of the maxillary are greater in the prepuberty stage.

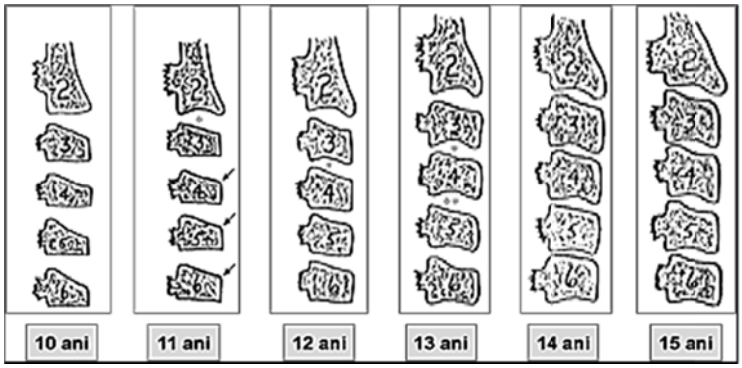

Fig.2 CVM stages and the correlations with the chronological age

CONCLUSIONS

The early stage of mixed dentition constitutes an excellent indicator for appreciating the degree of skeletal maturation in the growth period. The intermediate phase of mixed dentition does not represent a valid indicator for establishing the skeletal age.

The major advantages of CVM method are the following: the growth time span emphasized through method CVM coincides with the top moment of puberty development; the cervical vertebrae are visible on the side teleradiography which is a complementary examination often indicated for establishing orthodontic diagnose and treatment planning; evaluation of the form of cervical vertebrae is direct and relatively simple to examine; the identification degree of stages of development and cervico-vertebral maturation through CVM classification is high; the method is useful to foresee the top moment in the mandibular development in the puberty period.

Due to its practical applications, CVM method is an important diagnosis instrument. Implementing the method in taking decisions in the orthodontic field allowed an improvement of treatment results through the combination of efficient protocols with the planning of the best moment for the beginning of the treatment.

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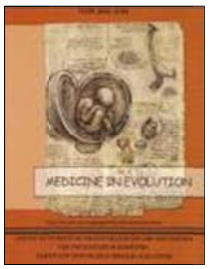
COMPLEX INTERDISCIPLINARY SURGICAL, SPEECH AND NEUROPSYCHIATRIC TREATMENT IN CLEFT LIP AND PALAT - CASE REPORT



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ABSTRACT

Speech is one of the main elements of human communication and social adaptation and production consists of articulated sounds for the communication of ideas.

Speech therapy recovery of children with cleft lip and palat depends on the severity of malformations, the outcome of surgery, the age at which speech therapy was started and not least the psycho-emotional features of the child.

Key words: *cleft lip, malformation, speech therapy.*

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INTRODUCTION

Speech is one of the main elements of human communication and social adaptation and production consists of articulated sounds for the communication of ideas.

Speech therapy recovery of children with cleft lip and palat depends on the severity of malformations, the outcome of surgery, the age at which speech therapy was started and not least the psycho-emotional features of the child.

Clefts lip and palat are the most common congenital malformations present on the face. There is no broad education of the population and people who fall enter this incidence, there is no concern in schools for this category of children.

The complexity of diagnosis and treatment, as well as therapeutic steps succession involves several specialists and depends solely on teamwork.

Part of the team are the pediatrician, the maxillo-facial surgeon, the psyho-speech therapist, the otorhinolaryngologist, the team can be supplemented if necessary.

CASE REPORT:

It is presented the case of patient KE, from Seitin city, Timis County, born on 28.04.2003, which was sent in Maxillo-Facial Surgery Clinic of Timisoara, at the age of 5 months by the family doctor for surgical treatment of the cleft lip and palat.

Reasons for referral to the doctor have been primarily swallowing functional disorders and therefore nutrition, but also the aesthetical, at this age the phono-articulatory function is not manifested.

From the mother's anamnesis, we learn that pregnancy progressed normally; delivery was performed to term and without complications, the child being born with this malformation.

Family conditions are satisfactory, the regime of life is ordered, the parents, especially the mother is very concerned with the education and child development. From the somatic point of view, the child is normally developed.

The presentation noted that until coming to the doctor, the patient was fed by bottle, food with slightly higher consistency, suppressing most of the fluids through the nose during lactation.

Labio-palato-velar cleft diagnosis was established and surgical treatment instituted according to the protocol.

The first surgical stage was performed at the age of 6 months, consisting in lip, alveolar ridge and nasal wing restoration. The restoration was made in three plans (cutaneous, muscular and mucous) and the nose wing was repositioned so as to achieve as much as possible symmetrical nostrils.

The second stage was performed at the age of 1.5 years and consisted of palate and soft palate plastic surgery, basic functionally elements for both swallowing and phonation. This step was intended to be made before the patient begins to speak. The palace was locked in two plans (nasal and oral) and the soft palate in three plans (pharyngeal, nasal and oral).

The intervention considered: separation of the oral from the nasal cavity; development of a veil, long and flexible enough; reduction of the oropharyngeal isthmus.

The third surgical stage was performed at 3 and 6 years and targeted the correction of postoperative scars in the soft palate consisting of velar impairment, the soft palate being short and stiff. A pharyngoplasty shall be made in order to lengthen the soft palate. The technique used was the one creating a posterior pharyngeal flap, based lower (Passavant).

After pharyngoplasty, the patient still has impaired phonation; there is a residual resonance and articulatory disorder.

Throughout the entire period, pre and postoperative from the 2.5 years of age, the child was carefully monitored by the psyho and speech therapist and the infantile neuropsychiatrist where EEG pathways were performed.

Their interpretation highlighted the theta-delta polymorphic route, without unloading the pathological elements, but also the microlezional cerebral route for which treatment with Tanakan, Encefabol, Millgama was recommended. Following the consultation conducted in Infantile Neuropsychiatry Clinic, the specialist established that in neuropsychiatric terms, the patient has a developmental delay due to the late appearance and development of the oral language in terms of fonoarticulatory execution of the acquisition and usage of vocabulary.

The child presents an increased psychomotor instability, attention is very labile, with a very low power of concentration and low analysis and synthesis processes that hinder the acquisition of speech. Understanding is largely preserved.

Speech therapy treatment aimed in the beginning restoring the confidence, raising awareness and creating a positive emotional tone. In the first sessions, the child was accompanied by the mother, thus creating a family atmosphere.

After surgery, speech therapy focused on: education of breath, respiratory system gymnastics, and exercises for the development of labial ability, mobility exercises for the development of tongue mobility, for the palate and pharyngeal muscles.

Along with exercises of respiratory gymnastics and the fonoarticulatory device it was pursued the development of phonemic hearing (by imitating sounds of nature, distinguishing the deaf consonants from the audible consonants). Audible attention and memory formation was pursued by reference to the finished goods (what is? how does? where is? "How many legs does it have? Pointing and showing at the same time). Language evolution was slow, wrapping characteristics caused by organic disorder. The first words attempts occurred after 2 years of age, being pronounced poorly because of the impossibility of articulating most of sounds and because of phonemic hearing disorder.

The need for repeat surgery and thus the impossibility of starting speech therapy, has led to the stagnation of the vocabulary and the possibility of communication.

Understandable vocabulary has increased much faster than the one used verbal means of communication being replaced with gestures, the mimics and verbal emissions being difficult encoded. The child attends kindergarten at the age of 5 years.

Specialized speech therapy observations have stated: Speech and language development are very limited due to serious changes in articulatory organs. The cleft caused a number of fonoarticulatory system disorders with consequences on articulation and tones sound system. Malformations of the upper jaw led to the muscular inertia of the tongue and upper lip. The upper lip being immobile, inert, the child cannot

pronounce the vowels "a", "u", "a". The child cannot close the mouth corners, and therefore cannot pronounce the consonants "p", "b", "s ", "z", "t". Dento-maxillary anomalies led to the deflection of the articulation points for the dentals "t",'d', 'n', by removing the tip of the tongue outside the dental arches. In general articulation points are all defective for consonants and vowels, abnormal position and function leading to polymorphic changes. Most consonants are replaced with a nasal breath; others are replaced ("v " with "f", "c" with "g") because of the inability to differentiate between hearings.

Being extremely disrupted, the phonemic hearing does not allow the patient to achieve phonetic differentiation, establishing the series of sounds, unable to properly notify the general structure of the phonemes and the words. Auditory attention is very low. There is a weak capacity to be attentive to what she hears, to differentiate between sound complexes. Inner speech is preserved. Expressive speech is very limited and distorted, is not aware of the mistakes and therefore neither monitored. Active vocabulary is extremely reduced.

Otolaryngology consultation was sought. In the intravenous sedation, rinoscopy and otoscopy is performed. At otoscopy, narrowing of the left external ear canal in the presence of an obstructive membrane in one third from average is revealed. Rinoscopy reveals an obstructive nasal syndrome, rhinitis and nasal discharge.

It is recommended to perform a review of an antimicrobial nasal secretion.

In the specialized service, an audiogram is performed, being diagnosed with perception hearing loss.

It was recommended a hearing aid, which she still bears.

The most characteristic sign of hearing deficiency at this age is deflection of vowels, with different degrees of reduction in the stock of words.

RESULTS

Complete diagnosis, following the evaluation of the case stated for a period of six years was: cleft lip and palat, retarded language, polymorphic changes on the organic background, organic changes (cleft caused by labio-palato-velar) otitis media, nasal obstruction syndrome, perception hearing loss.

Therefore a complex interdisciplinary treatment plan was established consisting of:

- surgery, performed in several distinct phases at intervals of over an year to create anatomic conditions close to normal;
- pre-and postoperative speech therapy care;
- neuro-psychiatric treatment;
- otolaryngology treatment with hearing aids;
- orthodontic treatment to correct malocclusions.

The interdisciplinary treatment was obtained following:

- *restoring of the lip* with good aesthetic and functional results of full recovery;
- *restoring of the hard palate and soft palate* with the restoration of swallowing function and creating the organic premises for the development of phonation and therefore the speech;
- after plastic surgery of the upper lip and palate, the evolution regarding the *rectification of language* is good;

- a good cooperation with the *psyho-speech therapist*, becoming more careful, more motivated, a rapid and dynamic activity integration was noticed from the beginning;
- throughout the therapy, we achieved a very good cooperation with the mother, and the fact that she continued speech therapy exercises at home, facilitated the positive evolution of this case;
- the patient hears the entire sound, which can locate their origin in space.

DISCUSSIONS:

Although the patient was submitted only for surgical treatment, has been shown that this is not enough for achieving a proper speech.

Following surgical treatment of the soft palate, scars appeared as velopalatine failure, which prevented the rapid development of the speech and then the psychosomatic development, requiring further intervention.

Cleft lip and palat was associated with middle ear disorders and hearing disorders that, combined, led to a delayed development of speech with neuropsychiatric consequences.

The maxillo-facial surgeon has, perhaps, the most important role in the treatment of these cases, him being the first in a succession of specialists facing the case, and also, is the one creating the functional premises for other treatments. He is the one who knows and sets the stages and the time of their surgery.

He observes the associated disorders of these patients and establishes the specialists' team required for achieving the interdisciplinary treatment.

It is very important that, the start time of speaking to capture the child in normal or nearly normal anatomical circumstances, the phonetic defects being significantly lower and easier to adjust in this case.

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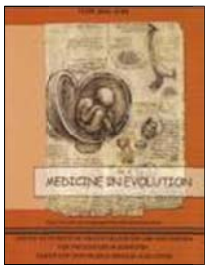
PREVENTION AND EARLY INTERVENTION STRATEGIES IN FIRST EPISODE PSYCHOSIS IN CHILDREN AND ADOLESCENTS



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ABSTRACT

Introduction: *The childhood psychoses represent a major public health problem. Through this, appears the necessity of early detection aiming the implementation of some early intervention strategies.*

Objectives: *the prospective identification of children with a high probability to develop a psychotic disorder, the recognition of the vulnerability markers in the "high risk" groups, the early detection and prevention of a first psychotic episode, the approach of optimal intervention strategies, the minimalizing of the duration of untreated psychosis-DUP.*

Methods: *In our study, accomplished during the period 2000-2010 on the two groups - 90 children with psychotic onset and the control group - 77 „high risk" children having psychotic parents, we applied the following standardized instruments: CBCL- Child Behavior Checklist, SCL 90 - Symptoms Checklist, FAD- Family Assessment Device, PANSS-Positive and Negative Symptoms Scale. From the 77 „high risk" children group, 37 received therapy and support.*

Results: *Through one way ANOVA, we obtained statistically significant correlations, p<0,001, between CBCL-SCL/SCL-FAD scores. CBCL showed high internalization=28 /externalization=32 scores, in both groups. Through the CBCL-SCL correlation: high obsessive values in parents determine high internalization scores in children. SCL-FAD correlation: a strong positive relation between the parent's symptoms and the disturbed family functioning. The total mean PANSS score was 89.03 ± 20.1, the positive symptoms score 23.8±6.5 and negative score 20.02±8.8.There were significant positive correlations between negative symptoms, long DUP and a poor outcome. (Spearman's p =0.012).*

Conclusions: *Through therapy, only 10% of the "high risk" children developed psychosis in comparison to 35% in the group of children who didn't receive therapy, proving the fact that the onset can be delayed or even prevented. DUP remained a significant predictor of outcome, proving to be a target for secondary prevention.*

Key words: *high risk, psychosis, prevention, early intervention, prognostic*

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INTRODUCTION

The fact that treatment delay - the duration of untreated psychosis (DUP) in children and adolescents - is associated with a range of poorer outcomes for patients with psychosis is well-known.

Treatment delay is also recognized as one of the few predictive indicators amenable to change, being therefore a high priority for clinical and research programmes engaged in the field of child and adolescent mental health.

We already know that DUP comprises several facets, including delay in help seeking, delay in referral to services and delay within mental health services. Each of these situations may require different intervention strategies to achieve the optimal effect.

It is understood that alongside this work, public health initiatives are vital to reduce delay by engaging the public with programmes increasing awareness and reducing stigma.

Service systems research indicates that effective health promotion programmes should include multi-level strategies comprising the children's families, neighbourhoods, schools and communities [5].

We will present a description of some of the novel approaches currently in progress, encouraging prompt access to appropriate treatment and early intervention.

OBJECTIVES:

Through the study, we aimed: the prospective identification of children with a high probability to develop a psychotic disorder, the recognition of the vulnerability markers in the "high risk" groups [1, 2], the early detection and prevention of a first psychotic episode, the approach of optimal intervention strategies, in order to reduce the duration of untreated illness -DUI, respectively of the untreated psychosis – DUP [9]. Through our applied research interventions we aimed at both understanding and influencing the reasons for delay in accessing appropriate treatment.

One of our objectives has been to increase awareness and to reduce stigma concerning psychotic disorders in children and adolescents.

MATERIAL AND METHODS:

Our study consists of a retrospective research (2000-2007) as well as a prospective research performed between 2007-2011 in the Clinic of Psychiatry and Neurology for Children and Adolescents Timişoara. The Ist step of the study was composed of the identification of children and adolescents, which needed ambulatory care or were inpatients of our clinic and developed a first psychotic episode. The present study is part of a larger pilot study on a number of 90 patients-children and adolescents with a diagnostic of first psychotic episode.

We assessed for each patient, besides the clinical parameters: the prodrome's duration, the duration of untreated psychosis (DUP) and the duration of untreated illness (DUI).

We included in our control group 77 help seeking "high risk" children, offspring of parents with schizophrenia or affective psychoses, who were in the

evidence of our clinic for different psychopathologic disorders.

Inclusion criteria:

1. A diagnostic of psychotic disorder, according to DSM IV, K-SADS-PL
2. Age < 19 years
3. The global PANSS score had to be in the value interval 60-120
4. Monoparental or biparental families, children being raised in the family
5. The informed consent to participate in the study, given by the parents as well as the child

For the selection of the „high risk" children cases we took as inclusion criteria the accessibility of children and families in order to apply our instruments and also the presence of one parent suffering from psychosis (nonaffective, affective) [3].

Our study group as well as the control group was examined for associations with variables contributing to delay in help seeking, delay in referral and delay in getting appropriate treatment. The compulsory evaluations included: the phase evaluation of the clinical, neurobiological markers and reevaluations applying the standardized instruments.The instruments were applied in parallel on the two groups: 90 patients with psychoses and 77 „high risk" children from families with one psychotic parent.

We approached the following instruments: CBCL-Children Behavior Checklist, SCL 90-Symptoms Checklist, FAD-Family Assessment Device, PAN SS-Positive and Negative Symptoms Scale.

Additionally we applied the SIPS-Structured Interview for Prodromal Symptoms in the „high risk" children group, in order to identify some markers of conversion to psychosis in this vulnerable population.

CBCL includes 118 items referring to behavioral and social competence problems of children, evaluated by parents.

The SCL 90 is very often used as screening for psychopathology (Kaplan, 2000). The 90 items are grouped in 9 scales. Concerning the validity of the test, the inner consistence for clinical situations, reported by the authors was between r = .79 and r = .89, the intercorelation of the scales being r = .45; the reliability test-retest after 1 week = .73 and .92.

Through FAD we evaluated the family functioning, being especially important for families with a member with mental disorder. Previous research showed that the risk of developing a mental disease gets higher when multiple adverse conditions are accumulated (Rutter, 1994; Kolvin, 1988).

PANSS was applied, in order to offer an objective measure for the psychiatric symptoms.

The description given for each symptom and the 7 ankor points set, specific for each symptom offered an coherent scoring method. Through PA NSS we evaluated the positive, negative and general symptoms in our study group [4].

We used: descriptive statistics-average, standard deviation, absolute and relative frequencies, parametric statistical tests-simple ANOVA and simple factorial ANOVA; the Pearson correlation test to check for the presence of statistically significant correlations between the CBCL-SCL 90 results, the CBCL-FAD and the SCL 90-FAD results; as well as the Pearson correlation test to check for the presence of statistically significant correlations between the course of illness and other various clinical parameters (DUP, the prodrome duration).

We had the support of the SPSS statistical program as well as MedCalc.

RESULTS

The results were analyzed through parametric statistical tests: simple ANOVA and simple factorial ANOVA, with the support of the SPSS statistical program. The independent variables were: the age, sex, clinical diagnosis, the family type (disordered parent). The dependent variables were the scores obtained through the application of the instruments.

The CBCL Scores Analysis

Concerning the CBCL total social competencies scores, the 90 patients with psychoses group registered lower median total competencies scores, especially lower social competencies scores than the "high risk" children group.

The "high risk" children group proves to have lower median social competencies total scores than the population in non-clinical range. These values in "high risk" children prove the fact that a high percentage of children with psychotic parents show a dysfunctional social functioning (Table 1). The scores for behavioral problems in both studied groups showed high values for aggressiveness and depression. For the group of children with a first psychotic episode (Bender 2006): all patients show high scores for aggressiveness, depression, the scores being much higher than those in the "high risk" group. In this group the externalization, as well the internalization scores are much higher than in the "high risk" group. In the high risk children group, all the children having a parent suffering from psychosis, showed high scores for depression, hyperactivity and aggressiveness.

The boys showed high externalization scores (hyperactivity, aggressiveness). The girls showed high internalization scores (depression, avoidance, and somatization).

For the comparison of the results obtained through CBCL for both children groups we applied One Way ANOVA test, this showing that there were statistically significant differences ($p<0,001$), between the scores obtained for each group. So that, the children from the group with a first episode psychosis showed higher global CBCL scores (fig.1).

The SCL-90 Scores Analysis

We obtained the highest scores for the variables obsessive-compulssiveness, depression, sensitivity and paranoid ideation for mothers as well as for fathers. The scores obtained by the mothers are higher, resulting the fact that the mothers are more affected by their children's psychopathology. As well, the scores obtained by the families with a psychotic parent are much higher than those obtained by the parents having a child with a first episode psychosis (fig.2).

FAD Results Analysis

We obtained high FAD scores for the "high risk" children group, especially for the mothers, respectively for the psychotic parent, for the variables roles, affective responsiveness, and for the fathers for the behavioral control. Both groups are strongly affected, concerning the global family functioning.

The Correlations Analysis: Through one way ANOVA correlations between CBCL-SCL / SCL-FAD scores, we found statistically significant values, $p<0,001$. The CBCL showed high internalization=28 / externalization=32 scores - depression, hyperactivity, aggressiveness and anxiety in both groups.

The SCL showed high anxiety, depression and obsessive-compulsive scores for the parents in both groups.

The FAD showed high scores for communication, affective responsiveness, role distribution and control problems. SCL-CBCL correlations: high obsessive values in parents determine high internalization scores in children and high depression and anxiety values determine high total CBCL scores and through SCL-FAD correlations: strong positive relation between the parent's symptoms (sensitivity, depression) and disturbed family functioning (affective responsiveness, implication).

The total mean PANSS score was 89.03 ± 20.1, the positive symptoms score 23.8 ± 6.5 and negative score 20.02 ± 8.8. We found, higher negative symptoms PANSS scores in the "high risk" group, the negative symptoms appearing as a genetic marker, ~2 years before the active psychosis phase [4].

There were significant positive correlations between negative symptoms, long DUP and a poor outcome. Poor insight was correlated with symptom severity and poor global functionning (Spearman's p =0.012).

We found statistically significant correlations between adequate therapy, early intervention strategies and the diagnostic evolution in the "high risk" children group, at follow-up after 5 years (Figure 3.).

