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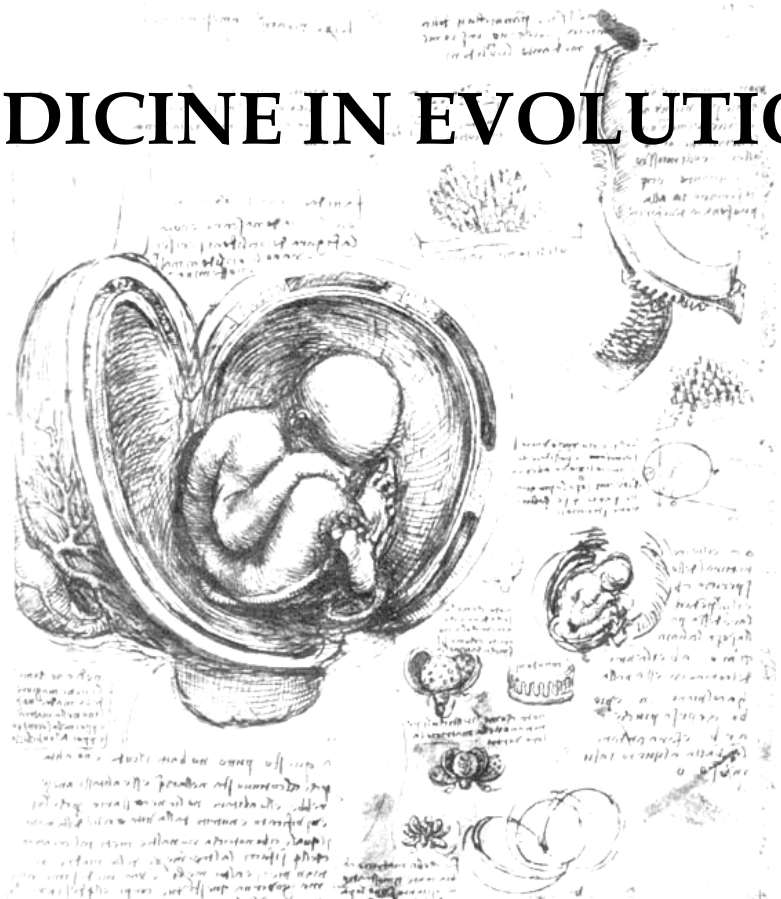

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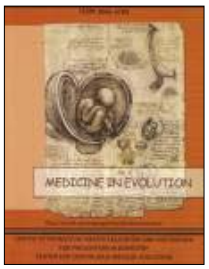
AMBULATORY BLOOD PRESSURE PROFILE, LEFT VENTRICULAR HYPERTROPHY AND MICROALBUMINURIA



ELENA ARDELEANU[1], VIOREL PÂRVULESCU[2], GRUICI ADRIAN[1], IOANA POPA, DANIELA GURGUS[1], DELIA GRIGORESCU, ELEONORA BURCĂ, ADRIANA RÂMNEANȚU, IOANA PURICEL

1. **University of Pharmacy and Medicine "Victor Babeş" from Timişoara**
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ABSTRACT

In essential hypertension microalbuminuria and left ventricular hypertrophy reflect target organ damage. Both are related to the level of blood pressure and they are associated with an increase in morbidity and mortality. We analysed the database for patients with essential hypertension of five family medicine offices. Our objective was to determine the level of association between microalbuminuria and left ventricular hypertrophy, which might explain the observed increase in morbidity and mortality in these patients.

***Materials and methods**: After the exclusion of patients with secondary hypertension, renal disease and diabetes mellitus, patients with complete data for microalbuminuria measurement, left ventricular mass (LVM) and 24 h blood pressure monitoring were selected. Data were complete for 258 patients 126 (49.9%) female and 132 male (51.1%), with age between 35 and 59 years (middle age 47±12 years). Of these, a number of 98 (38%) had a positive test for microalbuminuria, measured semi quantitatively by urine test strips.*

***Results:** Microalbuminuria was positively related to 24 h systolic blood pres¬sure and weight and was negatively related to age. Left ventricular mass was higher in patients with microalbuminuria (at men 265 ± 69 g; at women 207 ± 61 g), than in those without (men 250±64 g, $p < 0.05$; women 185±50 g, $p < 0.001$). After correction for the effects of gender, body mass index and 24 h systolic blood pressure, the presence of microalbuminuria was associated with an increase in LVM of 9.8 g ($P < 0.05$, 95%).*

***Conclusion**: microalbuminuria is associated with an increase in LVM in patients with essential hypertension, independent of other known determinants.*

***Key words**: essential hypertension, blood pressure monitoring, left ventricular hypertrophy, microalbuminuria.*

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INTRODUCTION

The European Society of Cardiology guidelines for hypertension shows that it becomes more and more important to determine the target organ damage secondary to hypertension [1].

Studies have demonstrated that the presence of microalbuminuria in patients with essential hypertension is related to cardiovascular morbidity and mortality, independent of other well-known risk factors.

Albumin excretion rate is related to the level of blood pressure in essential hypertension. The advent of rapid testing by test strips has facilitated the screening for microalbuminuria of the patients with essential hypertension.

Left ventricular hypertrophy has been established as a major independent marker of future cardiovascular morbidity and mortality in essential hypertension and depends mainly on gender, body mass and 24 h blood pressure load [2, 3].

The Objective of the Study

We analysed our database of patients with essential hypertension from five family medicine offices in order to clarify whether there is an association between microalbuminuria and left ventricular mass, which may explain the observed increased morbidity and mortality in these patients.

MATERIAL AND METHODS:

The general practitioners took a standardized history, performed a physical examination and measured height, weight, casual blood pressure and heart rate of the study patients.

Body mass index (BMI) was calculated as BMI = weight/height2 and body surface area (BSA) as BSA (m2) = 0.007184 X weight (kg) X height (cm).

A spot urine sample was tested for microalbuminuria at the general practitioner office with Akray test strips, which can provide a reading of "negative", a≥ 20 mg/L, a ≥ 50 mg/L and a ≥ 100 mg/L urinary albumin.

For the purposes of the present study, microalbuminuria was defined as any reading except "negative", than the patients with hypertension were referred by their general practitioners to Diagnosis Centres and Cardiology Hospitals. Blood was drawn for sodium, potassium, creatinine and glucose at the Diagnosis Centres and hospitals.

Patients underwent echocardiography with a Vivid 6 echo-Doppler system. Subsequent measurements were made on screen with electronic callipers by operators blind to the other clinical or biochemical measurements. Interventricular septum (IVS) and left ventricular posterior wall thickness (LVPW) were measured from leading edge to leading edge at end diastole. Left ventricular diastolic diameter (LVDD) was measured at end diastole. Left ventricular mass (LVM) was determined as LVM = 0.6 + 0.832 X ((LVID + PW + IVS) 3 -LVID3) g. Ambulatory blood pressure was recorded using a BTL monitor. Monitors were set to measure every 30 min on daytime from 6 to 22 h and every 60 min during night time, from 22 to 6 h. Average 24 h systolic and diastolic blood pressure, daytime and night times average systolic and diastolic blood pressure were calculated. Patients with a history of renal disease, with diabetes mellitus and with clinical suspicion of secondary hypertension, as well as patients with a random plasma glucose of > 120 mg/dl, a plasma creatinine>1.2 mg/dl for men or>1.1 mg/dl for women, or

significant haematuria or leucocyturia were excluded. Only patients in whom all measurements were complete for height, weight, plasma creatinine, plasma glucose, 24 h blood pressure monitoring and LVM, were included in the study.

Statistical analysis – Data are expressed as mean ± SD. The data analyses included Student's t -test, x2 test, logistic and linear regression analysis. Statistical significance was taken at a level of $p<0.05$.

RESULTS

A number of 258 patients' presented complete data. Of these, 126 hypertensives (49.9%) were female and 132 patients (51.1%) male. The middle age of the study population was 47±12 years, with limits between 35 and 59 years. The largest group was between 51-60 years and consisted of 132 (51.1%) hypertensives. The age group between 41-50 years had a number of 112 patients (43.4%); only 14 patients were less than 40 years old.

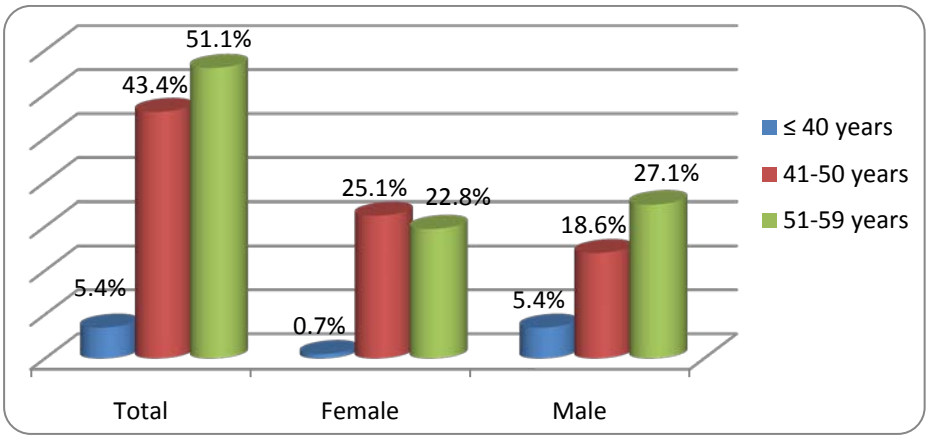

Fig.1. Repartition of the study population on age groups and gender.