Table 1. CBCL median competencies total scores for both groups

	Competencies Scales	PSYCHOSES	HIGH RISK
Mother	Activities	2	4
	Social Competencies	1.5	4.5
	School Competencies	2	3
	Total Competencies	**5.5**	**11.5**
Father	Activities	2.1	4.5
	Social Competencies	3	5
	School Competencies	2.4	3.5
	Total Competencies	**7.5**	**13**

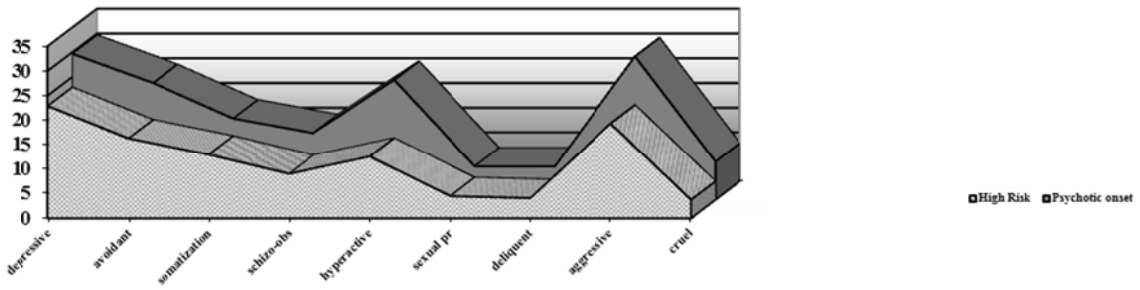

Fig.1 The Median Global CBCL Scores in both groups.

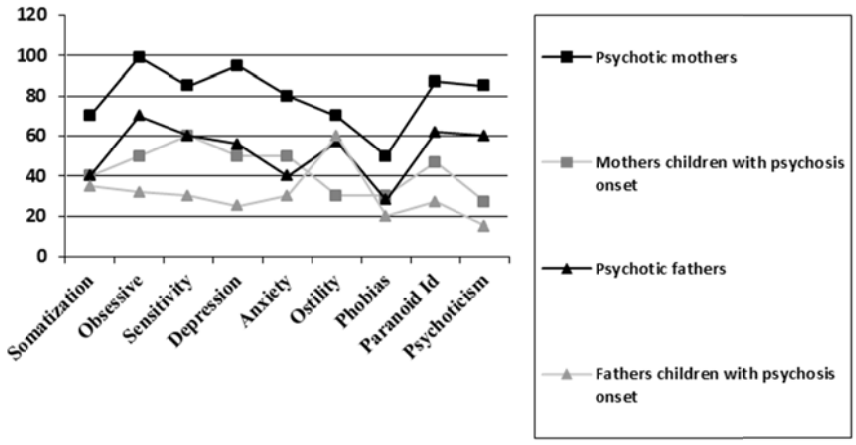

Fig.2 SCL-90 Median Total Scores in both groups.

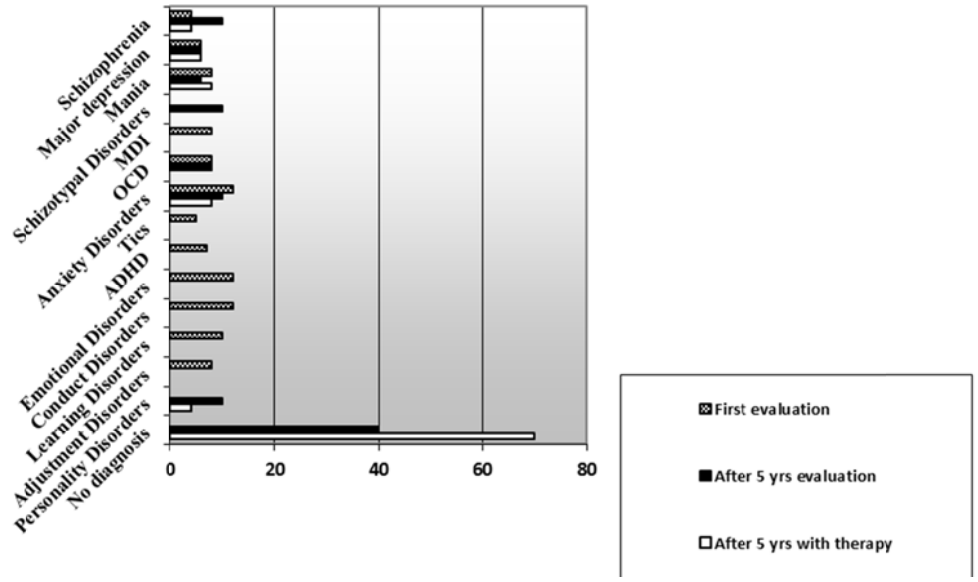

Fig.3 High risk group diagnostic evolution.

DISCUSSIONS:

Through our study, we observed that particularly, the awareness of insidious features such as functional decline and social withdrawal as signs of prodromal psychosis in children and adolescents, is a significant pathway for early detection and intervention.

In conformity with the actual international research results, we noticed that subclinical psychotic experiences during adolescence represent the behavioural expression of liability for psychotic disorder.

Although, some results of the present study are similar with results of other studies, it gives a greater importance and attention to the parameters of first psychotic episode in children and adolescents, but also for the response and evolution after specific intervenetions [6, 7, 12].

The revealed aspects through this study offer further implications and perspectives for future research in the field of mental health promotion, implementation of strategies and early

intervention programmes in child and adolescent psychoses, as well as for the necessity of future development of our services.

One of our future aims would be to develop a common care pathway for early intervention teams in the region with agreed standards.

CONCLUSIONS:

Ensuring adequate opportunities for the diagnostic and early intervenetion in cases of first psychotic episodes in children and adolescents can play a determinant role in the short and long term course of first psychotic episode [12]. Early intervention in the prodromal or even premorbid phase is very important for children and adolescents, because developing psychosis in this age has signifigant impact and outcomes, interrupting the normal course of development.

The vulnerable child has some characteristics, which put him in a risk position. If proper intervention strategies are applied, the vulnerability can be balanced through protective factors [11]. So that we have to work on the rehabilitation of the child as well as on the family disfunctionalities.

Through therapy, only 10% of the "high risk" children developed psychosis in comparison to 35% in the group of children who didn't receive therapy, proving the fact that the onset can be delayed or even prevented. DUP remained a significant predictor of outcome, proving to be a target for secondary prevention [8, 10]. Through proper intervention strategies the QOL-quality of life of the patients and their families can be ameliorated, as well as the prognostic of patients with psychosis. We achieved new perspectives, through new diagnostic and monitorizing methods, through the implementation of a complex model of interventions and strategies.

We found that all the diagnostic concepts were provisory through the evolution perspective, so that proper intervention strategies are significant for these age groups. On long term, we noticed high diagnostic interindividual variability. In our studied groups, the prognostic was very poor especially when the psychosis onset was very early (9-12 years).

We noticed a more severe prognostic for the cases with very early onset of psychosis or with a longer DUP and in the cases with predominantly negative symptoms [6, 7].

A better prognostic was achieved for the cases with an acute onset, with predominantly positive symptoms and with a good premorbid functioning.

Abreviations:
OCD- *Obsessive-Compulsive disorder*
MDI- *Multiple Developmental Impairments*
ADHD- *Attention deficit hyperkinetic disorder*

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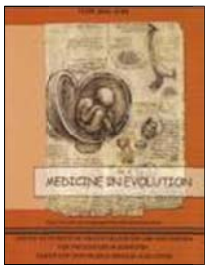
MANAGEMENT OF POST – AVULSION ALVEOLAR SOCKETS



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ABSTRACT

The authors present the prosthetic treatment planning and therapy in tooth avulsion cases. Most traumatic dental lesions in children and young adults affect the frontal teeth due to their position on the dental arch, the central incisor being the most frequently involved.

This article presents the treatment of a 17 years old patient who at the age of 7-8 years, while playing in his yard in the country, was hit by a horse´s hoof resulting in an injury of the upper lip and dentoalveolar trauma, with the avulsion of 1.1 and 1.2.

Key words: *prosthetic treatment, avulsion, traumatic dental lesion.*

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INTRODUCTION

Tooth avulsion represents 3% of total dentoalveolar trauma in the civilized world, the most common cause of avulsion being sports accidents. The maxillary incisor region is the most exposed to trauma during childhood and adolescence.

Besides the immediate prejudices generated by the loss of one or more permanent teeth, later appears the problem of managing the edentulous space. The lost teeth are not always recovered and brought to the dentist, also the patient´s presentation to the doctor after the accident, when the bleeding stopped, becomes rarer.

Andreasen´s advices for patients with avulsed teeth are welcomed:

- Replant the tooth (temporary teeth must not be replanted);
- If the tooth is dirty, wash it for about 10 seconds under cold running water and reposition it;
- If replantation is not possible, keep the tooth in the patient´s mouth, in a glass of milk or in saline;
- Seek emergency dental treatment immediately.

These advices should be spread and propagated in our country.

Aim

The present paper will attempt to evaluate the necessity of prosthetic therapy in cases of dental avulsion.

MATERIAL AND METHODS:

In the interval between 2001-2011 at the Department of Paedodontics and Orthodontics, 257 children and adolescents affected by dentoalveolar trauma presented. Most of them were extrusive luxations. Out of the 257 total patients, 27 presented dental avulsions; 15 of them were solved in our clinic and the rest were treated in the Prosthodontics Department. In this paper we will present the case of a boy from a disorganized family.

The patient P.M., aged 17, was brought in May 2002 to our clinic by his mother. According to his mother, at the age of 7-8 years old he was hit by a horse´s hoof resulting in the loss of two permanent teeth (1.1 and 1.2.) and a few temporary teeth. Until the age of 17 no doctor has seen him, the patient refusing any contact with a doctor.

After two years, he came back to the clinic with his father in order to request dental treatment.

Fig.1 initial case and study model

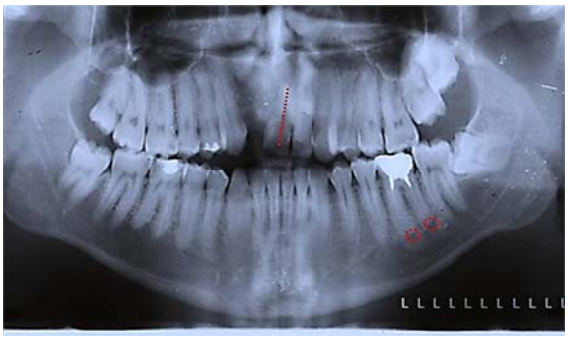

Fig.2 OPG presentation

Exo-oral exam:

- proportions of the face are normal;
- profile exam shows a false progeny.

Intraoral exam:

- underdimensioned frontal edentulous space;
- open bite;
- upper left central incisor (2.1) presents colour changes, does not answer to vitality tests.

After a discussion with the patient and his caregivers we learned his claims:

- Refusal of any fixed orthodontic appliance;
- Refusal of any surgical orthodontic intervention;
- Requests maximum aesthetic result with minimum suffering;
- Solving the open bite.

Our *treatment objectives* are:

- frontal space closure;
- optimum aesthetic result;
- 5-10° nasolabial angle closure;
- labiodont occlusion.

Phases of treatment:

- Endodontic treatment for 2.1;
- Resizing the edentulous space from 4 to 8 mm wide exclusive through prosthetic methods;
- Canine substitution (1.3 as 1.2);
- Tooth preparation (1.4, 1.3, 2.1, 2.2).

- A satisfactory temporary fixed prosthetic restoration was made and later a metalceramic fixed prosthesis with gingival mask (M.Barbu technique).

Fig.3 Provisional prosthetic restoration.

Fig.4 View of the final result.

DISCUSSIONS:

Management of maintaining a calibrated edentulous space during the growing and development period of the stomatognathic system is very important.

An interdisciplinary approach between paedodontics and maxillofacial clinics is essential in order to optimize working techniques and obtaining favorable results on the long term.

Prosthetic treatment in dental avulsion cases must not be confused with emergency therapy, when surgical measures like: replantation, transplantation, immobilization and contention stand out and when tooth recovery is on the foreground. Prosthetic treatment is usually a late measure that takes place when recovery of natural teeth is out of the question.

CONCLUSIONS:

1. Avulsions are the most serious, expensive and undesired type of dentoalveolar trauma;
2. After passing of the avulsion moment, a major part of the patients forget about their tooth loss;
3. Human aggression level is rising among young people;
4. Management of post-avulsion alveolar sockets is a problem that more of our contry´s paedodontists must take into consideration.

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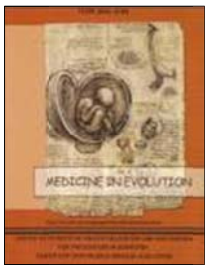
DIAMETRAL COMPRESSIVE STRENGTH PARAMETERS OF CHILDREN'S CORONARY RESTAURATIVE MATERIALS



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ABSTRACT

The progress in developing dental materials, the popularity of compozite restaurations, the increased need for esthetic function and appearance on the market with more and more products of direct dental restoration, gives the practicing dentist a wide range of options in choosing a restaurative dental material. Choosing the dental restauration material depends on the clinical case, dentist performance and not the least on the particular qualities of the dental material. In practice of pedodontics, beside all of these requirements, the clinician should consider a number of other factors such as morphostructural features of both temporary and permanent teeth in young children and the particular behavior of children.

In this study we took into consideration several classes of direct dental restauration materials and selected randomly some materials for each class: glass-ionomer cements, Ketac Molar Easymix and Fuji IX; resin modified glass-ionomer cements (compomers) Vitremer and resin based restauration materials conventional composites, Filtek Z250 and Gradia and nanocomposites , Filtek Ultimate and Premise.

We studied the diametral compressive strength on the 7 specimens we have made from every material (resulting 49 specimens for all selected materials) using Zwick/Roel machine. We evaluated and compared the results bringing additional information regarding which restaurative material should be chosen in direct dental restaurations in practice of pedodontics.

Key words: *diametral compressive strength, glass-ionomer cements, composites, dental materials*

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INTRODUCTION

The progress in developing dental materials, the popularity of compozite restaurations, the increased need for esthetic function and appearance on the market with more and more products of direct dental restoration, gives the practicing dentist a wide range of options in choosing a restaurative dental material. Choosing the dental restauration material depends on the clinical case, dentist performance and not the least on the particular qualities of the dental material. In practice of pedodontics, beside all of these requirements, the clinician should consider a number of other factors such as morphostructural features of both temporary and permanent teeth in young children and the particular behavior of children.

Choosing the dental material for tooth restauration, takes into acount several factors. The particularities in removig decay from teeth, for temporary and permanent teeth in young children, leads to cavities, which can not always take into acount Black's rules. From this point of view the dental material for tooth restauration should be the one that makes a connection between tooth and filling. This directs us to dental restoration materials such as conventional glass-ionomer cements, resin modified glass-ionomer cements, and resin based restauration materials (conventional composites and nanocomposites).

For Black's class one or two, where occlusal stress is high; we should choose a dental filling material that can withstand occlusal forces. Amalgam and resin based dental restauration materials such as conventional composites and nanocomposites withstand occlusal stresses, which makes them the best choise in these cases. Due to impact on the environment, mercury effect on the general state of the body, amalgam, which was in the past, the most used dental restauration material in pedodontics, makes its applicatibility in dentistry to be greatly reduced (Sweden restricted its use from 1995). Glass-ionomer cements can not withstand occlusal forces for a long period of time. They still can be used as dental restauration materials for temporary teeth which have a short period of time on dental arcades. For dental restauration on permanent teeth in young children and temporary teeth which must remain on dental arcades for a long period of time, we should consider resin based restauration materials such as composites that have the strength to bear occlusal forces, are rigid, have great wear resistance, make a connection through the adhesive to the tooth structure preserving tooth structure, strengthening teeth and providing a very good esthetic function to the dental restauration.

Because of the cariostatic effect at the side of the dental restauration, due to gradual release of fluorine, reminalising dental surfaces, the minimum sacrifice of dental substance, lack of pulpal toxicity, good biocompatibility, thermal expansion coefficient close to the tooth's structure and chemical adhesion to dental tissue, make glass-ionomer cements to be an option for direct crown restauration in pedodontics.

In practice of pedodontics, where the clinician uses resin based restauration materials, he should consider their requirements: elaborate technique, a long time to achive dental restauration, good isolation, creating a point of contact optimum in second class cavities (depending on the viscosity of the material, which ensures its condensation, depth of polymerization, etc..), etc. If

some of these goals can't be met, due to the particular behavior of children and the morphostructural features of both temporary and permanent teeth in young children, another choise should be made.

Beside the information given by the manufacturer and the clinical indications of these materials these study aims to bring additional information re-garding which restaurative material should be chosen in direct dental restaurations in practice of pedodontics.

Finding the values of diametral compressive strength should help us in choosing the restaurative material for first and second class cavities in Black classification.

MATERIAL AND METHODS:

In this study we took into consideration several classes of direct dental restauration materials and selected randomly some materials for each class: glass-ionomer cements, Ketac Molar Easymix and Fuji IX; resin modified glass-ionomer cements (compomers) Vitremer and resin based restauration materials conventional composites, Filtek Z250 and Gradia and nanocomposites, Filtek Ultimate and Premise. They are presented in the table below, as well as their abbreviation used in the study.

Researching the values of diametral tensile tensile strength of the selected direct dental restauration materials was made in 5 separate steps. The steps taken in this research study are:

- step 1: makeing the model patterns for the moulds;
- step 2: achieveing the actual moulds;
- step 3: achieveing the specimens for testing;
- step 4: testing the specimens;
- step 5: recording and evaluating results.

The category of direct dental restaurative material	The name of direct dental restaurative material	Abbreviation
glass-ionomer cements	Ketac molar	KM
nanocomposite	Premise	P
composite	Filtek Z250	FZ250
nanocomposite	Filtek Ultimate	FU
resin modified glass-ionomer cements	Vitremer	V
glass-ionomer cements	Fuji IX	F IX
composite	Gradia	G

Fig.1 Dental materials used in this study.

We have made 7 specimens of each dental material, resulting in 49 specimens. The specimens had the interior diameter of 6mm and 4mm in height. Initial samples were made from wax and later in acrylic material, and having those we made the moulds. In those moulds we have condensed the direct dental restauration materials selected in this study, resulting specimens with interior diameter of 6 ± 0.5 mm and 4 ± 0.5mm in height (fig. 2).

The specimens for glass-ionomer cements and resin modified glass-ionomer cements were made by mixing the powder with the liquid, in the pro-

portion indicated by the manufacturer, on a impermeable paper, and after that they were condensed in the moulds. A glass plate was put and we have applied a digital pressure until the excess has been eliminated. After setting, the specimens were finished, and stored in distlled water for 24h.

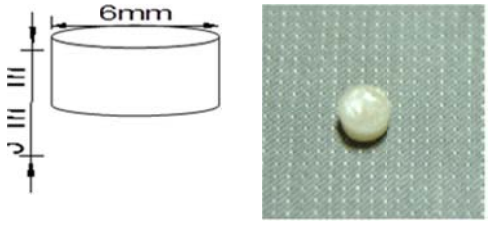

Fig.2 The specimen made from direct dental

Fig.3 Zwick/Roel machine together with the specimen to be tested.

The specimens from light-cure resin based dental materials were made by condensing them in two separate layers, each 1.5 mm, each cured separately, for 40 seconds ensuring the depth of cure. The specimens were tested to obtain the values of diametral compressive strength. They were put between two metal plates, in the Zwick/Roell Z005 machine, as shown in figure 3. A vertical force was applied on the specimens at a crosshead speed of 1mm / minute, and the force value was registred by the machine.

Then, this value was converted to MPa using the formula $\sigma t=2F/\pi dh$, where F is the force registered by the device, π is a constant value of 3.1416, d is the interior diameter of the specimen and h its height.

RESULTS

After performing the calculations using the formula presented above, we obtained the values of diametral compressive strength. Statisticaly, in the table below were placed the average values for each type of material. Diametral compressive strength values are expressed in MPa. Analyzing the results for each type of material, we have noted the following:

- *Glass-ionomer cement Ketac Molar* has the lowest diametral compression strength of all the materials used in this study.
- *Glass-ionomer cement Fuji IX* has an average diametral compressive strength value for glass-ionomer cements, and it is higher than glass-io-nomer cement Ketac molar. In the general picture, glass-ionomer cement Fu-ji IX is still one of the lowest values of diametral compressive strength, compared with the other materials used in this study, being smaller than that of resin mo-

dified glass-ionomer cement Vitremer, and significantly lower than composite resins.

- *Resin modified glass-ionomer cement Vitremer*, has the highest diametral compressive strength value of glass-ionomer cements but significantly lower than that of resin composites and nanocomposites.
- *Resin based restauration material, Gradia* has diametral compressive strength values significantly higher than glass-ionomer cements and for re-sin based dental materials shows one of the highest diametral compressive strength value, lightly lower than that of nanocomposite Filtek Ultimate.
- *Resin based restauration material, Filtek Z250* shows the diametral compression strength values significantly higher than the glass-ionomer cements and for composite materials has an average value of diametral compressive strength being higher than the nano-composite Premises but lower than composite Gradia and nanocomposite Filtek Ultimate.

The category of direct dental restaurative material	Diametral compressive strength in Mpa
glass-ionomer cements KM	9
nanocomposite P	45
composite F Z250	51
nanocomposite FU	58
resin modified glass-ionomer cements V	24
glass-ionomer cements F IX	13
composite G	55

Fig.4 Diametral compressive strength values, are expressed in MPa.

Direct dental restauration material, nanocompozite Filtek Ultimate, shows the highest diametral compressive strength values, both in its class of materials, composite resins, and in general of all the materials tested in this study, namely: glass-ionomer cements, resin modified glass-ionomer cements, composite and nanocomposites. Direct dental restauration material, nanocompozite Premise has the diametrical compressive strength values significantly higher than the glass-ionomer cements, but the lowest value of diametral compressive strength for resin based restauration materials.

DISCUSSIONS AND CONCLUSIONS:

The highest diametral compressive strength values are represented by resin based restauration materials: composites and nanocomposites. The highest diametral compressive strength values obtained in this study, which are close, are those of composite material Gradia and nanocomposite Filtek Ultimate, as the chart above shows. The highest value of diametral compressive strength has the nanocomposite Filtek Ultimate, meaning that, from all the materials tested in this study, it is the most resistant to diametrical compression (tensile strength, fracture).

For glass-ionomer cements, the best values of diametral compressive strength are those of resin modified

glass-ionomer cements Vitremer, and the lowest values recorded are those of glass-ionomer cements Ketac Molar. Among the three types of glass-ionomer cements we can observe significant differences.

Resin modified glass-ionomer cements Vitremer, has a diametral compressive strength value nearly triple to conventional glass-ionomer cement Ketac Molar.

Glass-ionomer cement Fuji IX has an average value of diametral compressive strength, being significantly higher than that of glass-ionomer cement Ketac Molar and lower than Resin modified glass-ionomer cements Vitremer.

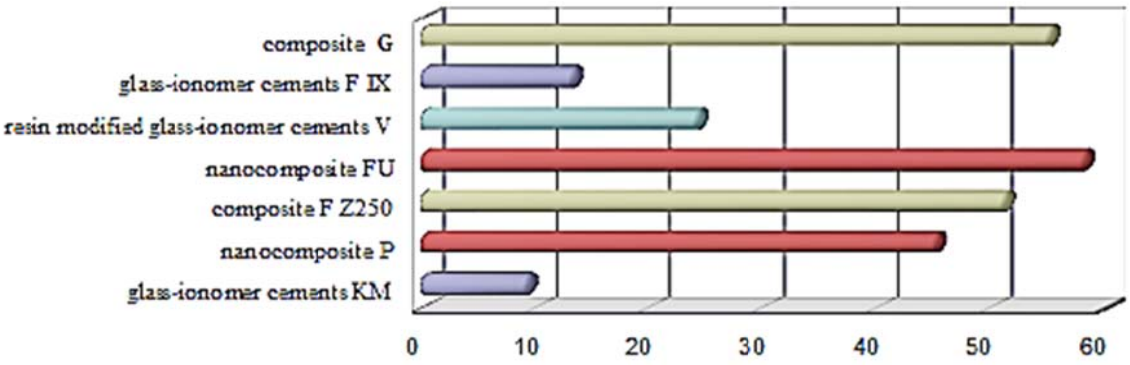

Fig.5 Diametral compressive strength chart for dental materials researched.

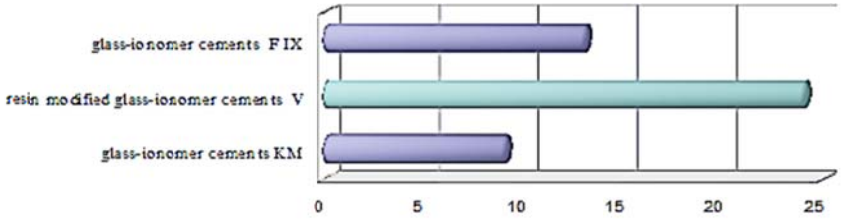

Fig.6 Diametral compressive strength chart for glass-ionomer cements.

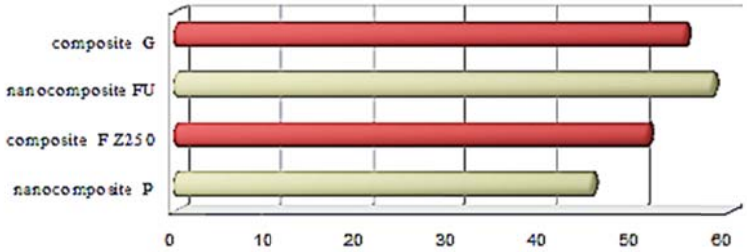

Fig.7 Diametral compressive strength chart for cured resin based restaurative materials.

Conventional cured resin based dental restauration material have average diametral compressive strength values, and both express higher values of diametral compressive strength than nanocomposite Premise and lower than nanocomposite Filtek Ultimate.

Microfill composite Gradia has a value of diametral compressive higher strength than composite Filtek Z250

and nanocomposite Premise but lower than nanocomposite Filtek Ultimate.

The nanocomposites tested in this study, have high diametral compressive strength values. Nanocomposite Filtek Ultimate has a significantly higher value of diametral compressive strength than nanocomposite Premise.

For cured resin based restaurative materials we can observe that the nanocomposite Filtek Ultimate has the highest diametral compressive strength values, detaching itself from the rest of composites, microfill Gradia being the exception with a close value to that of nanocomposite Filtek Ultimate.

Dental restauration material, nanocomposite Premise, has the lowest value of diametral compressive strength in its class, being lower than that of conventional composite (Filtek Z250 and Gradia) and significantly lower than the other nanocomposite restaurative material Filtek Ultimate, yet being significantly higher than glass-ionomer cements.

The lowest value of diametral compressive strength is that of glass-ionomer cement Ketac Molar while the highest value of diametral compressive strength is for nanocomposite restaurative material, Filtek Ultimate.

Although the highest values of the diametral compressive strength is recorded by light cured resin based dental restorative materials, in pedodontics practice, when the clinician, uses as restorative materials - composites (conventional composites or nanocomposite) he must take into account their special requirements, meaning: longer time to achieve a coronary restoration, more elaborate technique, isolation must be perfect, creating a perfect contact point for second class cavities (depending on the viscosity of the material which ensures its condensation, depth of cure, etc.), etc.

If, due to the particular behavior of children, particular morphostructural features of both temporary and permanent teeth in young children and length of time that the temporary tooth has on the dental arcade, some of these goals can not be met we should consider another choice.

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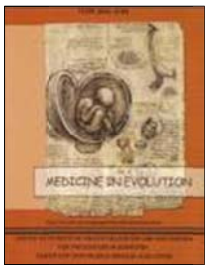
ATTITUDE TO ORAL HEALTH HABITS AND AWARENESS OF CARIES PREVENTION METHODS OF EXPECTING MOTHERS IN HUNGARY



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ABSTRACT

***Objective**: The aim of this study was to assess pregnant women's oral hygiene methods, attitudes to dental care and dental treatment, to evaluate their knowledge relating to preventive methods to be used on behalf of the child, and to investigate the correlation between these data and socio-demographic factors.*

***Material and Methods**: A structured questionnaire was used to collect data about oral health, oral health habits and preventive knowledge from 558 pregnant women at the Department of Gynecology and Obstretics Szeged/Hungary.*

***Results**: Tooth brushing twice a day was reported by 67.2% of the women, 30.8% used dental floss regularly. Their knowledge relating to the preventive methods for children's oral health was generally satisfactory; many of them were familiar with tablets containing fluoride. Women living in cities, having a higher education and working as professionals tended to report a better oral health attitude and had more information about prevention methods.*

***Conclusions**: Although these women had some useful information, well organized widespread programs should be developed to educate women on how to practice the preventive methods.*

***Key words:** caries, knowledge, prevention, pregnant women, oral health.*

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INTRODUCTION

Pregnant women's oral health and oral health awareness are important factors in many ways. A popular belief is that pregnancy is harmful to the teeth, although scientific proof is lacking.

A mother's knowledge relating to caries prevention methods is extremely important, because they are the first to educate their children both verbally and by example. A number of studies have shown an association between caries status and oral health habits of children [1] with their parents', primarily their mother's, oral health behavior and caries status.

AIM:

For these reasons it is of great importance to focus on the oral health and knowledge relating to the oral health of pregnant women.

The aim of this study was to assess expectant mother's self-perceived oral health status based on their answers, oral hygiene methods, and attitudes to dental care and dental treatment, and to evaluate their knowledge relating to preventive methods to be used for their offspring. A further aim was to investigate the correlation between these data and the age and social (residence, educational level, occupation) factors.

MATERIAL AND METHODS:

Women taking part in the prenatal care program in the Department of Obstetrics and Gynecology Faculty of Medicine at the University of Szeged were eligible for the study that was approved and accepted by the Ethics Committee of the University of Szeged. Pregnant women were recruited in 2008 and 2009. The objective of the study was explained and women who volunteered to take part gave an informed consent and answered the questionnaire anonymously. The questionnaire focused on the socio-demographic data (age, place of residence, highest education and occupation), oral health, oral hygiene habits and attitude, dental treatment during pregnancy and the knowledge about preventive measures in relation to children's teeth. During the two years 558 women completed the questionnaire.

Statistical analyses

For the preliminary assessment of bivariate independencies Spearman rank correlations were used. Average ages of varied groups were compared using a one way ANOVA or a two-sample t-test. Bivariate dependencies of categorical data were tested by chi-squared test or Fisher's exact test. To identify the significant effects of socio-demographic factors on positive attitude and other target variables stepwise logistic regression was used. The level of significance was set at $p<0.05$.

RESULTS

Socio-demographic data

The mean age of the pregnant women was 30.8 (min. 18, max. 43) years.

They were all Caucasian, and about four fifths of them lived in a city (Table 1). They had different levels of education. More than half of the women worked as professionals; the remainder was shared among manual workers, other workers and housewives, while 5.0 % was unemployed.

Table 1 Sociodemographic characteristics of pregnant women

Characteristics	N (%)
Residence	
City	438 (78.5)
Village	120 (21.5)
Educational level	
Primary school	25 (4.5)
Technical school	84 (15.0)
Grammar school	194 (34.8)
Higher education	255 (45.7)
Occupation	
Manual worker	98 (17.6)
Other	96 (17.2)
Housewife	44 (7.9)
Unemployed	28 (5.0)
Professional	292 (52.3)
Number of pregnancies	
First	311 (55.7)
Second	163 (29.2)
Third	67 (12.0)
Fourth or more	17 (3.1)

Table 2 Oral health, oral hygiene habits, methods and tools

Questions	Answers		
	NO N (%)	**YES** N (%)	**Total** (N=100%)
Having "bad" teeth	362 (65.2)	193 (34.8)	555
Bleeding gums when brushing	297 (53.5)	258 (46.5)	555
Swollen gums	498 (90.1)	55 (9.9)	553
Daily tooth brushing	6 (1.1)	552 (98.9)	
Frequency of tooth brushing			558
once a day		55 (10.0)	
twice a day		371 (67.2)	
three times a day		126 (22.8)	
Use of dental floss	386 (69.2)	172 (30.8)	558
Use of electric toothbrush	418 (74.9)	140 (25.1)	558
Use of Fluoride containing toothpaste	48 (8.8)	499 (91.2)	547
Use of Fluoride containing mouthwash	401 (72.5)	152 (27.5)	555

Self reported oral health

The patients gave information about their assumptions relating to their oral health, they were not examined. Many women thought they had "bad" teeth (caries, radix), but less than half complained about bleeding gums when cleaning their teeth (Table 2). Many of them noticed gingival bleeding only during pregnancy (189, 73.3% of those women who reported gingival bleeding).

Oral hygiene habits, tools

Almost all the women stated that they brushed their teeth daily; two

thirds of them stated they brushed twice a day (Table 2). About one third of the women reported the regular use of dental floss and every fourth woman used an electric toothbrush. Many of them used toothpaste containing fluorides, and 27.5% used mouthwash that also contained fluoride.

Dental visit

About a third of the subjects did not know that, by law, expectant women should visit the dentist at least once during their pregnancy.

As soon as pregnancy was confirmed about two thirds of the women visited a dentist (Table 3).

More than half of the subjects received treatment during pregnancy, which included professional tooth cleaning, filling, extraction or some kind of tooth replacement. Instruction in oral health care was given to 78.0% of the women who visited the dentist.

Table 3 Dental treatment during pregnancy

Questions	**Answers**		
	NO N (%)	**YES** N (%)	**Total** (N=100%)
Is dental screening compulsory?	151 (28.2)	384 (71.8)	535
Dental visit	169 (30.4)	387 (69.6)	556
Treatment (for those who visited the dentist)	138 (35.7)	249 (64.3)	387
Instruction in oral health care at dental visit	85 (22.0)	302 (78.0)	387

Table 4 Knowledge about preventive measures in relation to children's teeth

Questions	**Answers**		
	NO N (%)	**YES** N (%)	**Total** (N=100%)
Read about healthy nutrition	18 (3.3)	533 (96.7)	551
Feeding of the newborn			543
Breast feeding		539 (99.3)	
feeding/nursing bottle		2 (0.4)	
glass		2 (0.4)	
Too much fruit juice may destroy the teeth	120 (22.5)	413 (77.5%)	533
Drinking too many carbonated drinks may destroy the teeth	4 (0.7)	536 (99.3)	540
Giving sweets in small amounts and infrequently	31 (6.6)	440 (93.4)	471
When do you start to brush the child's teeth?			527
before 12 months		121 (22.9)	
between 12 - 24 months		22 (4.2)	
Later then 24 months		7 (1.3)	
when first milk teeth erupt		366 (69.6)	
when first permanent teeth erupt		11 (2.0)	
A child can brush teeth alone			531
1 - 2 years		162 (30.5)	
3 - 4 years		295 (55.6)	
later then 5 years		74 (13.9)	
Information about F prevention			
milk	485 (89.5)	57 (10.5)	542
water	379 (70.6)	158 (29.4)	537
salt	410 (76.6)	125 (23.4)	535
tablet	203 (37.5)	338 (62.5)	541

Knowledge about preventive measures in relation to children's teeth

Women seemed to be interested in a healthy diet during pregnancy; this was shown by the number of positive answers (96.7%) when asked if they had read about this subject (Table 4). Almost all mothers were planning to breast feed their newborn. Many of them knew that too much fruit juice and carbonated soft drinks may destroy the teeth. In their opinion a child may eat sweets on occasion and in small amounts, but many of them had not yet considered the question. They were aware of the importance of cleaning the child's teeth from an early age, i.e. when the first milk teeth erupt. Among those women who answered this question most thought that teeth should be brushed from the age of twelve months (14.1%). The answers were not standard in relation to the question; when is a child able to clean its teeth unaided? 40.5% of future mothers thought the age of three years was appropriate, not many were of the opinion that an older age (≥5years) is necessary for independent tooth brushing. More than half of the women had some knowledge about fluoride tablets as a method of caries prevention.

Correlation between oral hygiene and age, residence, education and occupation

According to the results of ANOVA (relating to age) and Chi square test (relating to other factors like residence, education and occupation) tooth brushing multiple times a day and using dental floss was related to age, educational level and occupation; women who were older, living in a city, having reached a higher educational level and working as professionals tended to have better oral hygiene practices and more information about oral health (Table 5).

Although there was a significant difference in the answers relating to daily tooth brushing among the women according to occupation, clinically it had no significance, since, with the exception of 6 women, they all stated that they brushed their teeth daily. Electric toothbrushes were used more by women who had a higher education and who were professionals. Older and better educated women had bleeding gums less often ($p = 0.039$, $p = 0.001$). The average age of women who gave a 'Yes' answer to the question if they had bleeding gums when brushing was 31.14 years, while women giving a 'No' answer were, on average, 30.31 years old. This difference has no clinical significance. Bleeding gums was reported by 80% of the women who had completed only primary school, 55.4% by women with a technical school certificate, and only 41.3% by women with a higher education degree. There was no significant difference in the frequency of dental visits, and having dental treatment in relation to age, residence, education or occupation. A significant difference in the opinion of the safety of dental treatment and getting local anesthesia and the socio-demographic factors was not found.

Correlation between the knowledge about the preventive methods for child's teeth and age, residence, education and occupation

Older women had more information about fluoridated water, salt and tablets. Women living in cities, who had a higher educational level and who worked as professionals knew about fluoridated water as a caries preventive method. The opinion, that drinking too much fruit juice may harm the teeth was more common among women with a higher education and who professionals were. Similarly starting tooth

brushing when the first milk teeth erupted depended on educational level.

A positive attitude to oral hygiene was regarded as tooth brushing 2 or 3 times a day, use of dental floss or electric toothbrush. The forward stepwise model showed a correlation only with age (p=0.40, OR: 1.050, CI: 1.002-1.100) and occupation (overall p=0.041), when the independent variables were age, residence, educational level and occupation. Regular use of dental floss was much more likely among women with higher education (p=0.019, OR: 12.079, CI: 2.158-122.610 versus basic education) and depended slightly on profession (overall p=0.049). The use of an electric toothbrush was more common in those with a higher educational level (overall p=0.010).

Appropriate knowledge about caries prevention in the child was categorized under the following headings: if a woman planned to breast feed, had information about the preventive effect of fluorides, if she planned to start brushing the child's teeth at the age of about 6 months or when the first milk teeth erupted, and if she planned to give sweets in a small amount and rarely. Preventive knowledge relating to the child's oral health depended only on residence (p=0.000, OR: 2.553, CI: 1.607-4.057), women living in a city had better knowledge compared to women coming from a rural area. Other factors like age, educational level or occupation did not play a significant role.

Correlation between beliefs relating to pregnancy and new caries, dental treatment and age, residence, education and occupation

Although 43.2% of the women believed that pregnancy itself caused new caries and almost every fifth woman thought that local anesthesia was not advisable during pregnancy, the stepwise regression model did not find a correlation with age, residence, educational level or occupation.

Women with a high school or university degree knew, that having new fillings during pregnancy is not harmful (overall p = 0.003); p = 0.001, OR: 9.008, CI: 2.596-31.251 for higher education versus pri-mary school, p=0.033, OR: 3.243, CI: 1.100-9.562 for higher education versus technical school.

Table 5 P-values of one-way ANOVA/t-test and Chi square tests relating to the question concerning a mother's oral health and her knowledge relating to a child's oral health care

Mother's oral health	Age	Residence	Education	Occupation
Daily tooth brushing	0.830	0.088	0.150	**0.013**
Tooth brushing more times/day	**0.002**	**0.001**	**0.011**	**0.000**
Use of dental floss	**0.029**	**0.014**	**0.000**	**0.000**
Use of electric toothbrush	0.067	0.091	**0.004**	**0.003**
Bleeding gums	**0.039**	0.137	**0.001**	0.057
Dental visit during pregnancy	0.496	0.147	0.243	0. 369
Dental treatment	0.998	0.209	0.579	0.834
Having new fillings is safe	0.110	0.492	0.079	0.934
Local anesthesia is safe	0.112	0.413	0.624	0.497
Child's oral health				
Knowledge-F-milk	0.240	0.143	0.123	0.899
Knowledge-F-water	**0.020**	**0.043**	**0.012**	**0.033**
Knowledge-F-salt	**0.022**	0.477	0.103	0.429
Knowledge-F-tablet	**0.002**	0.255	**0.012**	0.199
Too much fruit juice is harmful	0.215	0.071	**0.000**	**0.001**
Carbonated drinks are harmful	0.764	0.289	0.141	0.948
Start to brush when first milk teeth erupt	0.175	0.435	**0.000**	0.131
Start to brush at 6 months	0.904	0.125	0.128	0.796

DISCUSSIONS:

The high ratio of women with a higher education and working as professionals in the study population can be explained in that Szeged has a big university and many grammar and secondary schools. It may explain that, according to the answers, oral health behavior and knowledge was generally good. Although almost all the women reported daily tooth brushing, every third woman was aware of some dental problem and had bleeding gums during pregnancy. This indicated that tooth brushing may not have been carried out effectively.

In Hungary there is a decree, which regulates the prenatal care. At least one dental visit would be compulsory during pregnancy, but only two thirds of the women knew of this and actually went for dental screening. This ratio was worse than the results of a study conducted in Denmark, where 90% of the women attended a dental surgery during pregnancy [2]. Fortunately a great majority of the women found the dental treatment to be safe. It was interesting that mothers deemed their children able to brush their own teeth properly at the age of 3 years, although this depends on the children's skills. Generally children can be relied upon to do this more or less properly by the age of 5-6 years [3].

Although the general knowledge relating to the preventive methods that should be used for adults and children was appropriate in this study, a dental screening of young children at age 5-6 years showed a mean dmft as high as 4.5 in 1996 [4]. However there was an improvement between 1996 and 2001, when dmft was 3.9 at the age of 6, but this data was still worse than similar data from Western European countries during a similar period [5].

CONCLUSIONS:

Women with a higher education, or who worked as intellectuals had a better attitude towards oral hygiene; they also had more relevant information relating to their own and their child's oral health care and nutrition.

There is still a need for improvement of dental health education instruction, the practice of good oral health is necessary for those already in the prenatal period and also for potential mothers.

The role of gynecologists, dentists, dental hygienists and pregnancy care district nurses is enormous, but also society as a whole and the health ministry should share the responsibility. With these efforts it would be possible to reach the WHO targets relating to oral health in the future [6].

Acknowledgement

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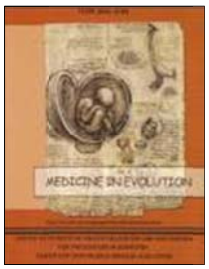
IMPORTANCE OF RADIOLOGY IN TIME IN PEDIATRIC DENTISTRY THROUGH A DENTAL REPORT



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ABSTRACT

This case report shows the importance of radiology in clinical management of pediatric patients through a concrete case.

This case shows 2 supernumerary teeth in the upper jaw, which could cause the eruption of the 21 tooth in atypical place.

In cases with supernumerary teeth the early diagnosis is very important to avoid the problems with the second dentition.

Key words: *eruption in atypical places, dental complication, supernumerary teeth, early diagnosis*

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INTRODUCTION

An accurate diagnosis and treatment plan is based on a comprehensive general, dental history, clinical examination and diagnostic radiographs. The radiograph in children is difficult to achieve not only from technical point of view but also due to parental fear.

It is fact that young, growing tissues are more radiosensitive than the mature tissue in adults, and the effect is cumulative but under radiation protection it is essential help for the dentist to set up the diagnosis and the adequate therapy. That is why radiographic examination should ask only if it is absolutely necessary.

However, in case of numerical disturbances (hypodontia, hyperdontia) of primary and permanent teeth it is impossible to make correct diagnosis without diagnostic radiograph.

Supernumerary teeth can occur mainly at the area of primary and permanent incisors. They can cause gap between the teeth (diasthema) or prevent the normal eruption of the neighbour teeth. These teeth can occur singly, in multiples, uni- or bilaterally, and in one or both arches. It is reported with many syndromes for example cleidocranial dysplasia, Gardner-syndrome, Ellis-Van Creveld syndrome. Anyway multiple supernumerary teeth with no associated syndromes or disease are rare [1]. As more than one supernumerary tooth can occur in one case, the most suitable method for diagnosing them is the orthopantomography (panoramic radiograph).