The history in time of the patients showed that the existence of the hypertension was less than 5 years at 34 (13.3%) patients.

Between 5-10 years of evolution were 146 patients (56.6%) and 78 (30.3%) had a hypertension that was older than 10 years.

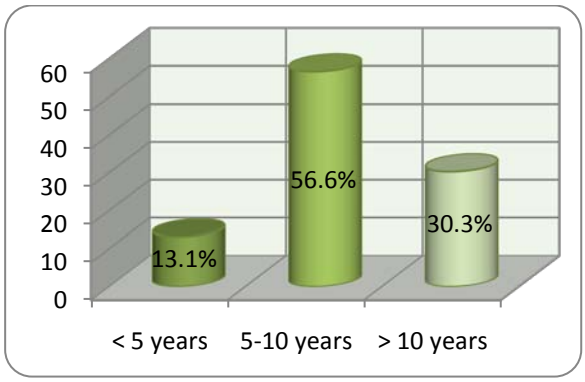

Fig.2. Evolution in time of the hypertension.

The severity degree of hypertension was evaluated after the recommendations of the Hypertension Guidelines of the European Society of Cardiology published in 2007. Depending on the hypertension profile, the patients were divided in two groups: the dipper group 46, 1%, in which the blood pressure values during night were lower with more than 10% than during day and the nondipper group 53, 9%, whose hypertension did not felt enough during night time.

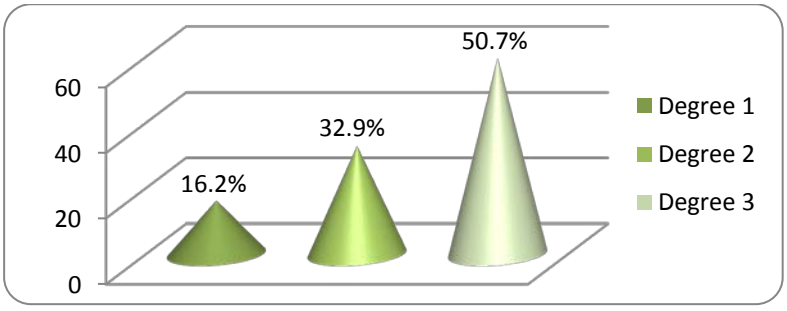

Fig.3. Severity degree of hypertension.

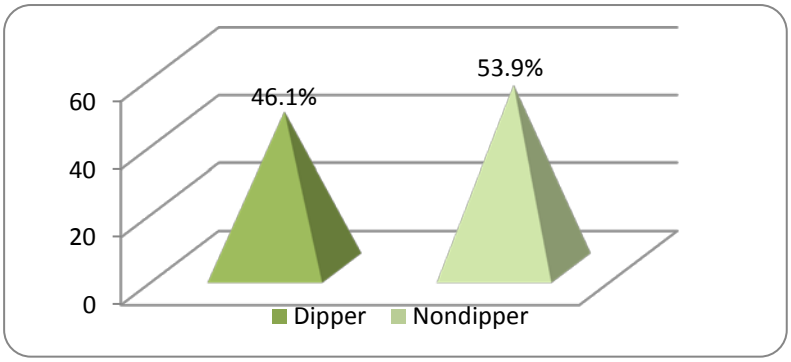

Fig.4. Repartition of the patients in the dipper and nondipper group

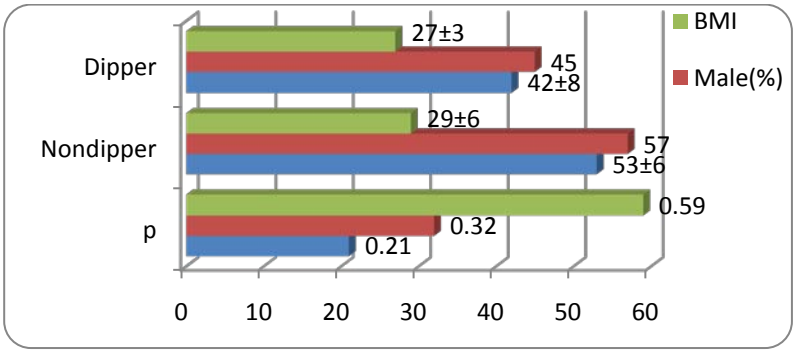

Fig.5. Characteristics concerning age, gender and BMI in the dipper and nondipper patients.

Hypertension risk classes of the study population were: low risk at 12 patients (4.6%) and middle risk at 48 (18.6%). The most important part, 198 (76.7%) patients presented a high cardiovascular risk.

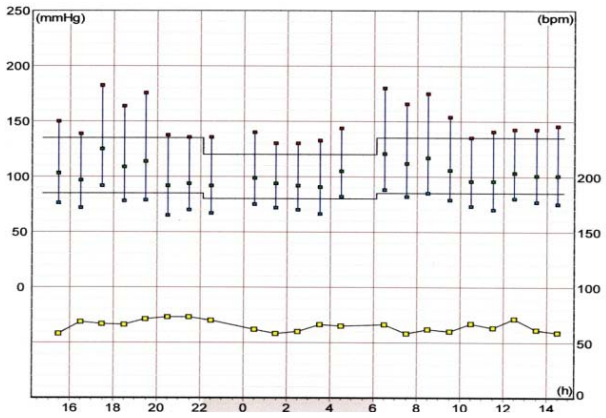

Fig.6. The blood pressure 24 hour monitoring shows a nondeeper profile.

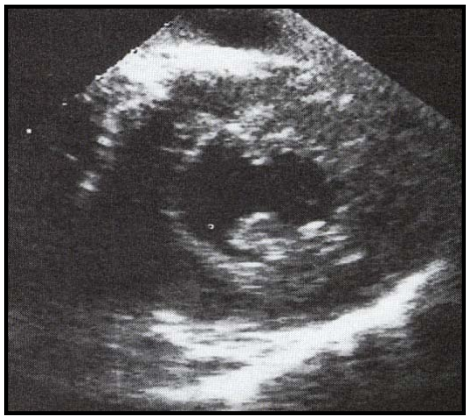

Fig.7. Echocardiography of a patient with left ventricular hypertrophy.

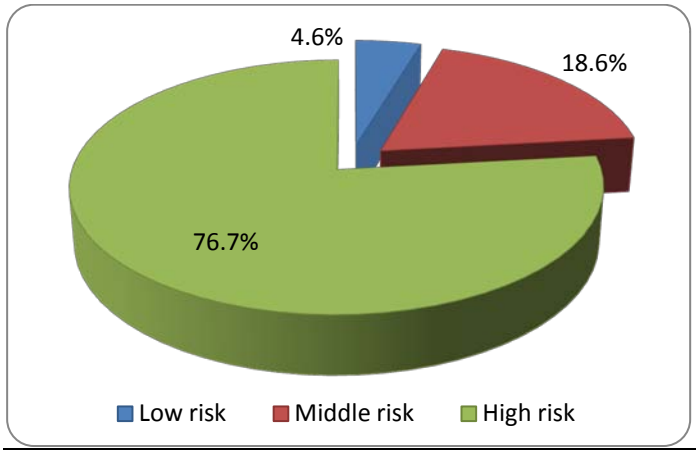

Fig.8. Cardiovascular risk classes of the study population.

The echocardiography examination of the study population referred to left ventricular systolic diameter (LVSD), left ventricular diastolic diameter (LVDD), interventricular septum (IVS), left ventricular posterior wall (LVPW), left ventricular mass (LVM), body mass index (BMI), left atrium (LA), relative thickness of the posterior wall (RTPW) and ejection fraction (EF).

Table 1. Echocardiography data of the dipper and nondipper study population

Measurement	*Dipper (n=144)*	*Non-dipper (n=114)*	*p*
LVDD (mm)	47 ± 4	50 ± 6	0.12
LVSD (mm)	30 ± 5	32 ± 5	0.15
IVS (mm)	11 ± 1	11 ± 6	0.53
LVPW (mm)	10 ± 1	11 ± 3	0.15
EF (%)	64 ± 7	62 ± 6	0.46
LA (mm)	32 ± 3	40 ± 7	<0.02
LVMI (g/m)	125 ± 28	157 ± 56	<0.04
RTPW	0.45 ± 0.01	0.45 ± 0.07	0.89

Microalbuminuria was present in 98 (38%) patients. Differences between patients with or without microalbuminuria are shown in Table 1. A stepwise logistic regression with the presence or absence of microalbuminuria as the dependent variable and as independent variables age, gender, height, weight, BMI, BSA, creatinine, 24 h systolic and diastolic blood pressure, yielded significant positive effects of 24 h systolic blood pressure (P < 0.0001) and weight (P< 0.001) and a negative effect of age (p<0.001). No other variable had a significant predictive effect on the presence or absence of microalbuminuria.

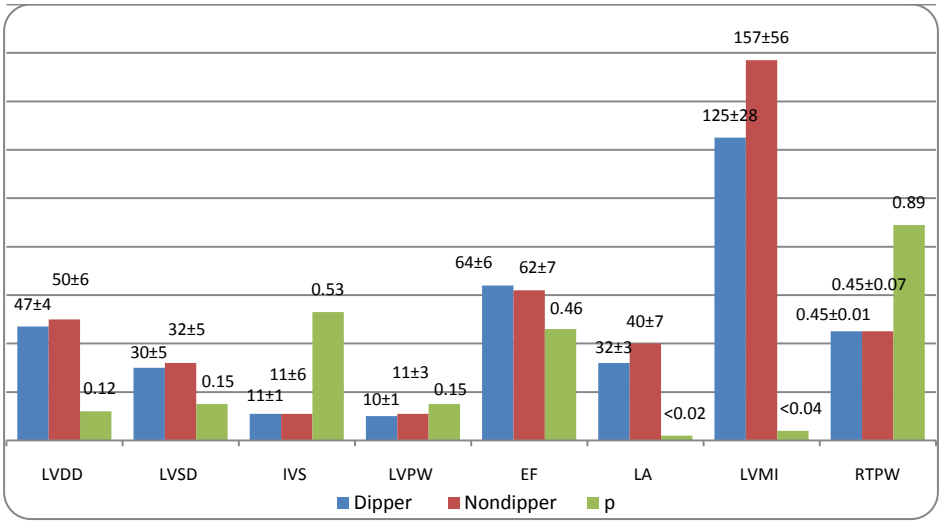

Fig.9. Echocardiography data of the study group.

Table 2. Univariate differences between patients with and without microalbuminuria

	No microalbuminuria ***n* = 160 (62%)**	**Microalbuminuria** ***n* = 98 (38%)**	*p*
Gender	42% male	58% male	< 0.01
Age (years)	52±7	49±10	< 0.001
Height (cm)	166±9	169±10	< 0.01
Weight (kg)	78±14	84±16	< 0.001
BMI (kg/m²)	27.5±4.5	28.9±5.1	< 0.01
BSA (m²)	1.9±0.3	2.0±0.4	< 0.001
Plasma creatinine mg/dl	0.8 ±0.03	0.8 ±0.04	NS (all)
Average 24 h BP(mmHg)	133/82 ±13/8	139/86 ±14/10	< 0.001
Left ventricular mass (g)	251 ±63 (men)	266 ±70 (men)	< 0.05 (men)
	185 ±50 (women)	207±61 (women)	< 0.001(women)

Data are expressed as mean ± SD, BMI= body mass index; BSA= body surface area.

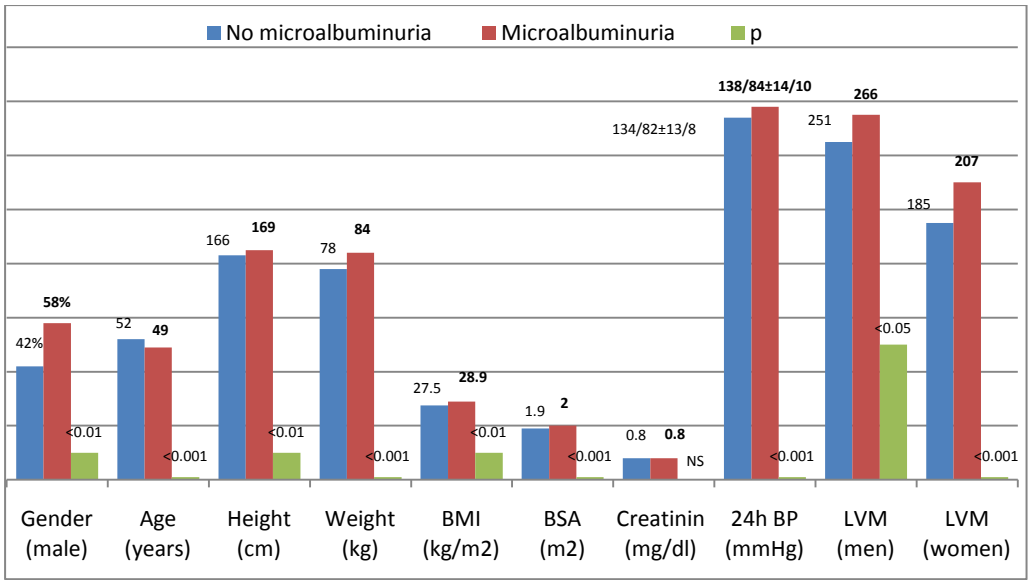

Fig.10. Differences between the patient groups with and without microalbuminuria.

Left ventricular mass was higher in patients with microalbuminuria than in those without. Since gender, BMI and average systolic blood pressure over 24h are all independent determinants of LVM, we performed a multiple regression analysis with these variables, to correct LVM for their effects. Applying this correction, the presence of microalbuminuria was associated with an increase in LVM of 9.9 g ($P < 0.05$).

DISCUSSION

Our study evaluates a population of patients referred to investigation to diagnostic centres and cardiology clinics by their family practitioners. We found a high prevalence of microalbuminuria (38%), which increases with the level of 24 h average systolic blood pressure and bodyweight and decreases with age. Our data confirms previous studies that have demonstrated a relationship between albumin excretion rate and the level of systolic blood pressure [5, 6]. As showed, most of the patients had severe third degree hypertension, with high cardiovascular risk. Our finding of a positive relation to bodyweight is corroborated by some survey studies. Most previous studies have not been able to demonstrate a significant relationship between microalbuminuria and age.

Therefore, the result of a negative relationship between age and the prevalence of microalbuminuria requires further confirmation. It has to be noted that albumin excretion was measured only semi quantitatively in this study population. Even though the test has a high sensitivity, the lower specificity might explain the unusually high prevalence of microalbuminuria. The presence of a considerable number of false positive results would be expected to have diluted our results, so that differrences between groups with and without albuminuria might in fact be larger than reported here [7]. We found that LVM is increased in patients with microalbuminuria, independent of the level of 24 h systolic blood pressure. This is consistent with previous studies. The observed effect is considerable, equivalent in its potential to raise LVM to

the effect of an increase of about 11 mmHg in 24 h systolic blood pressure in our population [8]. Therefore, this effect might quite well account for the observed increase in cardiovascular morbidity and mortality in patients with microalbuminuria.

CONCLUSIONS

In patients with essential hypertension microalbuminuria is associated with an increase in left ventricular mass, independent of other known determinants.

Further studies are needed to elucidate the underlying pathophysiological links between microalbuminuria and left ventricular structure.

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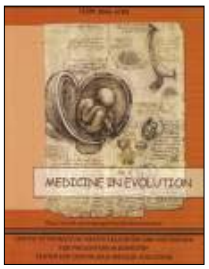
THE BENEFITS OF COLLAGEN GELS AND MATRICES WITH LIDOCAINE IN DENTISTRY



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2. **Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy from Bucharest**
3. **Collagen Department, Leather and Footwear Research Institute, Bucharest**

ABSTRACT

***Introduction**: Collagen-based biomaterials are increasingly appreciated by specialists in dentistry. Although they enjoy remarkable attention, they are still under research and/or clinical trial. The purpose of the drug delivery systems (DDS) is the controlled release of drugs on the affected tissue. Several interdisciplinary fields as polymer science, pharmacy, chemistry, molecular biology and dentistry are involved in the development of such complex biomaterials. The aim of this study is obtaining of DDS which has collagen (natural biomaterial with haemostatic properties) in form of gel or spongious (matrix) and as support and lidocaine (local anesthetics used to stop sending pain signals) as drug.*

***Material and method**: Both gels and matrices were obtained from type I collagen with concentrations of 1.0, 1.2 and 1.4% and 0.1% lidocaine. These were characterized by FT-IR and water absorption. Results In vitro lidocaine release from collagen supports were performed by a sandwich device adapted to USP apparatus simulating physiological conditions. Clinical trial reveals in vivo a shorter coagulation, bleeding, healing time, and a decrease of post-extractional pain.*

***Conclusions**: The drug release was performed for collagen matrices in order to evaluate the amount of lidocaine released post-extractional pain.*

***Key words**: collagen, gels, matrices, lidocaine.*

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INTRODUCTION

Collagen-based biomaterials are increasingly appreciated by specialists in dentistry. Although they enjoy remarkable attention, they are still under research and/or clinical trial. The purpose of the drug delivery systems (DDS) is the controlled release of drugs on the affected tissue. Several interdisciplinary fields as polymer science, pharmacy, chemistry, molecular biology and dentistry are involved in the development of such complex biomaterials. Collagen is a suitable support for drug delivery, offering the advantage of a natural biomaterial with haemostatic and wound healing properties [1, 2]. Lidocaine belongs to the local anesthetics class and it is used to relieve the pain by stopping nerves from sending pain signals [3].