Supernumerary teeth occur more frequently in permanent than in primary dentition [2]. Their aetiology is still not clearly understood. The most accepted reason is the independent and localized hyperactivity of the dental lamina [2]. Heredity has an importance as an aetiological factor in the occurrence of supernumerary teeth.

Anyway Brook has reported that genetics and environmental factors are combined and can cause together supernumerary teeth [3].

Supernumerary teeth can be categorized according to morphology and location. 4 morphological types have been described in the permanent dentition as: conical, tuberculate, supplemental and odontoma.

These teeth also may be classified according to location (mesiodens, paramolar, distomolar) [4].

Supernumerary teeth don`t cause malocclusion in every case. Sometimes unerupted teeth can be found accidentally during radiographic examination with no effect on the neighbouring teeth.

However, various complications are associated with supernumerary teeth, like failure of eruption, displacement or rotation, crowding, abnormal diasthema or premature space closure, formation of cysts, eruption into nasal cavity, dilacerations, and problems with the root development [4].

Therefore the early diagnosis and treatment are very important to avoid these complications.

MATERIAL AND METHODS:

A 9-year boy was referred to the orthodontist by the general dentist. The main complain was crowding and the big mesial diasthema in the upper jaw. Clinical examination revealed the problem of the atypical eruption of the 21 tooth. This tooth was placed labially to the 22 tooth and with a big diasthema

between the 11 and 21 teeth (fig. 1a). Mild deep bite and Class I occlusion in both buccal segments were observed. The panoramic radiograph orthopantomograph showed 2 supernumerary teeth in anterior part of the 2nd quadrant, at the real place of the 21 tooth (fig 1b). After orthodontic diagnosis and treatment planning, the supernumerary teeth were removed surgically. The patient got a fixed multiband orthodontic appliance (fig. c and d). Both arches were bonded with Roth 0.18 brackets and bands for the 1st molars. The archwires were: NiTi and stainless steel, round and rectangular. The 21 tooth was moved mesially to the right place with elastic chain (fig. e).

The active phase lasted for 16 months and the patient got upper and lower retention plate to avoid the relapse.

Fig.1 Initial situation with the atypical position of the 21 tooth. b: Initial panoramic view of the patient. c: Two extracted supernumerary teeth. d: Panoramic radiogram after 4 months of treatment with fixed multiband appliance. e: Moving of the 21 tooth with elastic chain. f: Clinical situation 5 month before the finishing of the treatment g: Result after 16 months. h: Result after removing the fixed appliance.

DISCUSSIONS:

Panoramic radiograph is used to diagnose missing and supernumerary teeth, gross pathology and development of the dentition. Ectopic eruption of the teeth, impaction, retained teeth and other eruption problem can also be revealed from panoramic radiograph. Nowadays electronic digital imaging affects the clinical practice of dentistry. All the advances made in this field have been directed to make radiographic investigation more accurate and safe for both the child and the dentist.

Supernumerary teeth are rarely noticed in primary dentition but if they are observed, it raises the possibility of hyperdontia in permanent dentition. The best age for diagnose supernumerary teeth is the early mixed dentition [5]. In case of the late eruption of one of the upper incisors is observed, a radiographic examination is obligatory and essential.

If it is diagnosed, supernumerary teeth should be extracted before the total eruption of the permanent tooth and it will facilitate orthodontic treatment and shorten the time of it.

Hyperdontia may cause clinical problems in the eruption and alignment of permanent dentition.

We present this report to emphasise that patients with supernumerary teeth need early recognition and treatment in order to avoid the later complications.

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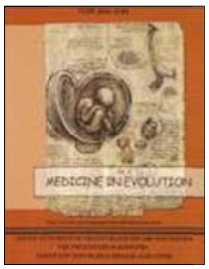
THE IMPORTANCE OF EARLY CHILDHOOD CARIES ASSESMENT



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ABSTRACT

Early childhood caries (ECC) is still a common disease in young children. It is defined clinically as the presence of one or more decayed (non-cavitated or cavitated lesions) that can develop extremely quickly and lead to the widespread and sometimes painful deterioration of the primary dentition.The preoccupation for maintaining dental health, resistant to the action of microorganisms starts from the 5-6 week of intrauterine life, when the embryogenesis of the child's teeth begins. Related to that, each stage has to be well differentiated regarding dental care measures and an evaluation of the oral heath is necessary because of several facts: it is the period of temporary and mixed dentition when the frequency of the dental lesions is very high with negative impact on the development of the cranio-facial system but also with an impact on the development of the hole body. The understanding of the complex nature of ECC depends on the multiple risk factors that have to be taken in consideration and the prophylactic and therapeutic measures are based on the accuracy of the evaluation of all this factors.

Key words: *early childhood caries, caries risk, fluoride, diet, oral health.*

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INTRODUCTION

Early childhood caries in preschool children has been discussed extensively in the scientific literature over the past 10 years. A review of the most recent studies shows that the dental community is looking at the problem with renewed interest and that more information is needed in regard to the epidemiology, etiology, diagnosis, prevention and treatment of caries in children ages 0 to 5 years. The multitude of terms to describe caries in children ages 0 to 5 is emblematic of the confusion that exists in the literature. The following expressions are used interchangeably: baby bottle tooth decay, early childhood caries, early childhood dental decay, early childhood tooth decay, comforter caries, nursing caries, maxillary anterior caries, rampant caries, and many more. Some of these designations are used specifically to illustrate the causes of tooth decay in preschool children. Baby bottle tooth decay is used in the literature to identify inappropriate baby bottle use as the main cause of caries disease. Other authors prefer the term nursing caries because it designates inappropriate bottle use and nursing practices as the causal factors. However, the term early childhood caries is becoming increasingly popular with dentists and dental researchers alike.

Caries can be viewed as an infectious disease and mutans streptococci are considered to be important bacteria for its development (Emilson & Krasse 1985, Loesche 1986), although no single type of micro-organism has been identified as the primary cause of either enamel, root or crown caries (Nyvad & Kilian 1987). The bacteria attach to the first primary teeth to erupt, especially to the fissures of the molars in 2–3-year-old children (Alaluusua & Renkonen 1983). However more recent studies indicate that the infection may occur at a younger age and that mutans streptococci can colonize the oral cavity of predentate children as young as 6 months of age.

The time of contamination is of a certain importance, as the later a child is infected, the less caries lesions develop in early childhood and later on (Alaluusua & Renkonen 1983, Köhler et al. 1988). Mutans streptococci are transmittable from the primary dentition to the permanent dentition (Gibbons 1984, Alaluusua et al. 1987), and also between individuals (Köhler & Bratthall 1978, Rogers 1981). The transmission occurs through contamination of the saliva (Rogers 1981) so that mothers are considered to transfer the infection to their child (Köhler & Bratthall 1978, Aaltonen et al. 1990). High levels of mutans streptoccoci in the mother's mouth contribute to maternal transfer as does maternal dietary habits and poor oral hygiene. It has been found that 20–50% of mothers in the Scandinavian countries have high counts of salivary mutans streptococci. Habitual xylitol consumption by mothers has been shown to lead to a significant reduction in mother-child mutans bacteria transmission when assessed in two-year-old children (Söderling et al. 2000).

Bacteria (mutans streptococci) in dental plaque metabolize sugars and produce acids, which lowers the pH in the mouth and promotes loss of minerals from the tooth surface. Minerals in the oral cavity including fluoride are redeposited on the tooth surface once the neutral pH is restored (normally after approximately 20min). This process is dynamic and as long as minerals are replaced the tooth surface remains sound and intact. However, a prolonged pH drop and frequent net loss of minerals lead to a weakening and eventual

break down (cavity) in the tooth surface. Early childhood caries (ECC) appears to be a particularly virulent form of dental caries causing extensive destruction of the deciduous teeth, often very rapidly. This may be due to extremes in one or more of the three factors above. Much research into the etiology and prevention of ECC has focused on the dietary substrate component leading to the terms 'baby bottle tooth decay' and 'nursing caries'. More recent research confirming the relative role of the microbial (plaque) and tooth resistance factors has fostered a better appreciation of the biological risk and protective factors in ECC.

Early childhood caries is a serious and sometimes painful disease characterized by early onset and very rapid progression. The caries develop quickly, usually right after the teeth erupt. Several teeth may be affected, beginning with the maxillary incisors, at the junction near the gums, followed by the canines. If the disease continues to progress, the molars are affected too, while only the mandibular incisors are spared.

There are four stages in the development of ECC (Veerkamp & Weerheim 1995). The initial stage is characterized by the appearance of chalky, opaque demineralization lesions on the smooth surfaces of the maxillary primary incisors when the child is between the ages of 10 and 20 months, or sometimes even younger. A distinctive whitish line can be distinguished in the cervical region of the vestibular and palatal surfaces of the maxillary incisors.

At this stage, the lesions are reversible but are frequently unrecognized by parents or the first physicians to examine the mouths of these very young children. Moreover, the lesions can be diagnosed only after the affected teeth have been thoroughly dried.

The second stage occurs when the child is between the ages of 16 and 24 months. The dentin is affected when the white lesions on the incisors develop rapidly, causing the enamel to collapse. The dentin is exposed and appears soft and yellow. The maxillary primary molars present initial lesions in the cervical, proximal and occlusal regions (Fig. 1). At this stage, the child begins to complain of great sensitivity to cold. The parents sometimes notice the change of color on their own and become concerned.

The third stage, which occurs when the child is between 20 and 36 months, is characterized by large, deep lesions on the maxillary incisors, and pulpal irritation. The child complains of pain when chewing or getting his teeth brushed, and of spontaneous pain during the night.

The fourth stage, which occurs between the ages of 30 and 48 months, is characterized by coronal fractures of the anterior maxillaries as a result of amelodentinal destruction (Fig. 2). At this stage the maxillary incisors are usually necrotized, and the maxillary primary molars are at stage 3. The secondary molars and maxillary canines and the first mandibular molars are at stage 2. Some young children suffer but are unable to express their toothache complaints. They experience sleep deprivation and refuse to eat.

A positive diagnosis is established on the basis of questions to parents regarding risk factors and a clinical endo-oral examination, completed by x-rays.

A differential diagnosis is based on observations of hereditary tooth structure anomalies such as infantile melanodontia, which primarily affects the maxillary incisors, and amelogenesis imperfecta, which affects the enamel of every tooth and is a hereditary disease of the dentin, characterized by an

opalescent, brownish tooth colour, and typical short roots. Enamel hypoplasia caused by malnutrition during the perinatal period or by a deficit in Vitamin A promotes a high caries susceptibility and is often associated with early childhood caries.

Early childhood caries can have serious general and local repercussions in the short and long terms. Following pulp necrosis, infection spreads to the periodontal region in one of two clinical forms: the acute form, characterized by cellulitis, adenopathy and mobility of the affected teeth, and the chronic form, which is the most common, characterized by abcesses and interdental septum syndrome. Depending on the severity of the disease, infection can spread to the buds of the permanent teeth, causing irreversible lesions. Complications from subsequent infections can occur in children already compromised by a generally weakened state of health.

Contrary to popular belief, the effects of caries in young children extend beyond the mouth. Tooth loss is sometimes inevitable, and it can cause not only orthodontic and esthetic problems, but more importantly, difficulties in pronunciation. Esthetic problems and pronunciation difficulties may result in psychological and relationship problems. In addition, children with ECC usually weigh less and are shorter than average (Thomas & Primosch 2002). Their growth is affected because they have difficulty sleeping and eating as a result of the infection and pain, and their quality of life is greatly diminished.

A review of the role of substrate in ECC by Reisine and Douglass found that the total weight of sugar in children's diet was not predictive of dental caries; however, the frequency of sugar intake was. Frequent consumption of sugar favors the establishment of cariogenic bacteria and provides continuous substrate that influences the initiation and progression of the caries.

Controversy exists as to whether infant formulas or bovine milk in bottles and breast milk given frequently to infants contribute to the development of ECC. The evidence of a relationship between bottle use and caries risk is weak and it is likely that the risk of caries may be sensitive to the interaction of multiple factors including other (non-bottle) dietary practices.

Prolonged or on demand breastfeeding has been implicated in the development of ECC. The American Academy of Pediatric Dentistry's policy (AAPD) on breast-feeding states that: "Although breast-feeding is essential in providing the best possible nutrition to infants, the AAPD cautions that frequent breast-feeding at night and on demand after eruption of teeth may be implicated in contributing to the development of early childhood caries (ECC)".

There are controversies about this issue. The international dietary guidelines recommend exclusive breastfeeding until 6 months and then continuing breast-feeding with complementary foods until 2 years or more.

More recent and methodologically stronger studies have suggested that breast-feeding per se is not significantly associated with ECC. Laboratory studies have noted that human breast milk does not appear to cause the drop in plaque pH required for the initiation and progress of dental decay and may in fact promote the deposition of calcium and phosphate ions on the tooth surface.

Several factors can predispose an individual or indeed a particular tooth to dental caries. These may include immunological factors, reduced saliva flow, immature enamel and defects of the tooth tissues.

Because enamel is immunologicaly inactive, the main immune defence against mutans streptoccoci is provided largely by Immunoglobulin A (IgA) or serum and gingival crevicular fluid. As children become infected with oral microorganisms, they develop salivary IgA antibodies. In addition to providing specific immunological factors, the saliva acts as an important protective factor. Saliva buffers plaque acids, aids in oral clearance and acts as a reservoir for minerals to assist in the re-mineralization of enamel.

Teeth erupt into the mouth with immature enamel. The process of enamel maturation continues following tooth eruption, so that teeth become less susceptible to decay over time. The enamel matures incorporating orally available ions including fluoride.

The ingestion of the fluoride, irrespective of the available form, acts pre-eruptive, during the mineralization period of the teeth, which is developed in 2 phases: the mineralization of dental hard tissues and the pre-eruptive maturation of the enamel. The period of time for this 2 phases, for both temporary and permanent dentition is 13 years and a half (without the third molar).

The mineralization of the temporary incisors starts at 3-4 months intrauterine life and is finished 4-5 months after birth. The mineralization of the permanent incisors starts at 3-4 months after birth, excepting the lateral incisor which begin the mineralization at 10-12 months and it ends at 4-5 years. The mineralization of the temporary canine starts at 5 months of intrauterine life and it ends at 9 months, while the mineralization of the permanent canine starts at 4-5 months and it ends at 6-7 years. The mineralization of the premolars starts at 1 ½ -2 ½ and it ends at 5-7 years. The temporary molars begin their mineralization at 5 months of intrauterine life and it ends at 6 months for the first molar, while the second molar stars at 6-7 months and ends at 10-12 months. The permanent first molar starts the mineralization at birth and ends at 2 ½ -3 years and the second molar achieve mineralization between 2 ½ -3 and 7-8 years.

The intervals presented are medium values for a certain population. There are variation conditioned by climacteric condition, race, region.

From this data it has to be revealed the fact that the pre-eruptive mineralization of the first molar is the shortest when it is compared with the other teeth. This explain, the great susceptibility of this tooth to dental caries.

On the other hand, the time of mineralization of the temporary teeth is 6 time shorter comparative to the permanent teeth, fact that can explain the susceptibility to caries.

Regarding the utilization of prenatal fluoride the American Dental Association asked during a debate the following questions:

- Is the passing of fluoride through the placenta safe?
- Does the child benefit from the fluoride?
- Is it a proven fact that fluoride in intrauterine is involved in the maturation of enamel?

The answer to the first question is that fluoride passes easily through the placenta from the 5th – 6th month of pregnancy. Regarding the second question, the answer is given indirectly through the epidemiologically studies that revealed a decrease of carious lesions in temporary teeth at children who had benefit from an optimum fluoride income during intrauterine life. At last, the answer to the third question is that fluoride is incorporated during the maturation of the enamel of temporary teeth, but at a lower concentration

than in adult teeth because the mineralization stages are shorter. It looks like the incorporation of fluoride is not just the result of absorption but also of the concentration of preexistent fluoride in the bony tissue. Ingestion of fluoride during the second half of the pregnancy, increasing the concentration of fluoride in the skeletal tissue of the child, is susceptible of influencing the ulterior incorporation of fluoride in the teeth. We can practically say that the ingestion of 1 mg F/day at young mothers is recommended from the fourth month of pregnancy. Therefore, a tooth is most susceptible to caries immediately after eruption until final maturation.

Many studies have found a significant relationship between developmental defects of the tooth surface and dental caries. Developmental disturbances to the tooth germ during embryological development can result in loss of integrity of the surface enamel which in turn allows additional plaque accumulation on what would otherwise be a smooth surface. Such developmental disturbances may include premature birth or low-birth weight, pre- and postnatal infection/illness, nutritional deficiency and a variety of environmental pollutants including maternal smoking.

Much of the literature uses terms (including nursing caries and baby bottle tooth decay) or case definitions that imply that the inappropriate use of the baby bottle plays a central role in the development of dental decay in infants and young children, however, supporting epidemiological data is difficult to find. For this reason the term early childhood caries (ECC) is the term now used to collectively refer to dental decay in infants and preschool children. In reality most babies are fed with a nursing bottle for at least some of the time and yet as Horowitz points out most of them do not develop ECC. Two bottle-related behaviours have attracted most interest in ECC research – the use of bottles at night/nap time and the use of the bottle beyond 12 months.

Reisine and Douglass found little strong evidence to support either of these ideas and suggest that this paucity of evidence may be due to the use of retrospective parental self-reports. The alternate explanation they offer is that the critical period may be soon after the eruption of teeth into the mouth and that early use of the bottle containing sweet fluids supports the early establishment and dominance of cariogenic microflora. This may be more important than bottle use after 12 months.

Litt et al. found that the use of the bottle at night-time was associated with sugar intake. The mothers who reported night-time bottle use were also more likely to have children with a higher sugar intake.

Because of this aspect is very important that the treatment of the pregnant mother should include education regarding preventive oral care of the infant and toddler. Too often a child's first dental examination occurs after the deciduous dentition or even much of the permanent dentition has erupted. By this time, much opportunity for the prevention of dental pathology has passed. The expectant mother and family should be instructed in the importance of early dental examinations for the child. A child should receive the first dental examination between 6 to 12 months of age. Early examination enables the oral health professional to identify detrimental feeding habits, educate the parent about oral hygiene procedures, determine fluoride intake status, introduce the child to dentistry in a non threatening manner, and prepare the parents for the child's future dental needs (Goepferd & Garcia-Godoy 1999).

Expectant mothers and their families should also be instructed in the care of the infant's mouth beginning at birth. The infant's mouth should be gently cleansed daily with a damp washcloth. As soon as teeth have erupted, they should be brushed daily with a soft toothbrush.

It is important to talk with parents about the following points: verifying and reinforcing the information and advice given during pregnancy; reinforcing that the child should not be given cariogenic substances in his bottle at bedtime; encouraging healthy eating and limiting sugary foods by suggesting other types of sweeteners; cleaning the child's teeth as soon as they begin to erupt; encouraging the child to drink out of a cup around his first birthday, and then progressively limiting the use of the bottle between the ages of 12 and 16 months; observing the baby's early habits such as thumb sucking; so that the caregiver can receive timely instructions in correcting it, even if that means giving the child a pacifier.

No connection has been noted between pacifier use (as long as it has not been dipped in a sweetener) and ECC. If the provider notices ECC once the primary teeth have erupted, he must evaluate the child's risk for caries just as he did with the expectant mother. He must also prepare a personalized prevention program and choose a fluoride therapy (systemic and topical) according to the caries risk and the patient's age in order to enrich the fluoride of the budding teeth's enamel and increase the caries resistance of the teeth that have already erupted. Fluoride supplements (0.25 mg) are not recommended for low-risk children under the age of three. For high-risk children, fluoride tablets (0.25 mg) are recommended beginning at the age of 6 months, i.e. when the child first visits the dentist [30]. In all cases, before prescribing it is very important to: evaluate the risk for caries; ensure that the child is not drinking fluoridated water or taking fluoride supplements (in vitamins); adjust the dosage schedule in consultation with the attending pediatrician; evaluate other possible sources of systemic ingestion (total daily ingestion must not exceed 0.05-0.07 mg F-/ kg31). The success of fluoride therapy depends on the parent's motivation and participation, regular check-ups and adjusting the dose depending on the dosage schedule.

Fig.1 ECC stages 1 and 2.

Fig.2 ECC stage 4 with abscess 5.1.

Brushing the teeth with a fluoride toothpaste must immediately be added to the child's daily oral health regimen as soon as his first primary tooth erupts. The use of topical fluoride in the form of a varnish or gel is beneficial but not recommended before the child turns one. It could be used to foster the protection of the smooth surfaces of primary teeth and the remineralization

of the first carious lesions. Chlorhexidine varnishes can be used in children between the ages of 3 and 4 with a high risk for caries, in order to reduce the quantity of streptococci within the dental plaque and as a tool for the bacterial control phase. Sealing agents are evidently entirely indicated to prevent occlusal caries of the primary molars and should be used beginning at age 3 after consideration of the caries risk and clinical recommendations. Substituting sugar with xylitol or other artificial sweeteners (sorbitol and mannitol) in candy, and the recent appearance of products made with casein phosphopeptide or amorphous calcium phosphate (in chewing gum and toothpaste) will have interesting applications in preventing EEC in the future. These products may help remineralize teeth by binding themselves to the biofilm, the dental plaque and the hard and soft tissues of the mouth and liberating calcium and phosphate ions into the saliva. Further research will be necessary to determine optimal frequency of use and the recommended applications according to age. Lastly, it would be important to schedule children at risk for regular three-month check-ups and to stay in touch with parents in order to provide proper follow-up.

Despite a dental health provider's efforts to implement a prevention program, sometimes the outcome does not meet expectations. The prevention program must be accompanied by individual counselling of the parents. A psychological approach should be emphasized, one that provides feedback on performance and encourages children to be proactive (by learning and integrating oral health techniques and adopting a healthy daily diet). The collaboration of practitioners with the public health network, particularly with respect to coordinating and developing dental health promotion activities, must be strengthened so that greater numbers of parents and/or children will receive advice and preventive care under the programs of the public dental health care network.