Aim and Objectives

The aim of this study is to develop wound dressings in form of collagen spongious matrices with lidocaine for usage in dentistry.

MATERIAL AND METHODS:

Type I fibrillar collagen gel having a concentration of 1.71% (w/w) was extracted from calf hide by the currently used technology in the Collagen Department [4]. Lidocaine was purchased from Sigma-Aldrich and glutaraldehyde (GA) was obtained from Merck (Germany). Sodium hydroxide and phosphate buffer solution (PBS), pH, 7.4 were of analytical grade. Collagen hydrogels with concentrations of 1.0, 1.2 and 1.4% in collagen and 0.1% lidocaine were obtained in aquous solutions, at 7.4 pH. These hydrogels were freeze-dried using the Christ Model Delta 2–24 LSC freeze-dryer (Germany) and proper collagen matrices (spongious forms) were obtained. FT-IR spectrum measurements were recorded by FT-IR spectrophotometer of Perkin Elmer type Spectrum 100. The water absorption was calculated using the method previous described [4]. *In vitro* release of lidocaine was determined in triplicate at 37±0.5°C using a modified USP paddle method ("sandwich" device). The amount of lidocaine released was spectrophoto-metrically determined at 263 nm. Clinical trials were carried out on 40 patients with rest roots that developed cronic apical parodontitis, which were extracted. In 10 patients the sockets were left to heal naturally. The witness group and the rest 30 patients were divided in 3 groups of 10 individuals, corresponding to the collagen concentrations (1.0, 1.2 and 1.4% in collagen/ group A, B, C).

RESULTS

The infrared spectrum of collagen exhibits several features characteristic for the molecular organization of its molecules: amino acids linked together by peptide bonds give rise to infrared active vibration modes amide A and B (about 3330 and 3080 cm-1, respectively) and amide I, II, and III (about 1650, 1550 and 1250 cm-1, respectively) [5]. Figure 1 shows the FT-IR spectrum for matrix with 1% collagen and 0.1% lidocaine. In the spectrum of the collagen matrix, shown in Figure 1, the five characteristic absorption bands can be observed at 3314, 2958, 1634, 1548 and 1238 cm-1. The characteristic collagen

bands indicate that triple helix structure was preserved in all the samples. Water uptake studies showed that swelling was influenced by the collagen concentrations (Figure 2).

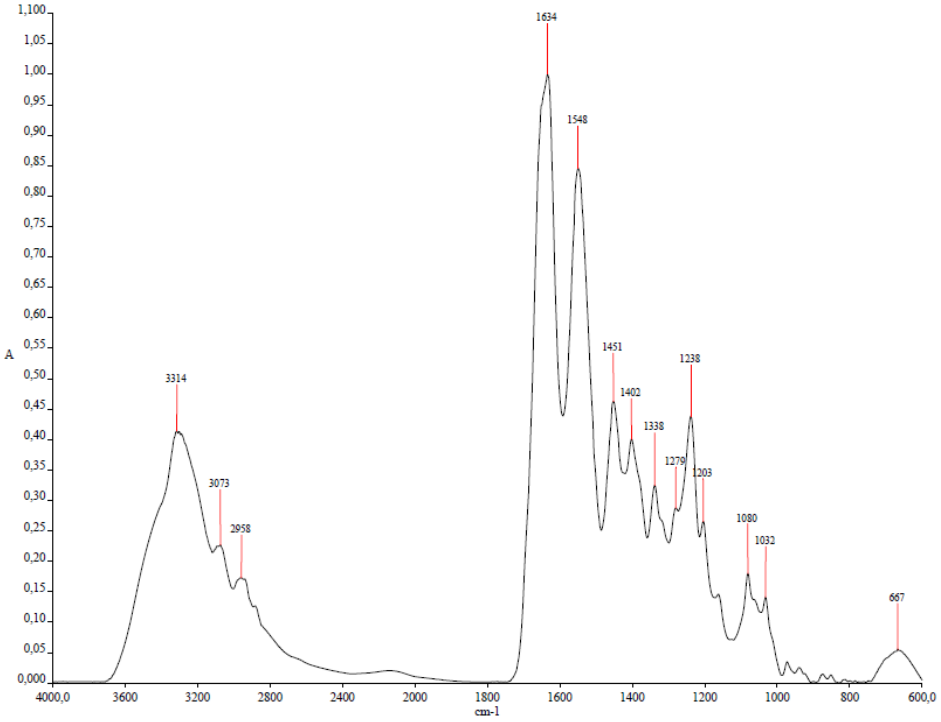

Fig.1. FT-IR spectrum for collagen matrix with 1% collagen and 0.1% lidocaine.

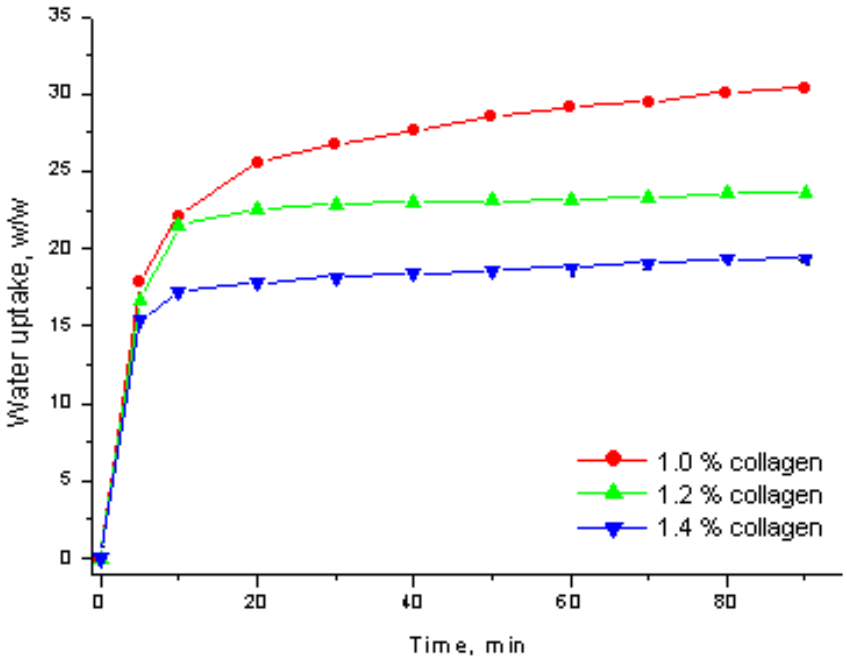

Fig.2. Water uptake for collagen matrices.

As Figure 2 shows, the higher collagen concentration, slower the swelling ability. The drug release was performed for collagen matrices in order to evaluate the amount of lidocaine released. The release profiles of lidocaine from the collagen matrices are presented in Figure 3.

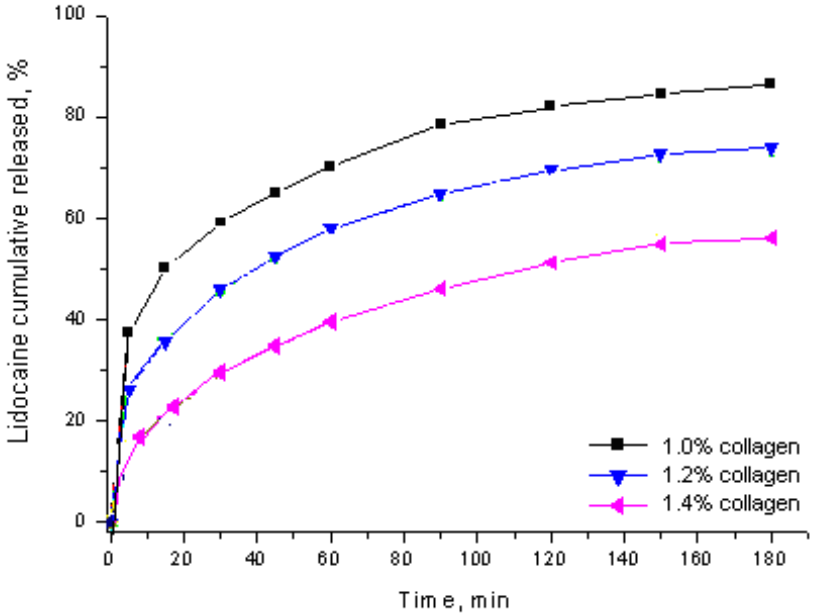

Fig.3. In vitro lidocaine release from collagen matrices.

Figure 3 show that higher collagen concentrations produce the decreasing of the amount of lidocaine released. The results for the lidocaine release are in close agreement with the spectral characteristics and water uptake data. The best results have been obtained in the group in which the matrix 1.4% in collagen concentration was applied (group C). In this group, the healing of the socket at 7 days from extraction is much better compared to the witness group and better in comparison to the other two groups of patients: A and B (fig.4-9).

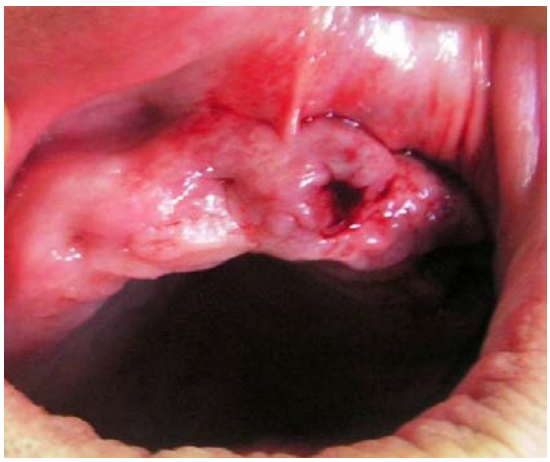

Fig.4. Witness socket.

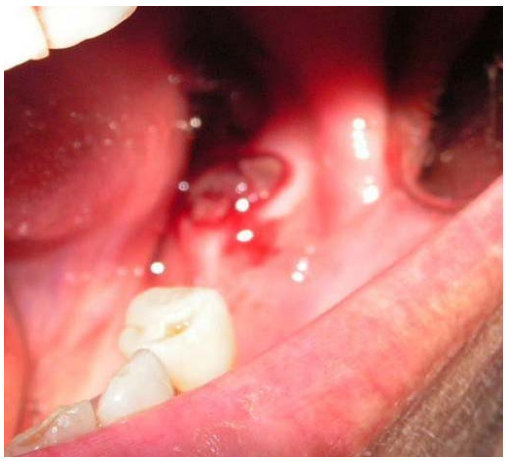

Fig.5. Healing with 1.0 collagen matrices.

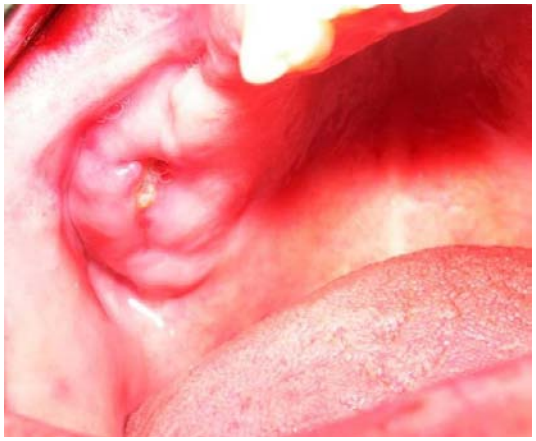

Fig.6. Healing with 1.0, 1.2, 1.4 collagen matrices.

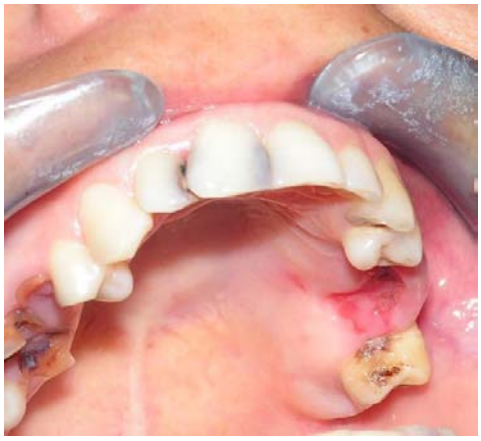

Fig.7. Healing with 1.2 collagen matrices.

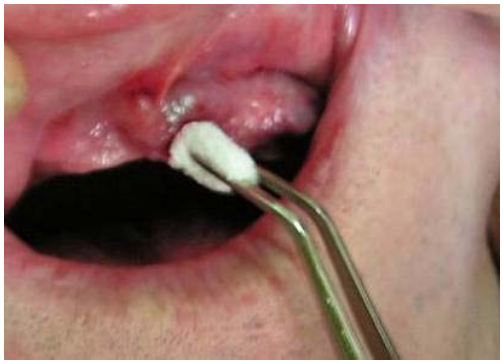

Fig.8. Placing the collagen matrices

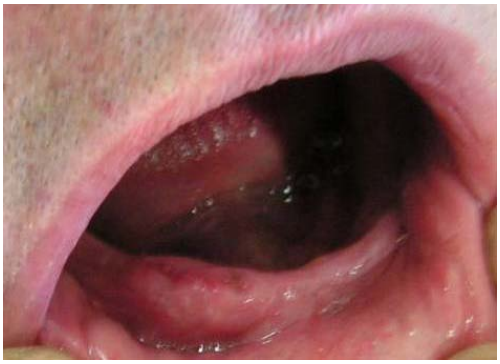

Fig.9. Healing with 1.4 collagen matrices

Compared to the witness group, the other three groups showed improved clinical parameters: coagulation, bleeding, healing time immediate post-extraction, and at 7 days post-extraction.

Aknowledgements

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CONCLUSIONS

Collagen matrices containing lidocaine were obtained from proper gels at pH 7.4 by the freeze-drying process. The FT-IR spectrum shows that the triple helical structure is preserved in all the studied matrices. The collagen matrices release lidocaine more slowly from samples with higher concentration in collagen. Clinical trial reveals in vivo the quality of healing at 7 days post-extraction, decrease of post-extraction pain and shorter bleeding, coagulation and healing time in the three groups in which the collagen matrix was applied compared to the witness group.

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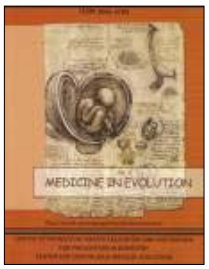
EFFECT OF VARIOUS ADHESIVE AGENTS ON SHEAR BOND STRENGTH OF AMALGAM AND COMPOSITE MATERIAL



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ABSTRACT

The objectives of the present in vitro study consist of evaluating the effect of four adhesive systems on the shear bond strength of amalgam and a composite material.

***Material and Methods**: In order to determine the shear bond strength of amalgam and a composite material, four adhesive systems were selected: ExciTE – Vivadent, Xeno III – Dentsply De Trey, Silan (Monobond S- Vivadent) and Prime & Bond NT – Dentsply De Trey and Clearfil Repair – Kuraray. Each group, in which an adhesive system was used, included ten samples. These were prepared using precapsulated amalgam condensed in acrylic matrixes. After amalgam setting, the surface was roughened with a diamond instrument and, after applying specific adhesive agents, the composite resin was fixed with an adhesive agent to the surface of previously conditioned amalgam samples. After 30 days storage in distiled water, each sample was subjected to a shearing test.*

***Results:** Statistical differences were found between groups (One-way ANOVA test). The highest value of shear bond strength (7, 45±0, 58 MPa) was found in group 3.*

***Conclusions:** The use of silane solutions associated to Prime&Bond NT leads to the highest value of shear bond strength as compared to other conditioning systems.*

***Key words**: composite repair, amalgam repair, amalgam shear bond strength.*

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INTRODUCTION

Marginal defects of amalgam fillings may lead to microleakage phenomena, secondary caries, pulp hypersensitivity, various stages of dental pulp damage and, eventually, to dental loss. Complete removal of the filling requires a longer time and may be more difficult. For these reasons reoptimizing these fillings by means of composite materials may represents an alternative for asymptomatic teeth in which radiologic examination does not reveal secondary caries. The amalgam-composite interface may be evaluated by monitoring the microleakage level of a staining agent by scanning electron microscopy, optic coherent tomogramphy or by the assessment of traction or shear bond strength of the two materials [5].

Aim and Objectives

The objective of the present study is to evaluate the effect of four types of adhesive agents on the shear bond strength occuring at the amalgam-composite resin interface.

MATERIAL AND METHODS:

The present study presents the effect of roughening the amalgam surface associated to the use of four types of adhesive agents on the shear bond strength occuring at the amalgam-composite interface. In order to assess the shear bond strength occuring at the amalgam-composite interface, the following experimental protocol was applied: Fifty cilinders were made of autopolymerizing acrylic resin (2 cm diameter, 1.5 cm height). On one of the cilinder bases a retentive cavity was practiced with a 6 mm diameter and 2 mm depth [1]. In these cavities, silver amalgam with spherical particles (MegalloyEZ - Dentsply De Trey precapsulated system, No. 2 capsules, normal setting) was manually condensed using a round-faced condenser, slightly overfilled, activated and triturated in an amalgamator (Duomat 3 - Degussa) for 10 seconds at 3800 rpm. The acrylic cilinders together with the amalgam were subjected to artificial aging by imersion in an environment with 100% relative humidity for 30 days at 37°C, followed by conditioning of the amalgam surface [4]. This was achieved by a medium granulation JOTA (ISO 534 107-181) diamond instrument, followed by 60 seconds 37% phosphoric acid treatment of each sample and subsequent washing and drying. Then, the 50 cilinders were randomly divided in 5 groups of 10. Fifty transparent polyethylene cilinders were made with an interior diameter of 4 mm and a heigth of 6 mm, meant to act as a matrix for composite resin application. CeramX duo (Dentsply De Trey) was chosen and its polymerization was accomplished by using the Elipar™ FreeLight (3M ESPE) photopolymerization lamp. In order to assess the shear bond strength at amalgam-composite interface, four types of adhesive agents were used, one for each group. The samples in group 5 were not treated with any adhesive agent and were used as control group. The following adhesive agents were used and applied according to instructions provided by manufacturers:

Grup 1 ExciTE – Vivadent

Grup 2 Xeno III – Dentsply DE TREY

Grup 3 Silan (Monobond S- Vivadent) and Prime & Bond NT – Dentsply De Trey

Grup 4 Clearfil Repair – Kuraray.