The deciduous dentition is critical to proper phonetic development, space maintenance for permanent teeth, and the child's self-image. The use of fluoridation, the sealing of pits and fissures together with oral hygiene implamantation and healty dietary habits are the 4 methods indicated by WHO (World Health Organization) for prevention of dental caries.

The dentist has to aplly the prophylactic measures, has to implement an adequate toothbrush teqniques contributing to the consolidation of oral health.

A healthy diet which must contain all the necessary nutrient elements is important from the pediatrician point of view for an adequate groth and development and also for the dentist in order to prevent the risk factor represented by the existence of a cariogenic diet –carbohidrate substrate.

The understanding of the complex nature of caries depends on the multiple risk factors that has to be taken in consideration and the prophylactic and therapeutic measures is based on the accurency of the evaluation of all this factors.

CONCLUSIONS:

In conclusion, early diagnosis of early childhood caries and the identifycation of risk factors are essential to the implementation of preventative and curative measures to mitigate complications and the repercussions of the di-

sease. Physicians and nurses have more opportunities to see expectant mothers and their newborns than dentists do. It is therefore vital to emphasize parental awareness of the seriousness of ECC so that proper attention is placed on early detection and the elimination of risk factors.

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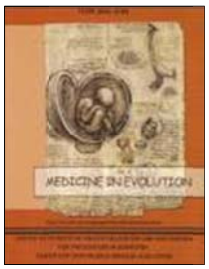
AN INTERDISCIPLINARY APPROACH OF A MANDIBULAR 1ST MOLAR EDENTATION – A CASE REPORT



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ABSTRACT

Tooth loss can lead to various disorders of the stomatognathic system, such as inefficient mastication, tipping and other types of pathologic movement of the remaining teeth, alteration of the occlusal plane by extrusion/egression of the antagonists, periodontal problems and, last but not least temporo-mandibular joint disorders.

The goal of our case presentation is to point out the impact of interdisciplinary treament on the results and further prognosis. The authors would also like to emphasize the importance of combining skeletal anchorage with a segmental orthodontic appliance in uprighting of a mesially tipped second permanent molar and in regaining space.

By using skeletal anchorage devices molar uprighting is easily performed with real benefits in treating cases of this type. The occlusal function is improved and any type of prosthodontic restoration can be performed under ideal circumstances.

Key words: *skeletal anchorage, interdisciplinary treatment, orthodontic treatment, molar uprighting*

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INTRODUCTION

The loss of one or more natural teeth can lead to various disorders of the stomatognathic system, such as inefficient mastication, tipping and other types of pathologic movement of the remaining teeth, alteration of the occlusal plane by extrusion/egression of the antagonists, periodontal problems and, last but not least temporo-mandibular joint disorders [1, 2, 3]. Mesial or distal tipping of the teeth into the edentulous space and vertical migration of the opposing teeth lead to distorsion of the occlusal plane with obvious consequences on function (premature contacts and occlusal interferences) [2]. There are various solutions in restoring the continuity of the arches and the choice on which to apply depends among other factors on the patient's age when the the first permanent molar is lost and the time passed between tooth loss and the patient's visit at the dental office. The level of education and the social background of the patient also play an important role in solving such types of cases. Orthodontic treatment is useful in uprighting the neighbouring teeth and in intrusion of the antagonists. In order to correct the position of mesially tipped molars a series of methods are found in literature, such as the use of uprighting springs, lingual arches or multibracket appliances along with extra-oral forces or class III elastics [4, 5, 6].

The newest approach is represented by using temporary skeletal anchorage devices also known as orthodontic miniimplants. These provide a very efficient anchorage thus preventing unwanted tooth movement [7, 8, 9]. The present paper presents a case of a single tooth edentation in the mandibular posterior area that has been resolved by interdisciplinary approach. The authors would also like to emphasize the importance of combining skeletal anchorage with a classical segmental orthodontic appliance in uprighting of a mesially tipped second permanent molar and in regaining space.

CASE REPORT:

The patient, PV, a 43 year old female, came into our practice complaining of chewing difficulties and requiring treatment. The intra-oral exam revealed a reduced edentulous space with 4.6 missing, mesial tipping of tooth 4.7 and vertical migration of 1.6 into the extraction site. Based on the clinical exam and other complementary investigations (paroramic x-ray and CBCT) we elaborated a treatment plan as follows: endodontic treatment and uprighting of 4.7, insertion of an implant in the region of 4.6 followed by a crown. The patient refused orthodontic intrusion of 1.6 so we opted for a prosthodontic solution.

The initial mesio-distal width of the edentulous space was 5 mm, measured between the marginal ridges of the neighbouring teeth. After completion of the root canal treatment of tooth 4.7 am orthodontic miniscrew was inserted (Dual Top Anchor System JD, RMO), 8 mm in length and 1.6 mm in diameter. The miniscrew was located between the roots of 4.4 and 4.5 in their middle third. Then, we bonded Mini Master (American Orthodontists) brackets (0.022") on 4.2, 4.3, 4.4, 4.5 and 4.7. We used a segmental 0.017"x 0.025" stainless steel arch from 4.2 to 4.5. The brackets were bonded in such a way that the arch could be passively

fitted. The above mentioned teeth were tied together by lace-back along with the miniscrew in order to maximize anchorage. For the molar uprighting we used a Titanol Uprighting Spring (Forestadent) that we inserted into the molar bracket and fixed on the segmental appliance between 4.3 and 4.4. Prior to insertion the uprighting spring was individualized. After uprighting we used a finishing wire of 0.019x 0. 025" TMA for a period of six weeks.

Fig.1 The initial clinical situation.

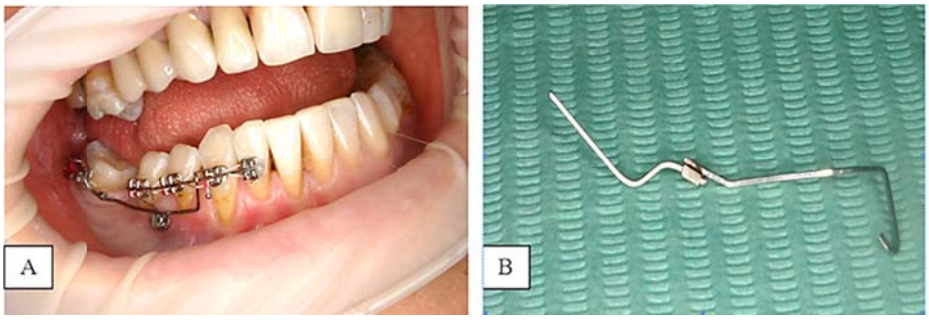

Fig.2 A. The orthodontic appliance and the miniimplant;
B. The Titanol Uprighting Spring (Forestadent)

The overall treatment lasted four and a half months and the width of the edentulous space after treatment was 8 mm measured by the same critertia as prior to starting treatment. After completion of the orthodontic phase and endosseous implant was inserted (3.75 / 11.5 mm, MIS Seven, MIS). After primary wound healing the orthodontic appliance was removed and a splint was made as a space maintainer for the osteointegration period. In order for the splint not to interfere with the healing process it was not in direct contact with the edentulous ridge at the implant site. The prosthetic device was a metal ceramic crown inserted four months after implant placement. The stages of the prosthodontic treatment were conventional ones. In the first phase, the implant was exposed and a transgingival healing screw was placed. One week after suture removal an impression was made using an individual open impression tray using a direct transfer device. Then, we chose a standard abutment and the crown was manufactured in a conventional manner by the dental lab. After completing all clinical and technical stages of manufacturing the crown was fixed upon the prosthodontic abutment.

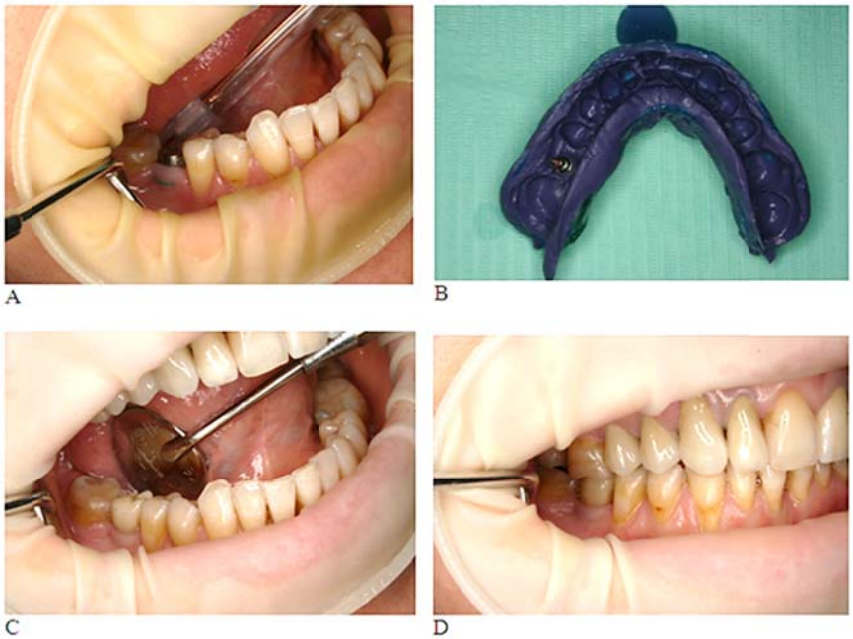

Fig.3 Stages of the implant prosthodontic treatment. A. Insertion of the transgingival healing screw. B. The impression. C,D. The final intra-oral aspect of the implant supported metal ceramic crown

DISCUSSIONS:

The Titanol Uprighting Spring (Forestadent) combines the elasticity and light forces provided by NiTi wire with the stiffness and stability of stainless steel.

One can also choose and control the movement type by bending and indi-vidualizing the wire into any of the three given alternatives (type 1, 2 or 3 geometry). In the presented case we used type 2 activation with a vertical arm of 3-4 mm. By this we achieved the uprighting without molar intrusion or extrusion thus gaining 3 mm of space, from 5 mm to 8 mm (Fig.4). The possibility to easily adapt the wire by a slight lingual bend compensates for the tipping forces that tend to move the molar lingually and the opposing teeth buccally.

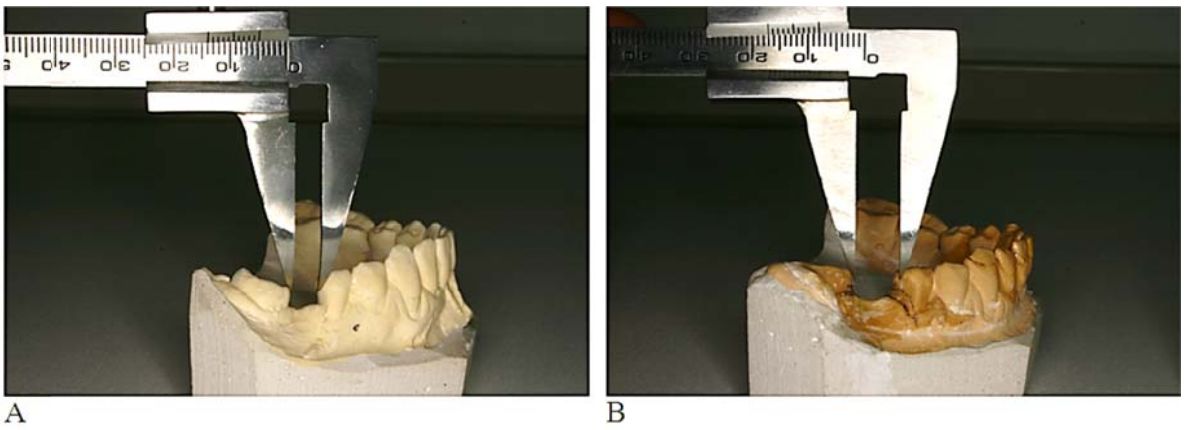

Fig.4 The width of the edentulous ridge before (A) and after (B) orthodontic treatment.

The greatest advantage of the treatment is the healing of the bone defect that could have been made worse by restoring the edentation with a tipped 4.7. The panoramic x-ray (Fig. 5) shows the newly formed bone and the line between the preexisting bone and the new one. Another aspect worth mentioning is the fact that by uprighting the tipped molar the control of dental plaque is more accurate and oral hygiene is more easily performed.

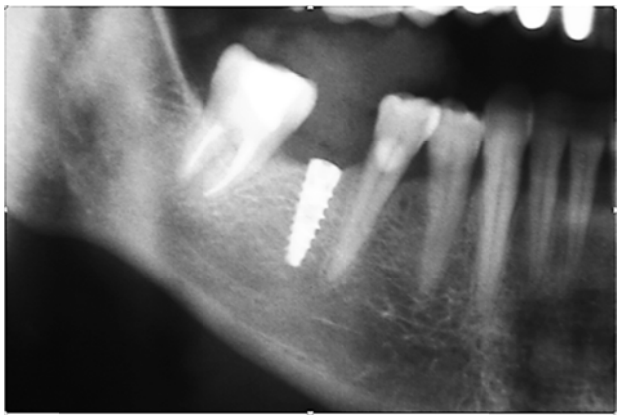

Fig.5 The radiologic image of the newly formed bone after molar uprighting.

CONCLUSIONS:

a. The case study shows the impact of interdisciplinary collaboration on the outcome of the treatment. Without the orthodontic component, a traditional fixed partial denture wouls have been manufactured and inserted with unwanted dental and periodontal side effects.

b. The used of segmental arches has a minimal impact on the patient's esthetics and is therefore the alternative of choice in cases with high esthetic requirements.

c. Skeletal anchorage is crucial in avoiding unwanted tooth movement. It is also a very useful treatment tool because of the easy handling and insertion. A key element is the fact that in the absence of patient compliance miniimplants are the only solution that can transform a compromised case into a successful one.

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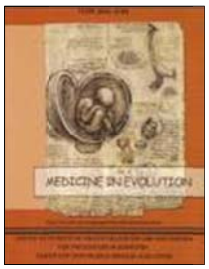
FORM AND FUNCTION CORRECTION BY USING COMBINED ORTHODONTIC AND ORTHOGNATHIC THERAPY



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ABSTRACT

One of the main goals of the modern oral and maxilo-facial surgery is the area of diagnosing maxillary deficiencies as well as the orthognathic surgery.

The indication of outgoing this modeling intervention must be directly linked to the objective need of the patient and the stability prognostic sustained by the specialists.

Key words: *maxillo-facial surgery, orthognathic intervention, orthodonthic treatment, class III skeletal anomaly, facial correction.*

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INTRODUCTION

In the combined orthodontic and orthognathic therapy occlusion, function and esthetics are highly important parameters [1, 2].

The goals of these conjugated treatments are [3, 4]:

- Obtaining of a neutral, stable and functional dental occlusion, in a physiological condilar position
- Optimizing of the facial esthetics
- Optimizing of the dental esthetics and periodontal health
- Result stability

Growth of the self esteem of the patients. It is well known that nowadays dento-alveolar anomalies can be treated successfully by orthodontic treatment. This may be followed, if needed by esthetic touch ups at dental level.

AIM AND OBJECTIVES:

Skeletal deficiencies, known also as disgnatia can be treated orthodonthic only to a certain level.

They are considered to be camouflage therapies.

Sagital severe deficiencies, like the class III Angle skeletal anomalies are even harder to camouflage. The orthodontic treatment is a compromise between esthetics and functionality and the obtained result is unstable. If the patient presents skeletal maturity, the election treatment is the combined therapy, including orthognatic surgery [5]. In this way we can allege that we obtain a real correction of the two jaws that are in discrepancy.

The aim of this article is to show the treatment possibilities of the skeletal cause of the anomaly by using a combined orthodontic-orthognathic-orthodontic therapy.

MATERIAL AND METHODS:

The indications of this combined therapy, that authors named Sandwich technique [6] are precise and come after a thorough evaluation of each case:

Functional deficiencies;

- Dental and facial esthetic deficiency;
- TMJ disfunctions;
- Periodontal diseases;
- Diminished or no possibilities of prosthodontic rehabilitation due to the present skeletal anomaly;
- Patients with clefts.

The logical answer to the question "which patient is a viable candidate for the sandwich technique?" is the patient which due to his dento-skeletal status cannot be treated only by the use of orthodontic methods.

The following issue is the ideal way of medical approach of the patient in order to the accurate resolving of the existing deficiencies. The medical history is of highly importance, as well as his motivations and expectations. There are also needed: clinical consultation, orthopantomography, and profile teleradiography, (Fig. 1) computer tomography with 3D reconstruction if possible, intraoral and facial photographs, and study mock-ups.

The pleasing results of this therapy depend on the expectations of the patient, after the medical outcome.

From the data gathered by Flanary, Jacobson and Kiyak the most im-

portant motive of agreeing to outcome this therapy is 79-89% the esthetic appearance [7]. The patients understand their skeletal anomaly only by esthetic reasons; they are used to the functional deficiencies. Kayak also reported that females are more preoccupied by this feature than the males [8].

Fig.1 Initial profile teleradiography.

Fig.2 Frontal and profile photos.

In order to draw a firm example of our founding, we present a male patient, aged 19, that is presented in our service in order to perform an orthognathic intervention. The clinical examination shows facial deficiency. He has frontal inverted bite that influences negatively the aspect of the facial appearance. (Fig.2) He has no general diseases. He has no orthodontic treatment before presentation in our service.

Photographs taken from the front and side present difficult labial contact and inverted labial step. We observe also left posterior cross bite. (Fig. 3) The dento-dental discrepancy in occlusion

measures 3 mm. The natural dental compensation has been made by the proclination of the upper central incisors, measured cephalometrically with the Steiner analysis (146,75°).

The ortopanthomography shows the presence of three third molars, which have been extracted before the orthognathic procedure.

The parameters indicate the so called "long face", and the cephalometrical numbers show a posterior growth type. The Steiner analysis presents SNA angle of 76, 73-maxilla retruded with retroclination of the lower incisors (11, 99). The Mc Laughlin analysis reveals maxilla retrusion (76, 73), mandibular prognatism (6, 73) and a low mandible plan (20, 54). The modified Steiner analysis shows a protruded inferior lip (2, 5) [10].

The Sassouni analysis presents:
Maxilla retrusion (-14, 48)
Mandibula retrusion (-5, 47)
Protrusive maxillar bases
Posterior placed Gonion.

This analysis cephalometrically reveals the presence of the "long face" and a posterior growth type corresponding to the "long face". He shows the retruded upper lip (98, 97) regarding the normal values (100-115) [4].

In order to establish a stable and functional occlusion, in a physiological condylar position [10], an improvement of the facial esthetics and of the labial closure we decided to go for a combined therapy.

The initial orthodontic treatment follows the leveling of the oclusal plan and the decompensation of the skeletal anomaly. We used metallic brackets, with metallic slots [13, 14]. 4-6 weeks before the surgery acrylic rails are made in order to obtain the physiological position of the condyles [11].

The orthognathic surgery is performed with the using of splints and follows the maxilla advancement by LeFort I osteotomy with 6 mm during the intervention we performed genioplasty to harmonize the facial appearance [8]. 7-14 days after the surgery the orthodontist may correct the dental interferences by using elastic ligatures to traction vertically. After removing the intermaxillar fixation, he preceded to the final touch ups of the occlusion. The whole process took about 5 months. After removing the brackets, the patient received two rigid acrylic trays [13].

Fig.3 Endooral aspect.

RESULTS

The intraoral photographies show the clinical situation after the combined therapy. We obtained neutral and stable occlusion bilateral, with leveled oclusal plans.

The facial photographs present a harmonized face; the "low face" disappeared. (Fig 4) The labial closure is made relaxed, without any effort.

DISCUSSIONS:

Functionally the patient reveals no dental interferences and has no pain. The teleradiography shows the final situation. (Fig 5) After the postoperatory recovery, the outcome is evident immediately, with class III modification into skeletal class I, and a considerable improvement of the facial esthetics. The patient is very pleased with his appearance [8, 12, 17]. Any patient, and also our patient, requesting orthognathic intervention have certain motivating factors; these may be functional, aesthetic or a combination of the two. So, there are cases, including the presented case, where surgical treatment represents the treatment of choice which leads to the principal aim of dento-maxillo-facial harmonization in conjunction with orthodontic treatment.

Fig.4 Postoperative photo.

Fig.5 Postoperative profile teleradiography

CONCLUSIONS:

a. The combined therapy in patients with skeletal anomalies and bone maturity is becoming more and more popular among the modern contemporary techniques. The motives are esthetic, functional and increase the self esteem.

b. Although the results are spectacular, they present no stability if the exact steps described above are not followed. Highly important are the cephalometrical measurements in diagnosing these anomalies.

c. Keeping in mind that the functional comes before the esthetics leads us to the idea of the conjunction of these two desiderates.

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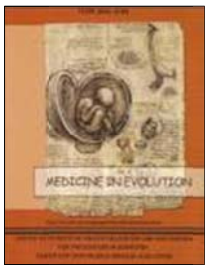
A HIGHER SUCCESS RATE OF DENTAL IMPLANTS THROUGH PROPHYLAXIS



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ABSTRACT

This study was conducted on a group of 240 patients that needed a dental implant and 12 practitioners in dental implantology. The patients were chosen randomly from the 12 practitioners' private practices.

The study is aimed at obtaining data concerning the way the implantologyst aproaches the patient in need of dental implants, how much importance is given to explaining the risks, as well as the benefits, how important the involvement of prophylactic measures is for the practitioner in ensureing the succes rate of the dental implant and how practitioners ensure the maintanance of the dental implants at follow-ups.

Key words: *dental implant, implantologyst, prophylactic measures, hygiene.*

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INTRODUCTION

Similar to the collaboration between general and specialized medical practitioners, the patient oral rehabilitation success rate significantly increases, when good interdisciplinary collaboration can be achieved. The success of the dental implant itself cannot be considered complete without proper preparation before the implant, close follow-up of the osteo-integration process after the implant and thorough patient education concerning dental hygiene.

The primary objective of this study is to underline the importance of including prophylactic measures in the therapeutical act of implantology and ensuering the succes of the dental implant throughout prophylactic maintainance measures.