After applying the adhesive agents on the amalgam surface of each sample and after photopolymerization, composite resin cilinders were made using the previously manufactured transparent polyethylene cilindric matrixes which were kept perpendicular on the amalgam surfaces on which adhesive agents were applied. For each sample, the composite material was inserted imediately after photopolymerization of the adhesive agent. Composite polymerization was performed in three 2 mm layers for 40 seconds laterally and 40 seconds from the upper part. After finalizing the photopolymerization by using the Elipar™ FreeLight (3M ESPE) lamp, the polyetilene cilinders were sectioned and removed. All 50 samples were stored for 30 days in an environment with 100% relative humidity at 37°C [4]. After that, they were subjected to shearing at a speed of 1 mm/min. The device used for this purpose was Multitest 5i (Mecmesin).

RESULTS

The shear bond strength values (Mpa) were calculated using the formula R = F/S where F is the force recorded during sample fracture and S is the adhesive surface ($S = (\pi \times r^2) = (3, 14 \times 4) / 1.000.000\ m^2 = 0, 00001256\ m^2$, r = 2 mm).

Table 1. Shear bond strength values for each sample (MPa)

Group Sample	**Group 1** Excite	**Group 2** Xeno III	**Grup 3** Monobond S and Prime&Bond NT	**Group 4** Clearfil Repair	**Group 5** Control
1	2.81	5.66	7.26	5.19	1.44
2	2.73	4.36	7.69	4.57	1.53
3	3.09	5.62	6.85	4.8	1.62
4	3.82	5.6	8.53	6.27	1.87
5	2.9	6.05	7.02	6.4	1.82
6	2.41	5.11	7.53	5.58	1.29
7	2.59	5.78	7.1	5.09	1.36
8	3.28	5.51	7.68	5.55	1.49
9	2.87	5.39	6.69	5.91	1.34
10	3.16	4.86	8.14	5	1.69

Table 2. Average shear bond strength values (Mpa) and standard deviation

GROUP	N	Average	Standard deviation
Excite	10	2.97	0.40
Xeno III	10	5.40	0.49
Monobond S and Prime&Bond NT	10	7.45	0.58
Clearfil Repair	10	5.44	0.62
Control	10	1.55	0.20

Table 3. Results of the one-way ANOVA test

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	214.403	4	53.601	231.280	0.000s
Within Groups	10.429	45	0.232		

The One-way ANOVA test showed statistically significant differrences between the 5 groups, with a signifycance threshold of α=0.001 (table 3).

In order to underline the statistical significance between 2 groups, the Multiple Comparisons – Post Hoc „Scheffe" test was applied (table 4).

Table 4. Results of the Multiple Comparisons – Post Hoc „Scheffe" test

Comparison	Significance	Significance level (α)
Excite -Xeno III	,000s	0.001
Excite - Monobond S and Prime&Bond NT	,000s	0.001
Excite- Clearfil Repair	,000s	0.001
Excite – Control	,000s	0.001
Xeno III - Monobond S and Prime&Bond NT	,000s	0.001
Xeno III - Clearfil Repair	,947 ns	0.05
Xeno III – Control	,000s	0.001
Silan PB Monobond S and Prime&Bond NT - Clearfil Repair	,000s	0.001
Monobond S şi Prime&Bond NT – Control	,000s	0.001
Clearfil Repair - Control	,000s	0.001

s – Statistically significant, ns – statistically nonsignificant

DISCUSSIONS

The use of the Monobond S and Prime&Bond NT determined the highest average shear bond strength (7, 45±0, 58 MPa), significantly higher than in the other groups, probably due to silane bonding to metal oxides formed on the amalgam surface. The only statistically nonsignificant difference was recorded between groups 2 and 4 (Xeno III – Clearfil Repair).The control group, where no adhesive agent was applied, presented the lowest shear bond strength values. Other authors have also investigated composite resins as possible repair options for dental amalgam. Lacy AM., Rupprecht R., Watanabe L. [2] attempted to repair old with new amalgam using various adhesive agents, their results proving that shear bond strength is not improved following the use of adhesive agents as compared to classical repairs where these are not involved. In studies performed by F - Shirani, MR Malekipour, P Mirzakouchaki, P Zia [5], Single bond, SE bond, Prompt-L-Pop adhesive agents were used, the results showing that, where the microleakage

degree between old and new amalgam is concerned, SE Bond was more effective than Prompt-L-Pop, with no statistically significant difference between SE Bond and Single Bond adhesive agents.

The results of M. Özcan, P. K. Vallittu, M.C. Huysmans, W. Kalk and T. Vahlberg [3] showed that the methods for roughening amalgam surfaces (sanding with 50 µm Al2O3 or with 30 µm SiOx particles) are not significantly correlated to shear bond strength. Regarding the used adhesive agents, high shear bond strength values were recorded when the roughened amalgam surface was conditioned by silica and silane treatment followed by fiber thin layer and opaquer application (23.6±6.9MPa).

In this study, conditioning by diamond instrument roughening was chosen as being the easyest applicable in clinical settings.

CONCLUSIONS

Within the limitations of this study, the following conclusions may be formulated:

The use of Monobond S solution associated to Prime&Bond NT leads to a significantly higher shear bond strength as compared to the other adhesive systems.

In circumstances when amalgam repair with composite materials is imperative, the use of an adhesive is mandatory.

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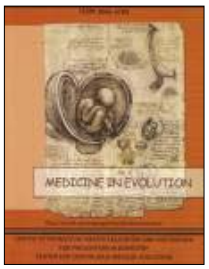
ANTITHROMBOTIC PROPHYLAXIS FOR WOMEN WITH THROMBOPHILIA AND PREGNANCY COMPLICATIONS



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ABSTRACT

Pregnancy is a hypercoagulable state with an increased thrombotic risk throughout gestation and the postpartum period. Women with thrombophilia may have an increased risk of placental vascular complications, including pregnancy loss, preeclampsia, intrauterine growth restriction, and placental abruption.This thrombotic risk is an important cause of maternal morbidity and mortality.

Preliminary data suggest that maternal antithrombotic prophylaxis may result in improved gestational outcome.

Although the most compelling data derive from women with antiphospholipid antibodies, the use of anticoagulation for prevention of these complications in women with heritable thrombophilia is frequent.

***Key words**: thrombophilia and pregnancy, antithrombotic prophylaxis*

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INTRODUCTION

Thrombophilic risk factors are common and can be found in 15% to 25% of white populations. Many studies suggest that there is a link between thrombophilia and adverse pregnancy outcomes such as fetal loss and venous thrombophilia. Since pregnancy is an acquired hyper-coagulable state, women harboring thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation or at the postpartum period.[1] Pregnant women with thrombophilia may present with gestational vascular complications including: venous thromboembolism (VTE), intrauterine fetal growth restriction (IUGR), preeclampsia, placental abruption and fetal loss. These complications are a major cause of maternal and fetal morbidity and mortality.[1] The use of anticoagulation for prevention of adverse pregnancy outcomes in women with heritable thrombophilias is increasing. Anticoagulant therapy during pregnancy is challenging because of the potential for fetal and maternal complications

Hemostatic changes in pregnancy

In normal pregnancy, there is a marked increase in the procoagulant activity, characterized by an elevation of factors VII, X, and VIII; fibrinogen; and von Willebrand factor.2 This is associated with an increase in prothrombin fragment 1+2 (PF12), and thrombin-antithrombin complexes.3 There is a decrease in physiologic anticoagulants manifest by reduction in protein S activity4 and by acquired activated protein C (APC) resistance.[5] The overall fibrinolytic activity is impaired during pregnancy.[6] This is largely due to placental-derived plasminogen activator inhibitor type 2 (PAI-2), which is present during pregnancy.[7] D-dimer, a marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses.[8] There is a 4- to 10-fold increased thrombotic risk throughout gestation and the postpartum period.