MATERIAL AND METHODS:

The study was carried out during a period of 4 years; in this time I had acces as an observer in 12 private practices in wich dental implantology is practiced.

Theese practices were located in Timisoara and the Timis county. Theese practitioners were between 25 and 40 years old. 82 percent were men and 18 percent were women. The number of patients that needed a dental implant and were presented a treatment plan which included dental implants was 240. Keeping deontological principles in mind, I cannot offer exact data regarding the names of the practices or the names of the implantologists involved in my study.

Fig.1

Fig.2

RESULTS

After the 4 years of study and analyzing the following results occured:

70 percent of the private practices in my study do not have a dental asisstant or a hygienist employed. During the implant insertion procedures, the implanttologists are helped by younger colleagues or Medical School students.

Almost 90 percent of the implantologists only explain the surgical procedure itself and the esthetic and functional consequences to pacients in need of a dental implant. Because of the lack of oral health education and the socio-economic condition, for almost 80 percent of the pacients, the primary factor in choosing the prosthetic restauration on dental implants as a treatment solution is the financial one. Only 10 percent of the pacients that accepted prosthetic restaurations on dental implants benefieted from a treatment plan that included professional complex hygiene methods before the implantation

and accurate guide lines on home hygiene post-implant, in order to increase the chances of maintaining their dental implants. Having witnessed the explaining of the treatment plan to a number of 240 potential pacients for prosthetic restorations on dental implants, in the end only 70 percent accepted the ideea of a dental implant treatment plan. Because of deontological issues and confidenciality, further data cannot be provided.

In the evaluation of the succes rate of a dental implant, very few practitioners evaluated the use of tobacco.

Most of the implantologists for the first follow up at 6 months after the insertion of the dental implants.

Most of the practitioners do not carry out a comprehensive case history of the pacient soon to undergo surgery.

The social and economical factors are not taken into consideration as much as they should be.

DISCUSSIONS:

The implanthologists should take more time to educate and inform their pacients.

The presence of a dental hygienist in a private practice of an implanthologist is mandatory. The pacient with dental implants must be called for follow ups at 1, 3, 5, 7 and 30 days after the implant insertion and then monthly during the osteointegration of the dental implant and before the prosthetic phase begins.

CONCLUSIONS:

The implanthologists should take more time to educate and inform their pacients.

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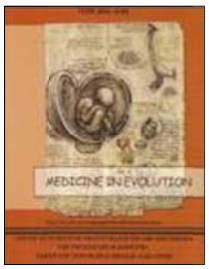
EXPERIMENTAL TESTS FOR A LOWER COMPLETE DENTURE



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ABSTRACT

***Objectives**: The goal was to determine the durability of complete dentures made from Supercryl Plus.*

***Material and Methods**: The estimation was realised by finite element analysis for a lower complete denture made of Superacryl Plus. For this, it is necessary to know the mechanical properties of the acrylic resin on samples. The reverse engineering technology was used (after a 3D laser scanning of prosthetic pieces), and the model calculation was finally validated by a fatigue experimental test.*

***Results**: At the static tensile tests for this resin there were obtained the following results: the ultimate tensile strength, R_m=66,32MPa; Young's modulus, E=5333MPa; total elongation at fracture, A_t=11, 96%. The fatigue strength, determined for the material, was σ_0=11,904MPa. The results showed a good fatigue resistance of the material Superacryl.*

***Conclusions**: Numerical simulation offers the solution regarding the effective performance of the dentures.*

***Key words:** complete dentures, acrylic resin, finite element analysis.*

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INTRODUCTION

Diversification, application of finite elements analysis in dentistry consists in nonivazive possibilities to testing new materials and improving the already existing technologies. These experiments permitted testing static, dynamic and fatigue mechanical properties, with aim of lifetime evaluation, which could be seen as usage warranty.

In the literature, the domains of interest concerning complete dentures, were centered especially on materials studies and achieving technologies.

Complete dentures are realized from different acrylic resins, from among the most used are the heat curing ones; but the material they are made of is usually fragile [1, 2, 3, 4, 5]. Thus, frequently there appear cracks and fractures of these dentures. Computerized systems could offer some explanations regarding reasons of dentures deterioration, and could mark the minimum resistance zones [6, 7, 8, 9], in function of variants of forces application, support aplication and material type.

Numerical simulation, as a preliminary stage, can offer the solution regarding the effective performance of the dentures and allow validation of some hypotheses regarding dentures fracture appearing [2, 7].

OBJECTIVES:

This studies were centered on finite element analysis by ***static tensile tests*** (stress and deformation) of complete dentures realized from Superacryl Plus (heat curing acryllic resin), through which we can make some predictions regarding place and time for apparition of tension and deformation, which determine fracture risk.

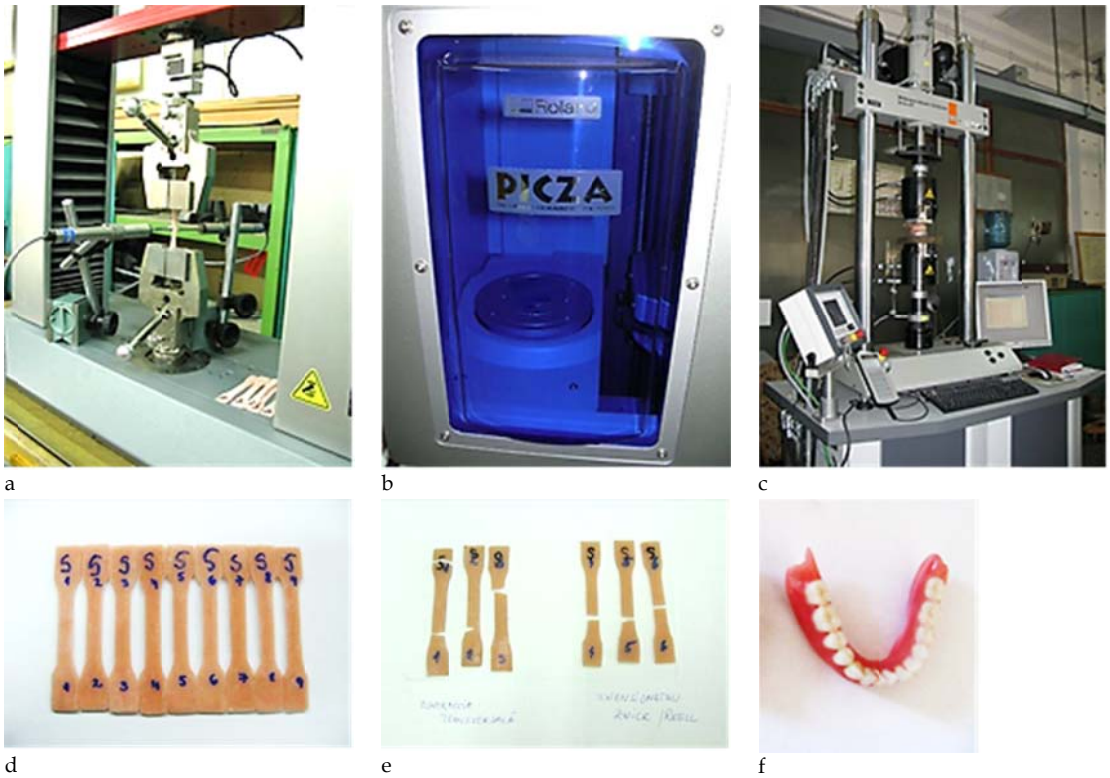
MATERIAL AND METHODS:

For testing and evaluating, there were used Superacryl Plus (Spofa-Dental, Markova, Czech Republic), a heat curing dental resin as samples and complete denture (classical technology).

There were determined the mecha-nical properties of Superacryl Plus, on samples, through tensile tests, like: the longitudinal elasticity modulus, the tensile strength and the deformability properties at static tensile tests. For this study was used a geometrical model obtained by 3D scanning process and reverse engineering technique. Dentu-res were 3D scanned (using laser sca-nner 3 D LPX 1200 Roland) and sub-mitted to some noninvasive tests thro-ugh FEM proceedings. The geometrical model was 3D scanned with help of Dr. PICZA program.

The point cloud resulted from scanning process was imported in PIX-FORMPRO software and has been transformed by ,,reverse engineering'' technique into a network surfaces. These surfaces were exported as igs file and open in SolidWorks CAD software as solid model. This model was imported into finite element software – Ansys Workbench (ANSYS Multiphysics). Experimental tests are made on virtual model, in order to analyze complete dentures by *static tensile tests and fatigue degradation*. Further, the work hypotheses on computer were confirmed or infirmed by the real fatigue tests, with

pulse loading cicles for which maximum force was considered 700N,500N, 400N, 300N si 200N.



a b c

d e f

Fig.1 Working equipments & Materials: a. Zwick Roel equipment b. 3 D Laser scanner LPX 1200 belonging to Roland company- external aspect; c. Multipurpose Dynamic Test System, series LFV; d,e. Superacryl samples realized by classical method of heat curing; samples fractured during mechanical tests; f. lower complete denture

RESULTS

At the static tensile tests there were obtained the following results: the ultimate tensile strength, Rm = 66, 32 M Pa; Young's modulus E = 5333 MPa; total elongation at fracture, At= 11, 96%.

Analysis of tension and deformation for the denture submitted to different loadings is marked by chromatic spectres which are visible on dentures components, where stress is always marked in warm colours: red, orange, yellow, while quiet zones are marked in blue. The method became necessary, because it represents the ground for more advanced analyses (at various applications), for explaining more complex phenomena which lead to dentures degradation. This way, we can underline the minimum resistance zones, where the denture fractures itself (fig. 2). A very important signification has the denture's loading. This is because: if denture's support is insufficient or unequal distributed, the forces that push the denture towards the prosthetic field determine different effects. It results that, an insufficient support leads to a more rapid denture breaking.

For the denture's clamping to the fatigue testing machine with loading cycles, in which the maximum force ranged between 80N and 200N, there was used a rigid support (made of Melot) with a lower plane surface. Between the rigid cast support and the denture, there was used the elastic/flexible material Oranwash-Zhermack, with a thickness of 1-1.5 mm (for simulation of

patient's fibromucous tissue behaveour). The durability calculus performed for ideal situations confirms the denture reliability for a guarantee period of minimum 5 years. According to our tests, the fatigue resistance for Superacryl Plus is 12 MPa, which shows a high durability (fig.3).

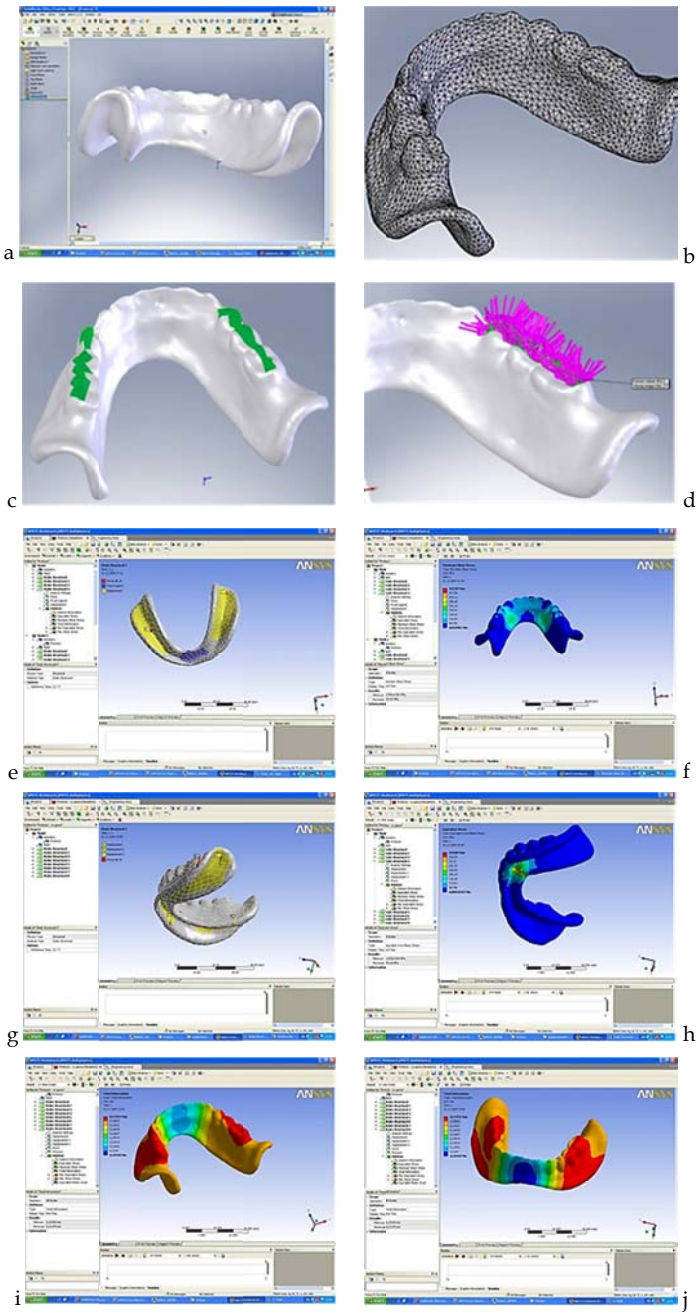
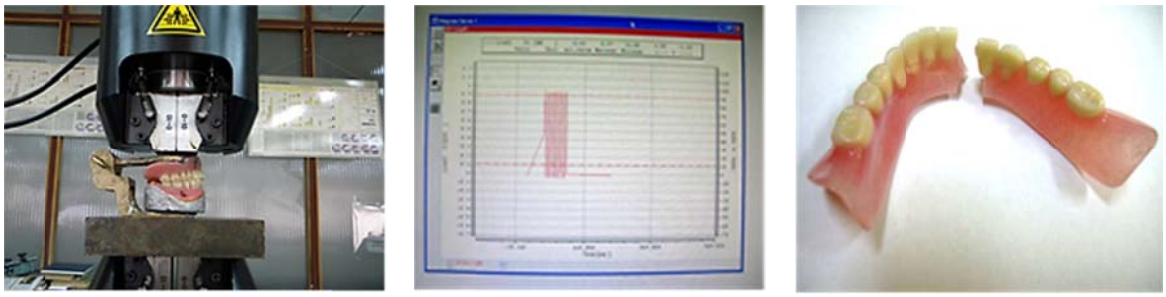


Fig.2 Finite elements analyses: a. scanned lower denture; b. meshing of the geometric model of the complete denture for the calculation model; c, d. force application; e, f, g, h presentation of the safety factor variation obtained by finite element analysis- code Ansys Workbench (ANSYS Multiphysics) representation of stress distribution dependent on loading and support; i, j. total deformation of the complete denture at its displacement towards the prosthetic field.



a b c

Fig.3 Fatigue loading cycle's registration;
a. Walter Bai equipment; b. cycle's registration c. Brocken lower denture after fatigue tests

DISCUSSIONS:

The advantages of using the numerical analysis with finite elements method are connected to the possibility of handle complex geometries; solve complex engineering problems from the field of materials' strength, solids' mechanics, kinematics, electrostatics, aeronautics etc. The material's properties from the real structure are integraly reproduced in its elements [2, 3, 6, 7, 8]. Disadvantages are connected especially to the data consistency of the introduced parameters for system's examination; if these aren't optimal, then the solutions are wrong or approximate. The field's importance is marked by those over 400 books, web pages. One needs to notice that, within the finite elements method the approximation is physical, namely a modified structural system substitutes for a real continuously one. Mathematically, one doesn't make any approximations in regard to the real structure. This represents the essential diference between the finite elements method and the finite diferences method, where the equations of a phisical system are solved by approximate methods. By using of bidimensionals or three-dimensional elements, the finite elements method doesn't affect the structure's continuity.

Fatigue depends on material structure [1, 2, 4, 5, 6]. Fatigue degradation process is characterized by the fact that, plastic deformations are situated around defects or cracks. Fatigue breaking has a progressive- hidden character; the prosthetic piece conducts itself normally, untill the crack extends to a certain length and then the final breaking starts, by overstressing the material from the remained section [4, 5, 7]. Evaluation of material fatigue resistance is a characteristic in estimation of complete dentures' durability. The results showed a good fatigue resistance of material Superacryl. According to our tests, the fatigue resistance for Superacryl Plus is 12 MPa.

CONCLUSIONS:

a. Experimental study of the denture's mechanical properties by finite element analysis is used for knowledge of risk zone for fracture.
b. Knowing the fatigue properties for this material, the safety degree in using the denture by patients can be guaranteed on a period of 5 years.
c. There also can be tested new materials, which can be successfully used in prosthetic dentistry.

Acknowledgements:
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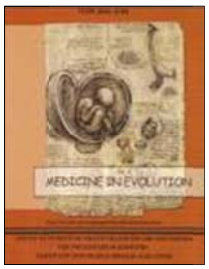
ORTHODONTIC (CLASS II ANGLE) EXTRACTION THERAPY. INDICATION, ANCHORAGE AND TORQUE CONTROL



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ABSTRACT

In most malocclusions, extraction of teeth is required to solve the crowding of teeth and/ or to produce a desired lip profile. When teeth are removed (usually the first or second premolars), the posterior teeth are tipically moved mesially in varying amounts to close the extraction sites. We must know if we want the posterior teeth to remain stationary or can be moved up to half the extraction site: 3, 5 mm.

In case of a Class II deepbite, it will be a camouflage therapy and the result will be: class II molar and class I canine in both sides and an overbite of 2 mm.

The materials that I used were: braces in the upper and lower jaw, "Nance –Eva device" (we get an armonios occlusal plane), closed the space with NiTi closed coil springs for the canine and after that I used the "Compound Retraction and Torque archwire" (stainless steel without torque for the lateral posterior teeth, NiTi with torque for the front teeth and two hooks for individual bending). The retraction and torque archwire is used for bodily retraction and torquing of anterior teeth.

The aim of this study was to describe how simple and very easy could we use this appliances and the results are very good in a short time. It is also very confortable for the patient.

Key words: *Deepbite, Nance- Eva appliance, Retraction arch, class II Angle.*

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INTRODUCTION

The anomalies of the position of the teeth may be solved by orthodontic measures independent of the growth of the facial bone structure, the therapy of the skeletal anomalies is dependent compulsory by the expected growth of the skull.

If the anterior positioning of the mandible does not succeed, namely the growth in length is not successful during the stage of growth and development, there remain two alternatives of treatment to be implied:

In case of favourable premises, after the growth of the jaws has finished or in case of the insufficient growth in length of the jaw, one may resort to the therapy of camouflage. In this case, after the extraction of two premolars of the superior jaw we will maintain the distal occlusion in the posterior lateral zones to be followed by the retraction of the canine tooth before or together with the superior front incissors, so that to be able to obtain the neutral occlusion at the canine level.

However, we have to specify that this therapy may not be used in all the cases of class II Angle, but only after a correct diagnosis has been established after the study of the model, the analysis of the orthopantomography and a profile teleradiography.

As long as the extractions of the premolars of the superior jaws are unadvisable and thus, the camouflage therapy cannot be applied, there surely remains the alternative of the medial positioning of the mandible to be applied as a solution for the treatment.

We have to take into account that, after using any method of treatment, there will be manifested extraoral changes. When using both the camouflage therapy and the more anterior positionning of the mandible there can appear changes of patient's profile. These changes may be either favourable or unfavourable. If, by mistake, we choose the "unfavourable" therapy, we may face several problems as to patient's hardness accepting nonadvantaging changes of the profile, as well as the idea that he may no longer resort to the previous aspect [1].

Very often, the solution the orthodontist proposes the patient does not fit the one the patient asks for. The avoiding of the osteotomy of remodeling the jaw is placed on the first position in the list of patient's wishes. Therefore the orthodontist has to choose between the optimal solution finally leading to long-expected results or the expectations the patient wishes to reach the result as quickly as possible and without a long effort.

The patient resorts to appreciate the result in case the alignment of the teeth in their frontal zone more visible. The aesthetics is by far more appreciated than the optimal functioning of the dento-maxilar zone. The anomalies class II Angle, the position of the superior front teeth are those that bring to patient's consulting the dentist more often [4].

The termen "camouflage" represents a masking and it has been borrowed from military vocabulary. Behind this notion they hide any therapy form that tries to compensate dento-alveolary a skeletal anomaly.

A skeletal anomaly class II Angle is to be compensated by extracting the teeth of the superior jaw, while an anomaly class III Angle is to be done by extracting the teeth of the inferior jaw.When the latter therapy is to be chosen, the orthodontist informs the patient in connection to his dental – facial modifications he will have after the extractions, and, at the same time

the dentist has to show the patient all the possible alternatives of treatment [2].

In case of the prime permanent molars there have not encountered massive reconstitutions, the molars are tho-se to be extracted first, so that in the lateral zones still remain teeth enough to do the anchorage; in the frontal zone there remain less teeth which have to retracted.

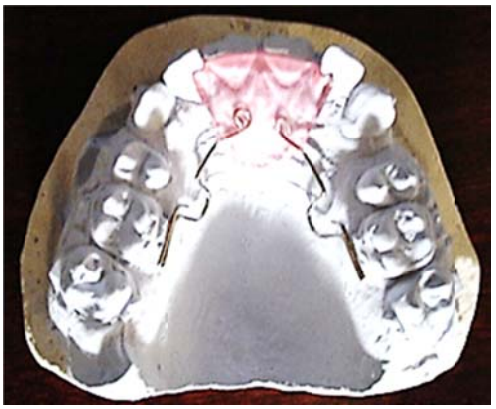
Thus, at the same time one can perform even a light raise of occlusion. This therapy is especially indicated in case the skeletal deviation is small and there exists dental crowding on the arch.

MATERIAL AND METHOD

14 years old patient, cames into my dental office with teeth crowding, palatal compression, deepbite, 1.3. ectopic canine, 2.7. is in eruption and it's in buccal-inclination.







Consequent to this analysis of the model of study, of orthopantomography and of the teleradiography of profile we have resorted to apply the following plan of treatment:

The extraction of 1.4 and then of 2.4., to be immediately followed by the multiband device for the upper jaw and in an other appointment we made it for the mandibular arch. Then there followed a series of NiTiwires: 0.14, 0.16, and 0.20. After three months we applied the Nance device meant to raise the occlusion, the inferior inccisors occlude with the acrylic pelota to be intimetely attached to the anterior part of the Palate, stretching on the palatinal surface of the front teeth- inccisors.

At the same time we used the Nance device for strengthening the anchorage of the lateral zones and distalizing the canine.

Z1-WinCeph 5.0	Dr. Melinda Ana Onet (342234)	Seite 1 von 2

PatNr. : 11
Name : NEAMT, DIANA
Geschlecht : w, kaukasisch
Geboren am : 05.07.1996 (13 J + 5 M)
Datum : 12.12.2009
Behandler : DR: ONET MELINDA
Gedruckt am : Fr, 06.05.2011, 21:06:39

AnMyoGdncGan-Analyse

Parameter	Norm	Messw	Kommentar / Befund
Pal-Mand	28.5 ± 4.5	19.6 °	geschlossen
FMA-Mand	23.0 ± 5.0	20.9 °	
SGn-FMA	59.5 ± 2.5	58.5 °	
A-N	1.0 ± 2.0	3.2 mm	prognath
SNA	79.5 ± 3.5	87.9 °	prognath
N-Pog	-7.0 ± 3.0	-1.6 mm	progen
SNB	79.0 ± 4.0	83.0 °	
ANB	3.0 ± 1.5	5.0 °	Skel. Kasse II
Wits	0.0 ± 1.0	5.0 mm	Klasse II
1OK-1UK	127.5 ± 2.5	132.1 °	
1UK-ME	93.5 ± 4.5	96.5 °	
1UK-NB	3.5 ± 2.5	7.0 mm	protrudiert
1UK-APog	2.0 ± 2.0	2.7 mm	
1OK-SN	102.5 ± 3.5	105.5 °	
1OK-APog	4.5 ± 2.5	8.6 mm	protrudiert
1OK-A-FMA	4.0 ± 2.0	-6.4 mm	retrudiert
SnW	100.0 ±10.0	116.8 °	
LbSup-ELinie	1.5 ± 2.5	-2.3 mm	hinter
LbInf-ELinie	1.5 ± 2.5	-0.2 mm	

Lineare Werte berechnet für Fokus-Filmdist.: Inf. cm / V = 1.000

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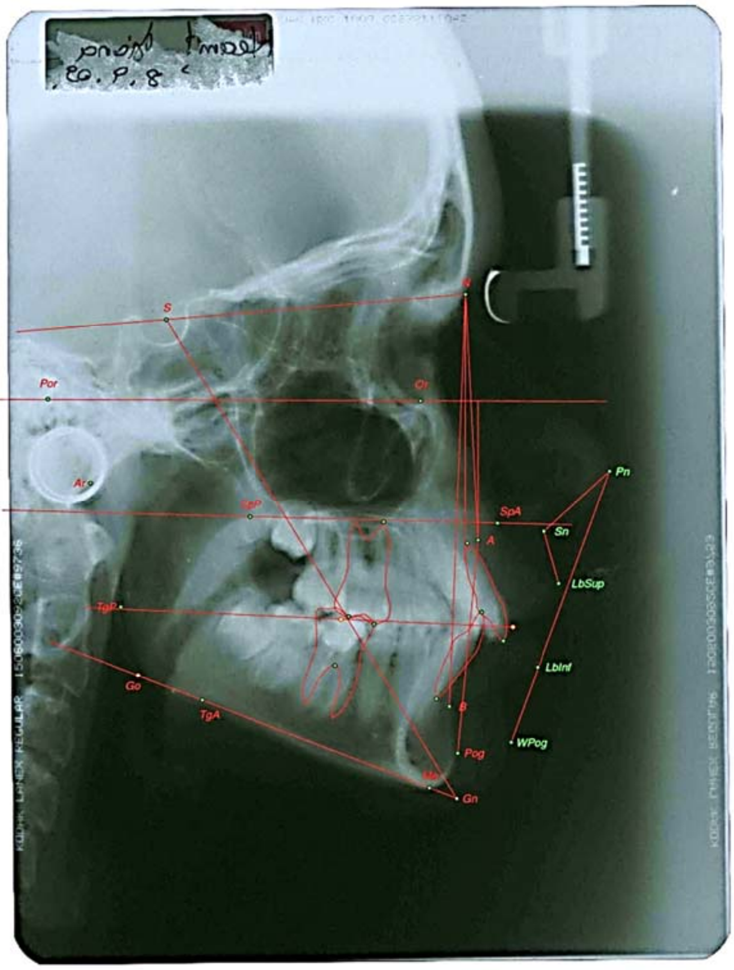

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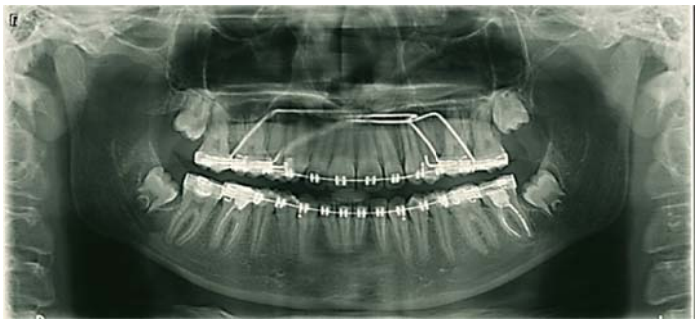
Wachstumsrichtung

FMA-Mand	N-Pog	ANB	Wits	
			-3.5mm	horizontal
5.5°	-17.5mm	-2.3°	-2.5mm	
10.5°	-14.5mm	-0.8°	-1.5mm	
15.5°	-11.5mm	0.8°	0.0mm	neutral
23.0°	-7.0mm	3.0°	1.5mm	
30.5°	-2.5mm	5.3°	2.5mm	
35.5°	0.5mm	6.8°	3.5mm	vertikal
40.5°	3.5mm	8.3°		

Gesichtstyp

	SGn-FMA	A-N	
retrognath	51.2°	-5.7mm	vertikal
	52.0°	-5.0mm	
	52.8°	-4.3mm	
	53.7°	-3.7mm	
	54.5°	-3.0mm	
	55.3°	-2.3mm	
	56.2°	-1.7mm	
orthognath	57.0°	-1.0mm	
	57.8°	-0.3mm	
	58.7°	0.3mm	neutral
	59.5°	1.0mm	
	60.3°	1.7mm	
	61.2°	2.3mm	
	62.0°	3.0mm	
prognath	62.8°	3.7mm	
	63.7°	4.3mm	
	64.5°	5.0mm	
	65.3°	5.7mm	
	66.2°	6.3mm	
	67.0°	7.0mm	
	67.8°	7.7mm	horizontal

The very moments we closed the space between 1.3 and 1.5 and, the same way the space between 2.3 and 2.5, we strengthened the lateral group together with the canine with a metallic ligature, bilaterally. We applied "Compound Retraction Archwire:, NiTi superelastic 18/25 on the front part which was adapted before the ligature to the mezio-distal dimension of the superior incissives, having a frontal tourque of 30 degrees and, while on the lateral parts the arch was made of Steel (SS) 17/25. By now, we apply in the finishing stage 17/25 SS and 18/25 steel wire, then, after several weeks we will have to return to the round arch of 0.18, then interjaw tractions without arch in the lateral zones in order to obtain a better intercuspidation.



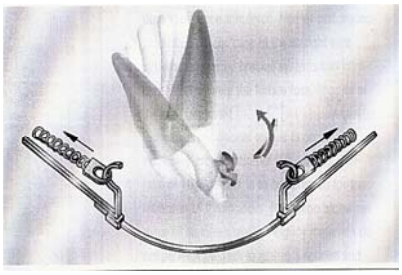
RESULTS

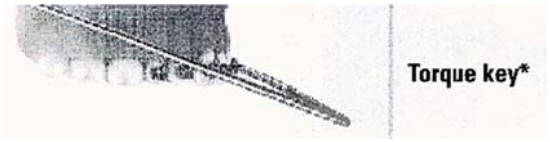
The results are obtaineed in a short period of time. The devices are easily accepted by the patient.

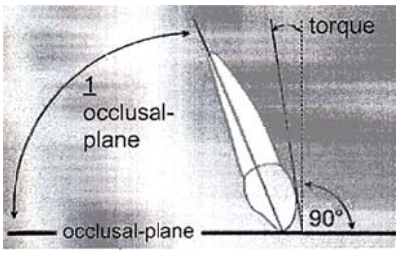
The Nance-Eva appliance levels the occlusal plane in 4 month. The compound retraction archwire is once adjusted in the pacient's mouth and can be removed when the space is closed. Readjustment or reactivation is not necessary. We have control of the axial position of the incisors. If the long arm of the torque-key points cranially to the occlusal plane, we have a steep incisor position.

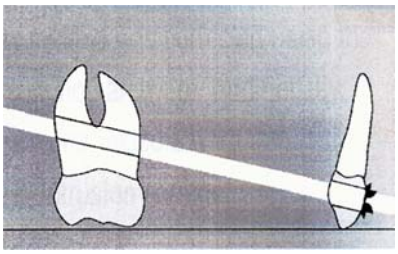
If the torque-key points parallel to the occlusal plane, we have an appropiate position of the incisor axis, when applying a Straight-Wire-Tehnique. If the torque-key points caudally to the occlusal plane, we have a protruded situation of the incisor axis. The retraction of the front teeth was obtainned in 4-5 month. The finishing stage takes 2-3 month, than the multiband appliance is

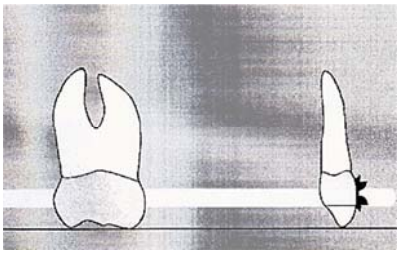
removed and in this moment we must apply the retention trays.

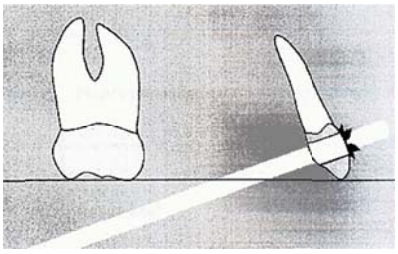












DISCUSSIONS:

Function of patient's age, the moment the treatment begins; we may choose various ways of advancing the mandible.

One has to take into account the growth of the mandible once age advances.

The functional devices Activator, Bionator, the duble Plate of mezialing the mandible, may stimulate the growth in length during puberty, while the effect of this measure depends of both the reaction of the tissues and the adaptability of the patient which diminished as age advances.

We ought to take a decision: should the advancing of the mandible done by the devices described before or to be done later, with the device Herbst or Easy Fit Jumper, which may be applied only then when auth the permanent teeth have turned eruptive [3].

Once age advances, we may rather obtain a dento-alveolar compensation than a correction of the skeletonic support.

CONCLUSIONS:

The extraction of the first premolars constitutes an alternative of treatment that might be applied in some situations of anomalies class II Angle. This option has to be chosen only by having a complete and correct diag-

nosis at the beginning of the treatment, as well as during it, so that the treatment should not deviate towards a wrong direction.

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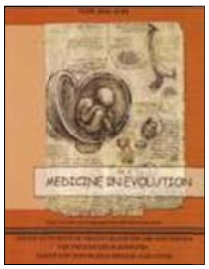
TELESCOPES IN DENTAL PROSTHODONTICS



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ABSTRACT

Even though the telescopic technique was first described over 120 years ago, today it still represents a high quality therapeutic option for removable restorations. The clinical utility, upgrading and changes made to telescopic systems are linked to the names of Karl Häupl, Hermann Böttger, Karlheinz Körber and Manfred Hofmann. During early stages, the retention of telescopes was achieved by friction and later galvanic telescopes were introduced, characterized by hydraulic retention based upon the Hagen Poiseuille principle. Galvanoforming telescopes are used in traditional as well as in implant supported prosthetics, predominantly in the latter, as thus the much desired passive fit may be achieved.

The aim of the present paper was to present a highly precise technology with very good long term results in constructing overdentures.

In the Clinic for Dental Prosthodontics and in „Prof. Dr. Bratu" Clinic, 17 telescopic restorations on natural teeth and 15 telescopic implant supported restorations were made. In natural teeth, the primary crowns for telescopes were made either of metal or of zirconium oxide. In the case of implants, primary crowns are avoided, the implant abutements being made of metal.

In our cases, after 5 years, we observed an 85% survival rate of the supporting teeth in patients who came to be re-examined, this situation being influenced by the location and number of supporting teeth. The retention of galvanic telescopes was longer, the patients being very satisfied with their restorations.

***Key words**: telescopic technique, implants, overdentures*

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INTRODUCTION

Telescopic crowns used in fixed as well as in removable prosthetics were first described about 120 years ago by the American dentist R. Walter Starr from Philadelphia. Telescopes are thus an American invention and document the high standard of medicine and dental technique on the Eastern coast in 1886. Despite this, in the English-American influence area, telescopic crowns have not become widely used. In the 20th century, in Europe, they were developed and widely used in Germany. The clinical use, development and changes in telescopic systems are linked to the names of Karl Häupl, Hermann Böttger, Karlheinz Körber and Manfred Hofmann. In English literature, the term of "german crown" is occasionally used proving that this type of crown is internationally percieved as a German speciality. Telescoping is an older procedure which had an early stage of retention by friction.

Telescopic crowns represent one of the simplest special systems for maintainance, support and stabilization (SSMSS) being composed of two elements: an internal crown (primary cap) and an external crown (secondary cap) very well adapted to one another.

The crown telescoping system is composed of two elements (fig.1)

- the primnary crown which is fixed on the crown abutment (or the thimble which does not respect any morphology);
- the secondary crown, which is part of the metal structure of the denture

The secondary crown slides on the primary coping achieving telescoping by friction. Between the two components of the system a friction force is generated which is proportionnal to the contact surface and the parallelism of the external walls of the primary crown. Körber2 classifies telescopic crowns as:

- Cylindrical telescopic crown;
- Conical telescopic crown;
- Resilient telescopic crown;
- Ovoidal telescopic crown;
- Telescopic crown with an indefinite shape.

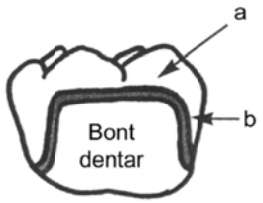

Fig.1. The component parts of the telescopic system: a) secondary crown ≥ 1 mm; b) primary crown ≥ 0, 5 mm.

The name of Prof. Dr. Karl Heinz Körber is linked to the conical telescopic crowns. The main purpose of the development of conical telescopic crowns was the elimination of the unwanted retention of telescopic crowns. Up to present, this is indeed the only retentive element in which unwanted retention may be calculated and physically reproduced [3, 4].

During early stages, the retention of telescopes was achieved by friction, with the further developemnt of galvanic telescoping characterized by hydraulic retention based upon the Hagen Poiseuille principle which states that flow resistence in a fluid is inversely proportional with the space between the two parallel surfaces which delimitate the flow. Galvanic telescoping is used in traditional as well as in implant supported prosthetics, with preponderance in the latter, because by galvanic telescoping the much desired passive fit may be obtained.

The aim of the present paper was to present an extremely precise technology with very good long term results in constructing overdentures.

MATERIAL AND METHOD

In the Clinic for Dental Prosthodontics in Timisoara the galvanoforming procedure is used since November 2002, with countless galvanic telescopes made until the present day. The Department of Dental Prosthodontics of the "Victor Babes" University of Medicine and Pharmacy Timisoara owns a Preciano CL-GF (Heraeus-Kulzer) galvanoforming equipment. Galvanoforming is a "noble" technology for making metallic components, consisting of electricly winding a metallic layer on the surface of a duplicate abutment or directly on the implant abutement until a 200-300 µm thick coping is obtained. The desirable metal is pure gold and, paradoxically, the hardness of the resulting structure is much superior to that of cast gold (130 – 150 HV, as compared to only 20 – 30 HV in the case of casting) (fig. 3). The weight of a mixed crown structure is 0.3-0.5 g as compared to 1.5-3 g for cast crowns. Galvanic winding occurs directly on the duplicate abutment, the ionic gold in the solution transforming into atomic gold on the catode, thus resulting a chemically pure metallic crown. In order to facilitate electrical winding, an electroconductor varnish containing silver particles is applied on the surface of the plaster abutment. In all commercially available systems, the electrolyte is a watery solution of a complex gold salt, in most cases a quaternary amonium compound.

Work is performed at an intensity of 0, 5 1, 5 A. Any minute deviation from these values may compromise the prosthetic device. The work temperature is between 45 – 65ºC, depending on the system. The most modern AGC (AuroGalvaCrown) equipments produced by Wieland (Pforzheim, Germany) is AGC Speed, AGC Micro and AGC Micro Plus. AGC Micro and AGC Micro plus are two rapid equipments which allow the simultaneous production of a maximum of 6 and 16 crowns, respectively, during 5 hours (for a 200 µm thickness). The equipments automatically calculate the needed electrolyte volume. AGC Micro Plus has specially designed accessories for galvanoforming total denture structures. All AGC equipments may be connected to and operated by computer.

Abutment preparation

The abutment preparation technique for galvanoformed prosthetic restorations does not substantially differ from preparing for a conventional mixed crown. A 1.2 mm reduction of the hard dental tissues is needed vestibularly, orally and proximally and of around 2 mm incisally and occlusally, respectively. The marginal limmit (cervical termination) will be mandatorily conformed in chanfrein or rounded shoulder.

The work model and the model for galvanoforming

It is mandatory to construct a model with mobile abutments. The abutments are duplicated using a duplication material which allows an acurate record (usually, silicone with addition reaction). A layer of silver varnish correctly applied has an uniforme thicknes of 7 – 10 µm. At present, there are automated spraying application systems for silver varnishes. These have the advantage of a more even application and a smoother resulting surface. With the aid of fine rubber polishing burs, any existing prominent margins of the galvanoforming crowns are removed down to the level of the prepared abutments. Then, the abutment-galvanoforming crown complex is immersed into an acid solution with

the purpose of dissolving the plaster, which is delivered by the manufacturer, in an ultrasonic cleansing bath at 40 °C, for 15 – 20 minutes. When extracted from the solution, the internal surface of the gold crown is covered with the layer of electroconducting varnish, the plaster abutment being entirely dissolved. The silver varnish is removed using a 25-50% azotic acid or 20% hydrofluoric acid solution.

In the Clinic for Dental Prosthodontics and in the"Prof. Dr. Bratu" Clinic, 17 telescopic restorations on natural teeth and 15 telescopic implant supported restorations were performed. The galvanoforming crowns were made with the AGC micro (Wieland) and Preciano CL-GF (Heraeus-Kulzer) equipments. Conical telescopes polished at 2˚ were used. In natural teeth, the primary telescopic crowns were made either of metal or of zirconium oxyde. In the case of implants, primary crowns are avoided, implant abutements being metallic. In fact, in implantology, primary crowns are used in cases where the vertical occlusion dimension requires or allows them.

Figures 2 and 3 show a case of telescopic restoration with primary crowns polished in zirconium oxyde and with galvanoforming secondary crowns.

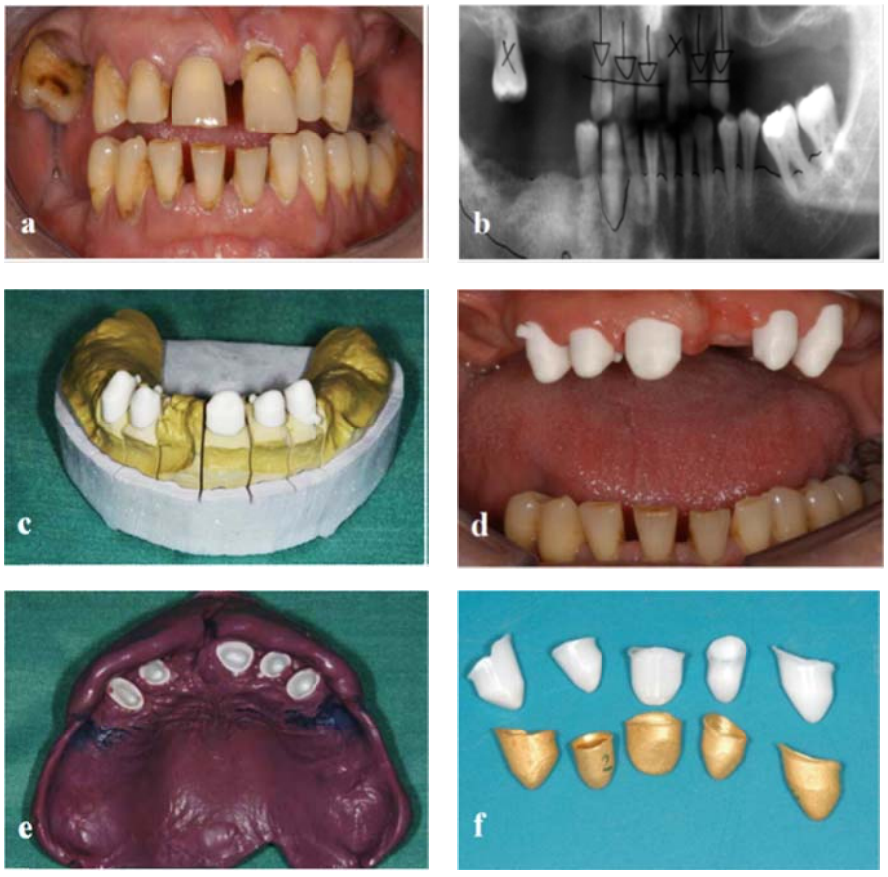

Fig.2 A.G ♂, 55 years. Prosthetic treatment by overdenture on galvanoforming crowns. a) Initial clinical situation b) Orthopan radiograph on patient first visit; c) Primary zirconium oxyde crowns on the work model; d) Checking the oral adaptation of primary crowns; e) Overimpression of primary crowns with individual impression tray and polyether; **f**) Primary zirconium oxyde crowns and secondary galvanoforming crowns (Archive of the Department of Dental Prosthodontics).