Hereditary thrombophilias

Approximately 50% of gestational VTE are associated with heritable thrombophilia. Many studies have examined the relationship between hereditary thrombophilias and pregnancy related VTE. All congenital thrombophilias with the exception of homozygosity for the thermolabile methilene tetrahidrofolate reductase variant (MTHFR C677T) were found to be associated with a statistically significant increase in the risk of pregnancy-related VTE1 (Table 1). Given a background incidence of VTE during pregnancy is approximately 1 in 1000 deliveries, it is clear that the absolute risk of VTE in women without a prior event remains modest for those who have the most common inherited thrombophilias, (heterozygosity for factor V Leiden or prothrombin G20210A variant).[1,11]

Antithrombotic agents in pregnancy

An ideal antithrombotic agent in pregnancy should be effective and safe for women and fetus, should have predictable activity without need for monitoring at reasonable cost. Potential fetal complications of maternal anticoagulant therapy include teratogenicity, bleeding and loss.[1] Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and danaparoid

cannot cross the placenta and, therefore, are safe anticoagulant choices for the fetus. Vitamin K antagonists cross the placenta and have the potential to cause all these complications.[11] Maternal complications of anticoagulant therapy are similar to those seen in non-pregnant patients and include bleeding (for all anticoagulants), as well as heparin-induced thrombocytopenia (HIT), heparin-associated osteoporosis, and pain at injection sites for heparin-related compounds.[11,12] LMWH is now commonly used for prophylaxis and treatment of maternal VTE. LMWH is preferred to UFH because of its better bioavailability, longer plasma-half-line, more predicttable dose response, and improved safety profile with respect to heparin-associated osteoporosis and HIT.[11,13]

Maternal bleeding risk of UFH and LMWH are low and both agents are safe in the lactating mother. [1,14]

Prophylaxis of VTE

Gestional VTE is a leading cause of maternal mortality[14] and long-term disability resulting from postphlebitic syndrome.[15] Since the prevalence of VTE in pregnancy in women heterozygote for factor (F) V Leiden or FII G20210A is low (1/200, 1/500)16,17, antepartum prophylaxis is not recommended. As the risk for VTE is increased after delivery, antithrombotic prophylaxis during the postpartum period has been advocated for women with thrombophilia.[17] Women with severe thrombophilic risk factors such as antithrombin deficiency, homozygous FV Leiden and combined thrombophilia should receive antepartum and postpartum prophylaxis with UFH or LMWH.[17,18,19] In the case of prior VTE the risk for recurrence at index pregnancy is increased (by 10-30-fold) resulting in gestional thrombosis in 6-11% of women with thrombophilia.[19,20]

Prevention of VTE in pregnant women

Women with thrombophilia and those with a history of VTE have an increased risk of VTE in subsequent pregnancies. Thromboprophylaxis during pregnancy is problematic because it involves long-term parenteral UFH or LMWH. Both are expensive, inconvenient and painful to administer and associated with risks for bleeding, osteoporosis, and HIT.[1,11] Rational administration of prophylaxis depends on quantifying the risk of thrombosis and identifying those women whose risk is high to merit intervenetion.[1,11,14] The threshold for recommending postpartum prophylaxis is lower than for antepartum prophylaxis due to the shorter length or required treatment (i.e., 6 weeks), the higher average daily risk of VTE in the post partum period, and the fact that warfarin can be used safely during this time even in women who are breastfeeding, since it does not appear in the breast milk.[11,12]

Given limited knowledge of the natural histories of the various thrombophilias the low predicted absolute rates of thrombosis, in those with the most common thrombophilias, and the lack of trials of VTE prophylaxis in this population, the management of pregnant women with known thrombophilia and no prior VTE remains controversial.[1,11] Postpartum prophylaxis for approximately six weeks using either warfarin targeted on an INR of 2,0 to 3,0 with a short initial course of UFH or LMWH or prophylactic doses of LMWH is recommended for all women with a hypercoagulable state, even in the absence of prior VTE.[11] Antepartum, both careful clinical surveillance and pharmacologic prophylaxis are acceptable management

options. The indication for active antepartum prophylaxis appears stronger for women with antithrombin deficiency, homozygosity for the factor V Leiden or prothrombin gene variant, persistent positivity for antiphospholipid antibodies, or combined thrombophilias.[11,21,22,23]

Table 1. Risk of pregnancy-associated venous thromboembolism (VTE) in thrombophilic women without prior disease

Thrombophilia	Relative Risk of VTE OR (95% CI)	Estimated absolute risk of VTE events per 1000 patients*
Factor V Leiden (heterozygous)	8.32 (5.44-12.70)	8/1000
Prothrombin gene variant (heterozygous)	6.80 (2.46-18.77)	6/1000
Factor V Leiden (homozygous)	34.40 (9.86-120.05)	34/1000
Prothrombin gene variant (homozygous)	26.36 (1.24-559.20)	26/1000
Antithrombin deficiency	4.69 (1.30-16.96)	4/1000
Protein C deficiency	4.76 (2.15-10.57)	4/1000
Protein S deficiency	3.19 (1.48-6.88)	3/1000
MTHFR C677T (homozygous)	0.74 (0.22-2.48)	1/1000

*Assuming a baseline risk of 1 event per 1000 pregnant patients without a known thrombophilia

Data are from Robertson et al.

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; MTHFR, methylene tetrahydrate folate reductase

Prior VTE and pregnancy

The extent to which pregnancy influences the risk of recurrent VTE remains somewhat uncertain. The women with prior VTE have an increased risk of recurrence during pregnancy, the absolute recurrence rates are unknown.[11,22] There have been no large clinical trials assessing the role of prophylaxis in pregnant women with previous VTE. All decisions should be considered on an individual basis, taking all the woman's risk factors for VTE, along with patient preference, into consideration.[1,11] Clinical surveillance or prophylaxis antepartum can be defended in pregnant women with prior unprovoked VTE or VTE associated with a thrombophilia.

Antepartum prophylaxis is easier to justify in women with higher-risk thrombophilias, and in those with more than one prior event.[13,14] Table 2 lists common prophylactic regimens.

Postpartum prophylaxis with either warfarin targeted to an INR of 2.0 to 3.0 or prophylactic LMWH is suggested for pregnant women with prior VTE.

Recurrent fetal loss

Recurrent fetal loss (RFL) is a common health problem with three losses affecting 1% to 2% and≥two losses affecting up to 5% of women at the reproductive age.[21,24] Several etiologies have been implicated to cause RFL, including chromosomal translocations and inversions, anatomic alterations of the uterus, endocrinological abnormalities and autoimmune disorders.[25,26] Association of acquired thrombophilia such as phospholipid antibodies with RFL is well established.[33] Studies in women with inherited thrombophilia have also suggested an association with fetal loss. The pregnancy loss in women with thrombophilia is distributed throughout gestation.[25] However, while most pregnancy losses occur during the first trimester, late pregnancy wastage occurs more frequently in women with thrombophilia than in those without thrombophilia. Thus, it was recommended that women with pregnancy loss that is either recurrent or late in pregnancy (second and third trimester) should be evaluated for thrombophilia.[27]

Late pregnancy complications

Late gestional vascular complications including pre-eclampsia, IUGR and placental abruption are the major cause of maternal morbidity and death. These complications often result in early delivery and severe prematurity stress. Pregnancy complications are often associated with reduced placental perfusion demonstrated by Dopller Sonography [28] and by increased fibrin deposition and thrombus formation at the uterine vessels and placental intervillous spaces. [29] A growing body of evidence suggests that these complications may be associated with maternal thrombophilia. The association is significant in women with severe complications such as severe early pre-eclampsia, severe IUGR and placental abruption. [30,31,32]

Hereditary thrombophilia and pregnancy complications

Adverse pregnancy outcomes are not infrequent; 25% of human conceptions and in miscarriage. Of those, 5% of women experience 2 or more successive losses and 1% to 2% have 3 or more consecutive losses. Maternal or fetal anatomic, chromosomal, endocrinologic or immunologic problems are detected in a small number of cases of recurrent loss but for most a case is not identified. Pre-eclampsia, a leading cause of both fetal and maternal morbidity and mortality, is seen in 3% to 7% of pregnancies, while placental abruption is uncommon (0,5% of gestations) but carries a high risk of fetal mortality.

In view of the data showing an association between hereditary thrombophilia and adverse pregnancy outcomes, clinicians are increasingly using antithrombotic therapy in women at risk of these complications.[34,35]

Prospective cohort studies of pregnant women with hereditary thrombophilia with current pregnancy losses have reported an increase in the frequency of live births with LMWH compared with a previous untreated pregnancy or current untreated patients. Data on antithrombotic prophylaxis for IUGR at index pregnancy and on subsequent gestations are limited. In view of the risk for recurrences of other gestational complications, including IUGR, prophylaxis can be considered. It can be managed with LMWH at a prophylactic dose (0.5 mg/kg enoxaparin or 5000 U dalteparin) once daily throughout gestation, and for 6 weeks in the postpartum period.[34,35]

The association of preeclampsia and thrombophilia is controversial. A number of case-control studies have demonstrated an association, while other studies have refuted this occurrence. An association between the presence of FVL and a history of severe forms of preeclampsia was reported.[36]

Other studies failed to find an association between a common genetic risk factor for thrombosis and the occurrence of preeclampsia.[37]A recent meta-analysis has demonstrated an association with FVL and factor II 20210G_A only in women with severe early onset of preeclampsia.[30] HELLP syndrome is a severe form of preeclampsia. This syndrome has been associated with thrombophilia particularly with the factor V Leiden mutation.[31] However, the risk in this woman is high and therefore counseling should take into account her age, the severe obstetric history, and risks of recurrence on subsequent gestation.[11] Prophylaxis during pregnancy should probably include LMWH at a moderate to high prophylactic dose throughout gestation and the postpartum period, aiming for anti-Xa levels of 0.4 to 0.6 U/mL 3 hours after injection. Whether aspirin

should be added is currently unknown.[11]