Fig.3 A.G., ♂ 55 years - continued: a) Metallic titanium overdenture structure on work model; b) Galvanoforming crowns fixed into the overdenture; c) Finalized denture on the work model; d) Finalized denture, mucosal aspect: Fixed denture design in the area of the remaining teeth, acrylic shoulders in edentulous areas, main palatinal plate-type narrow connector; e) Checking the oral adaptation of the denture; f) Final clinical aspect.

DISCUSSIONS:

Mock et al[5] report the results of a prospective study on 92 telescopic dentures and a total of 299 abutement teeth. The average surveillance period was 7.4 years, 67 dentures were partial telescopic dentures and 25 were overdentures. The first eight checkups were performed every six months and the rest were done yearly. The survival rate of abutement teeth according to Kaplan-Meier is 86.3% at five years and 72.4% after ten years. Upon analysis of the factors which may influence the life span of abutement teeth, a higher risk was demonstrated in the case of overdentures, the number of abutement teeth being able to influence the failure rate and stability of mandibular dentures. The most frequent re-optimization consisted of re-cementation of a primary crown (37% of patients). Generally, the periodontal parameters of

abutement teeth did not significantly alter. In the case of overdentures, an increase of the dental motility, an augmentation of plaque accumulation on the abutement teeth and an increase in the inflammatory response were observed, these symptoms being also demonstrated by a previous study[9].

Rehmann et al[8] conducted a retrospective longitudinal study of data on 554 telescopic dentures with 1758 abutement teeth, among which 30 dentures were additionally anchored with cast loops. The average surveillance period was 5.3 years. Patients were suggested the reexamination schedule which was adhered to by 57% of them. The 5 years survival rate of abutement teeth according to Kaplan-Meier was 93.9% while after 8 years it was 84.5%. The survival rate was significantly better in abutements which were not reconstructed on pins (87% as compared to 67.5% after eight years) or in those patients who attended the reexamination programme (88.1% as compared to 53.9% after eight years). When the number of abutement teeth decreases, the survival rate decreases as well, but the difference is not significant, while Eisenburger et al.[1] found lower values for abutement teeth numerically decreased after a four years interval (94% for 3 teeth, 92% for 2 teeth and 75% for one tooth). In this study we show that the location of abutement teeth in a partially edentulous maxillary influences the restoration survival rate, thus failures were frequent when the denture was supported by mandibular incisors (failure of dentures in 50% of cases after 3.3 years).

Previous studies on telescopic crowns showed good survival rates over 90% after 5 years and over 80% after 10 years, respectively[6,7,9].

This is the case of a selected group of patients[7] (male army staff), and in the thorough research performed by Möser[6] data on remaining teeth are missing.

In these two studies, insertion of dentures occured at a rather young age using telescopic crowns and not including all the teeth in the restoration.

In our cases we observed an abutement teeth survival rate of 85% after 5 years in patients who came for reexamination, depending on the location and number of abutement teeth.

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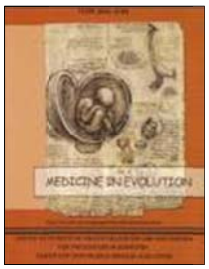
THE EFFECTS OF USING A PLASTIC DRY SALT INHALER™ (DSI) ON ADULTS WITH ASTHMA AND COPD



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ABSTRACT

Introduction: *Speleotherapy and halotherapy are relatively old therapeutic methods sometimes recommended for chronic obstructive disorders. Treatment in natural salt cave (speleotherapy) has been known for a long time.*

Study Objective: *The purpose of our study is to prove the efficacy of the Dry Salt Inhaler on adults diagnosed with asthma and COPD regarding the quality of life and the improvements of spirometry values.*

Material and methods: *The study was conducted on a patient pool of 38 individuals until abstract submission out of a total 128 until study closing (2011). The treatment period was 6 weeks of standard asthma / COPD therapy according to GOLD 2005 guidelines, and one 15-20 minutes inhaling session, preferably during the evening, using the DSI device. For evaluation of patients we used 2 methods: a quantitative evaluation based on spirometry and a qualitative evaluation based on a life quality-improvement questionnaire.*

Results: *Our results have shown an overall improvement of the quality of life. Both asthma and COPD patients have spoken of a "feeling of breath relief" even after only one day of use, and also they mentioned the improvement of their functionality. All the patients mentioned the increase production of expectorated sputum after 2 – 3 days of use and, differentiating from placebo group.*

Key Words: *dry-salt-inhaler, asthma-treatment, copd-treatment, speleotherapy, haloteraphy, life-improvement, salt-therapy*

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INTRODUCTION

Speleotherapy and halotherapy are relatively old therapeutic methods sometimes recommended for chronic obstructive disorders. Treatment in natural salt cave (speleotherapy) has been known for a long time. The purpose of our study is to prove the efficacy of the Dry Salt Inhaler on adults diagnosed with asthma (both mild and severe) and COPD regarding the quality of life and the improvements of spirometry values.

OBJECTIVES:

Primary objective: our aim was to evaluate the effects of inhaled dry salt in stage 2 and 3 COPD patients and also patients with asthma, in terms of ventilatory parameters – based on spirometry and the quality of life – based on our own design questionnaire.

Secondary Objective: we also aimed to achieve long-term improvements of life quality and decreased incidence of respiratory infections – mainly on patients that have persistent symptoms of asthma and COPD.

MATERIAL AND METHODS:

The study was conducted on a patient pool of 38 individuals selected as following:

Inclusion criteria: a subject was considered eligible for inclusion if all of the following applied: diagnosed with stage 2 or 3 COPD, more than 1 year in treatment, diagnosed with asthma (mild, both persistent or intermittent, moderate or severe), more than 1 year in treatment, was able to understand and endorsed the written informed consent and presented no other serious respiratory pathology (such as tuberculosis, lung cancer, pulmonary fibrosis, etc).

Exclusion criteria: had a current cardio-vascular diagnosis such as (arterial hypertension, heart failure, arrhythmias), had a life threatening diagnosis or one that could interfere with study procedures, being pregnant or having the intention to remain pregnant, being under 18-years old (as there is no data to sustain safety in child administration), being sodium chloride intolerance, having a psychiatric / severe neurologic condition or abandoned the study.

The Study Design

Sample size: 38 patients concluded until abstract submission, 128 until study closing period. We designed this study to be a double-blind, randomized trial, single crossed. The initial pool of patients was divided in 2 arms of population:

The PII group was the group that initially took placebo for the first time and then continued to DSI inhaler for the next 2 periods

The IPI group was the group that took DSI inhaler device for the first time and at the second visit (V1) they were crossed with the ones in PII group.

The treatment period was 6 weeks of standard asthma / COPD therapy according to GOLD 2005 guidelines, and one 15-20 minutes inhaling session, preferably during the evening, using the DSI device. For evaluation of patients we used 2 methods: a quan-

titative evaluation based on spirometry and pulmonary function report printed after the spirometry and a qualitative evaluation based on a life quality-improvement questionnaire that we design for this – questionnaire meant to evaluate how patient felt while on treatment with DSI device in terms of ease of breath, relief of chronical symptoms, improvement of overall patient's functionality.

RESULTS

Our results have shown an overall improvement of the quality of life, expressed both orally by the patients and observed after the gathering of data from the forms.

Both asthma and COPD patients have spoken of a "feeling of breath relief" after only one day of use, and also they mentioned the improvement of their functionality.

All the patients mentioned the increase production of expectorated sputum after 2 – 3 days of use and, differentiating from placebo groups, the ones using active-substance DSI did felt better overall at the end of the in-between-visits period.

As shown in Figure 1, the FVC is improving with about 9% from the placebo use to active-substance use, proving the efficacy of the DSI device therapy and, correlating these results with the increased sputum expectoration, we can conclude that, in terms of air quantity, the DSI device increases the flow of air after use.

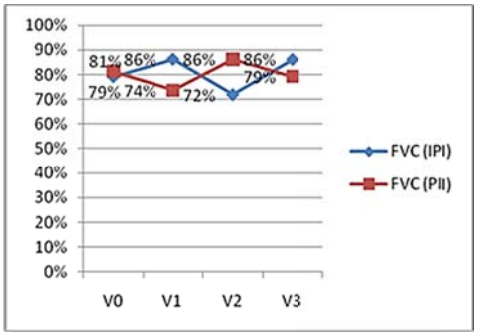

Fig.1 The Evolution of FVC parameter. IPI = population Inhaler - Placebo Inhaler. PII = Population Placebo - Inhaler - Inhaler

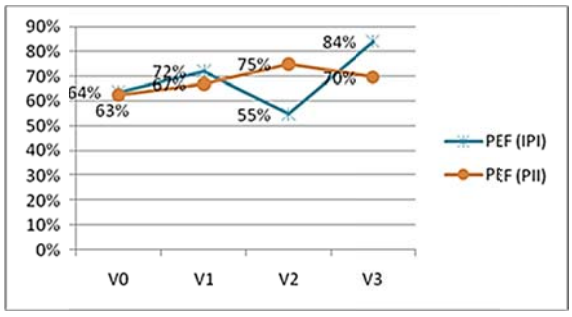

Fig.2 The Evolution of PEF parameter. IPI = population Inhaler - Placebo Inhaler. PII = Population Placebo - Inhaler - Inhaler

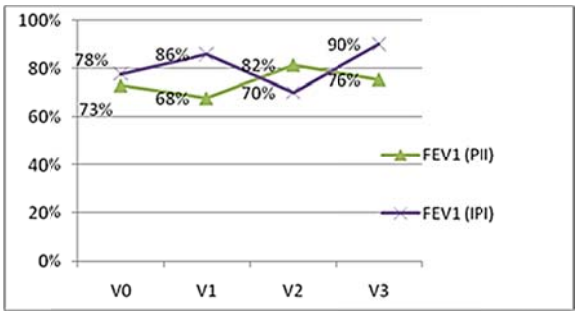

Fig.3 The Evolution of FEV1 parameter. IPI = population Inhaler - Placebo Inhaler. PII = Population Placebo - Inhaler - Inhaler

During the investigation of FEV1 parameter we have found that both populations (PII and IPI) improved their breathing parameter, as shown in Figure 3 - The Evolution of FEV1 parameter. IPI = population Inhaler - Placebo Inhaler. PII = Population Placebo - Inhaler - Inhaler, the best improvements being shown versus placebo periods both in IPI and PII populations.

PEF parameter also showed improvements (Figure 2 - The Evolution of PEF parameter. IPI = population Inhaler - Placebo Inhaler. PII = Population Placebo - Inhaler - Inhaler) mostly on the population that started with the active-substance DSI device, fact that lead us further to the conclusion that, being used constantly and continually – without interruptions, for a long period of time, the DSI device may consistently contribute to improvements in overall functionality of patients. Since PEF is a high indicator of functionality from the larger airways, once again we can conclude that using the DSI device, additionally to sputum expectoration, the bronchial lumen is more relieved.

Since the ventilatory parameters of a patient with asthma or COPD cannot be spectacularly boost even with standard brochodilatators in such a short time, the differences between the average values obtained in FVC, FEV1 and PEF between V0 and V4 are clear signs of improvement and the differrences between the two populations show that continuously usage of the DSI is better and indicated.

In terms of quality of life, our results showed definite improvements and the consented values come to strengthen the patients' stories about the sensation of relief and better breathing. The overall unanimous perception was that since they started to use the DSI device, the quality of breathing and their functionality improved as well as the relief of the resident symptoms. Analyzing this data we were surprised to notice that the two populations, both IPI and PII, had different initial scores – after the first use, since some of them used the Placebo-device and the others were using the active-substance DSI device.

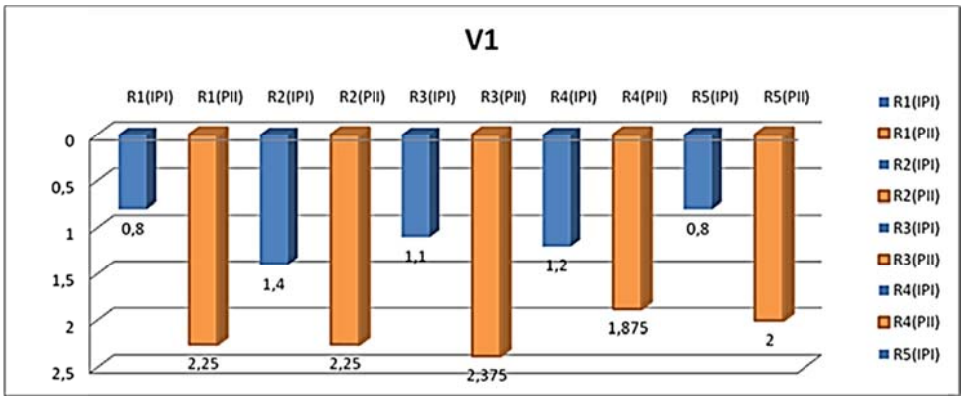

Fig.4 Scores of the 2 population during the First visit (V1). R1 - R5 are the answers to the 5 questions from the questionnaire at the first visit. For example, R1(IPI) means the answer to the first question given by the population that took Inhaler-Placebo – Inhaler, so it is their first answer (being at visit 1) and after the use of the active-substance inhaler (IPI).

Figure 4 - Scores of the 2 population during the First visit (V1). R1 - R5 are the answers to the 5 questions from the questionnaire at the first visit. For example, R1 (IPI) means the answer to the first question given by the popu-

lation that took Inhaler-Placebo – Inhaler, so it is their first answer (being at visit 1) and after the use of the active-substance inhaler (IPI). Shows the answers of the two populations at the first visit. The final average scores and the differences between them are shown in the following figures (lower values are better).

This figure shows the clear differences in average scores from the two populations, registered from the entire questions (R1 – R5). Furthermore, at V3, after all the patients took both placebo and active substance, the answers have scores close to "0" meaning definite improvement in both functionnality and quality of life.

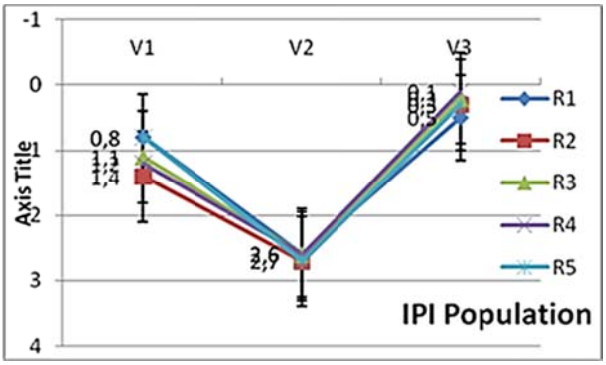

Fig.5 The scores given by both populations during the all 3 visits. V1, V2, V3 are the 3 visits, R1-R5 are the answers to the questions from 1 to 5 in questionnaires and each answer has a designated color – the same throughout the 3 visits. IPI means the population that initially took active substance inhaler and then placebo (V1-Inhaler – V2-Placebo – V3-Inhaler) and PII means the population that started with Placebo and then continued with the Inhaler (V1-Placebo – V2-Inhaler –V3- Inhaler).

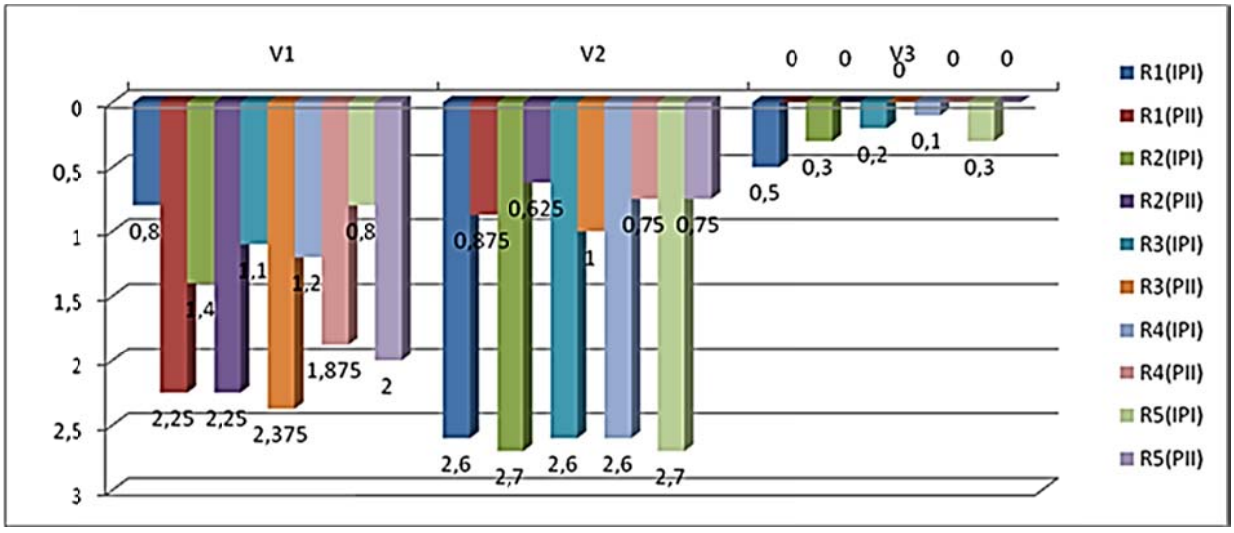

Fig.6 The evolution of scores within IPI population (Inhaler - Placebo - Inhaler). V1,V2,V3 – are the 3 visits and R1-R5 are the answers to the 5 questions from the questionnaire.

Looking separately at the two populations, we found that the IPI pool improved their scores with an average of 70% from V1 to V3 showing a decrease of their life quality by rating with higher grades (worse) the answers during the V2 – which, for them, it was the visit after placebo. Spectacular is the comeback of the scores towards below 1 during the V3 interview, showing

that the placebo interruption worsened the good evolution they had in terms of life quality.

The PII population, as shown, had a better evolution, indicating that the usage in a constant manner of the DSI device, without interruptions, may produce definite life-improvement on a long-term period. The PII group showed improvements from V1 to V2 on an average of 63% and total improvement from V1 to V3 – as no patient responded that their symptoms bothered them after using the DSI device for a 30 day period.

This result translates in the mandatory conclusion that the DSI device is an enhancer in terms of improving the quality of life along with the standard medicines one patient has to take.

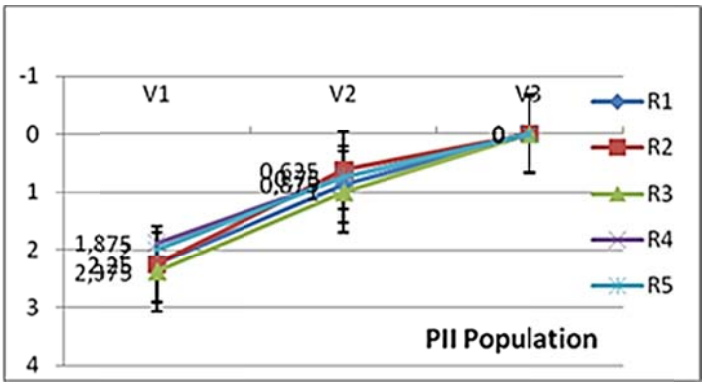

Fig.7 The Evolution of Scores within PII population (Placebo – Inhaler – Inhaler). V1,V2,V3 – are the 3 visits and R1-R5 are the answers to the 5 questions from the questionnaire.

CONCLUSIONS:

As we studied both the quantitative and the qualitative parameters on a significant pool of patients, we were able to draw conclusions regarding the use of the DSI device on patients with asthma/COPD. Although we found improvements of FVC, FEV1 and PEF parameters on spirometry, the average improvement of these parameters doesn't impress but it cannot be ignored. It is well known the fact that an asthmatic or COPD patient's spirometry values are in dependency with the atmospheric conditions, his life environment, exposure to pollution, etc – these factors being able to change the results of the evaluation. But correlating with the qualitative results, we found that the DSI inhaler has proved its efficacy versus placebo – improving the life quality and the breathing quality of all patients. Due to the fact that patients have been breathing better and they all were on regular asthma/COPD medicines, the added DSI device increased the sputum expectoration and additionally helped to the relief of respiratory air-ways. This fact has a major importance in both prevention and speeding up the healing of respiratory infectious diseases that, in some cases, may be life-threatening to a COPD patient.

Nevertheless, the DSI device usage on a regular basis and for a long period of time improves the patients' global functioning along with the quality of his life – making them able to do a better job in daily activities and at home, as shown in reading the results from the Life-Quality Improvement Questionnaire.

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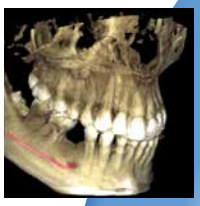

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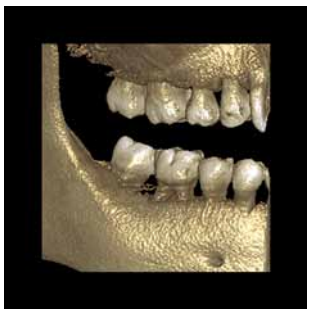

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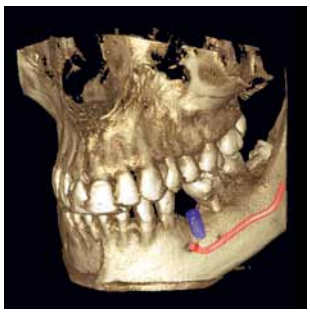

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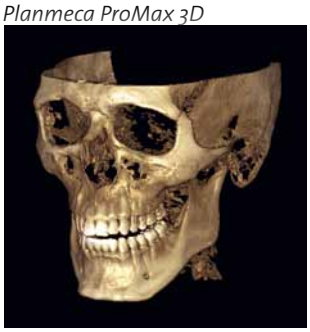

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