Combined thrombophilic risk factors

Antithrombin deficiency is an uncommon severe thrombophilia often manifest clinically by gestational vascular complications with significant increased maternal and fetal risks. The risk is estimated to be increased by 100- to 150-fold, which translates to clinically overt VTE in 7% of antithrombin-deficient pregnant women and up to 40% in cases of severe familial VTE.35 Antithrombin deficiency has been associated with other pregnancy complications including pregnancy loss and late gestational complications.[11]

Hyperhomocysteinemia and MTHFR 677

Homocysteine levels decrease in pregnancy by 50%. Gestational vascular complications can be associated with hyperhomocysteinemia documented in 26% of women with placental abruption, in 11% of cases with intrauterine fetal death, and in 38% of women delivering babies with intrauterine growth restriction. Nelen et al[40] reviewed 10 case-control studies that examined the association of RFL and hyperhomocysteinemia and reported a 3- to 4-fold increased risk, while in 6 other studies the odds ratios for homozygosity for MTHFR were not significant. These data suggest that while hyperhomocysteinemia is a risk factor for RFL, homozygosity for MTHFR as a solitary thrombophilic defect is not. However, testing for MTHFR 677TT may be of value in women with relative decreased folate and vitamin B12 levels commonly acquired during pregnancy and for identifying women with a combination of MTHFR 677TT and additional thrombophilia who may be at higher risk during gestation.[11] In this patient with severe combined thrombophilia ample intake of folate and vitamin B12 is advocated. Close monitoring of fetal growth and estimation of placental perfusion by Doppler velocimetry are advocated. Prophylaxis should be given throughout gestation and the postpartum period.

Inherited thrombophilias and abruptio placentae

Placental abruption is an uncommon devastating clinical presentation occurring in 0.5% of gestations but carrying a high fetal mortality and significant maternal risk. Risk factors for placental abruption include preeclampsia, prior abruption, sudden uterine decompression, chemical teratogens, external trauma, and uterine malformations.[41] A potential association with thrombophilia is suggested by a number of studies. Van der Molen et al[42] found that the prothrombotic risk factors for placental vasculopathy are decreased levels of APCR and protein C, elevated homocysteine, MTHFR TT, and combinations of these factors.

Asymptomatic factor V Leiden carrier

The risk for VTE during pregnancy in an asymptomatic woman heterozygote for factor V Leiden is around 0.2% to 0.5%.[43] The risk may increase somewhat in the presence of significant familial history of thrombosis but is still too low to confer the need for antepartum prophylaxis.[11] Thromboprophylaxis is not recommended and this woman should be managed by clinical surveillance.[11,43] In women with severe or combined thrombophilia the risk is increased, and therefore antepartum thromboprophylaxis should be considered.

Table 2. Dosing regimens for venous thromboembolism prophylaxis*

Regimen	Dose
Prophylactic UFH	UFH 5000 U subcutaneously every 12 hours
Intermediate-dose UFH	UFH subcutaneously every 12 hours in doses adjusted to target an anti-Xa level of 0.1-0.3 U/mL
Prophylactic LMWH	Enoxaparin 40 mg subcutaneously every 24 hours
	Dalteparin 5000 units subcutaneously every 24 hours
	Tinzaparin 4500 units or 75 units/kg subcutaneously every 24 hours
Intermediate-dose	Dalteparin 5000 U subcutaneously every 12 hours
prophylactic LMWH	Enoxaparin 40 mg subcutaneously every 12 hours
	LMWH subcutaneously every 24 hours adjusted to achieve a peak anti-Xa level of 0.2-0.6 U/mL

Abbreviations: *UFH, unfractionated heparin; LMWH, low-molecular-weight-heparin*

CONCLUSIONS

The role of antithrombotic modalities deserves prospective clinical trials in order to improve results in a large population of women who currently experience poor gestational outcome. Future trials should focus on efficacy and safety of tailored therapy for specific thrombophilic polymor-phisms in a particular gestational complications setup.

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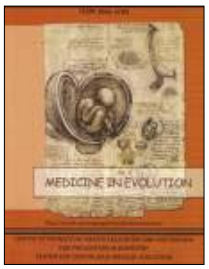
INFECTION CONTROL IN THE DENTAL LABORATORY



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ABSTRACT

Any instrument or piece of the equipment used in the oral cavity is a possible source of crossed infections. On the other hand, the dentures or trial stages coming from the laboratory may contaminate the patient, if they are infected. The main line of transmission to patients via laboratory techniques is through contaminated impressions and dentures.

Dental impressions easily become contaminated with patient's blood and saliva. Impression materials can be disinfected in two ways: immersion and spray. The most commonly used disinfectants are sodium hypoclorite, glutaraldehyde, iodophors and phenols. Unfortunately, not all impression materials are compatible with all disinfectants.

Different valuables can affect this material during disinfection, including the disinfectant's composition and concentration, as well exposure time and its compatibility with specific impression materials.

Concentration and the disinfection times vary greatly in the literature so it is difficult to establish a protocol. The risk of interaction between impression material and disinfectant means that compatibility tests and experimental protocols must be drawn up for the new impression materials and chemical disinfection products. All this promote appropriate hygiene conditions for the patient and clinic personnel along with obtaining optimum clinical results.

***Key words**: infection control, dental laboratory*

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INTRODUCTION

Any instrument or piece of the equipment used in the oral cavity is a possible source of crossed infections[3]. The repercussion of increased awareness on the dangers of crossed infections during dental procedures due to viruses, fungus and bacteria is being felt in dental clinics and laboratories. On the other hand, the denture or trial stages coming from the laboratory may contaminate the patient, if they are infected[1].

The aim of this paper is to point out the most proper techniques of avoiding cross-contamination.

MATERIAL AND METHOD

The main line of transmission to patients via laboratory techniques is through contaminated impressions and denture. Dental impressions easily become contaminated with patient's blood and saliva. Micro-organisms can remain both inside and on the surface of the impressions. It has been demonstrated that a small quantity (10-15%) remains after 10-15 seconds rinsing in water so it is necessary for it to undergo disinfection or sterilization methods. Sterilisation is ideal, but is not possible as the temperature and time required would destroy the impressions. Impression materials can be disinfected in two ways: immersion and spray. Disinfection by immersion is the most efficient because it exposes all the surface area to the disinfectant whilst the spray tends to act only on the application zones. The most commonly used disinfectants are sodium hypoclorite, glutaraldehyde, iodophors and phenols [2,4].

Unfortunately, not all impression materials are compatible with all disinfectants [8] (Table 1). Possibly remaining microorganisms on the impression may contaminate the surface of the model. When casting the model the technician must wear protection gloves and the model must be stored, until set, on a piece of paper or plastic, in a less contaminated area of the laboratory (never in the area where the impression are received or the casting of the model is carried out). When unwrapping the model after setting the technician must also wear protection gloves. The model may be sprayed with disinfectants.

Table 1. Compatibility between impression materials and disinfectants

	Glutaraldehydes 2%	Iodophors	Sodium Hypoclorite 0,5%	Phenols
Alginate	No	Yes	Yes	No
Polisulfides	Yes	Yes	Yes	Yes
Silicones	Yes	Yes	Yes	Yes
Polyethers	No	No	Yes	Yes
Hydrocolloids	No	Yes	Yes	?
Compound	No	?	Yes	?

All the prosthetic pieces which leave the laboratory must be also disinfected for preventing the transmission of possible microorganisms present in the laboratory to the patient [5,10]. The same procedure may be followed for disinfecting different stages of the prosthetic piece, after trying them in the patient's oral cavity.

Most dentures and appliances, as well as impression materials, can not withstand standard heat sterilization procedures. The alternative for most dentures is treatment by immersion, after a thorough precleaning. The best way to decontaminate soiled dentures is chairside disinfection immediately after removal (Table 2).

Table 2. Chemical disinfection for dentures and appliances

Dentures/Appliances	Glutaraldehydes	Iodophors	Chlorine Compounds
Fixed (metal/porcelain)	Yes	?	Yes
Removable (acrylic/porcelain)	No	Yes	Yes
Removable (metal/acrylic)	No	Yes	Yes
Appliances (all metal)	Yes	?	?

RESULTS

As far as impression materials are concerned, it has been proven that alginate retains the highest number of micro-organisms. Not all impression materials are compatible with all disinfectants, as some of them can affect the quality of the impression, altering its dimensional stability, humectancy and surface roughness. Different valuables can affect this material during disinfection, including the disinfectant's composition and concentration, as well exposure time and its compatibility with specific impression materials. Concentration and the disinfection times vary greatly in the literature so it is difficult to establish a protocol [6,7]. The current recommendation is as follows (Table 3).

Disinfectant spray application causes less dimensional changes than immersion in liquids, but it is not appropriate because it blocks areas in porous zones and reduces disinfection effectiveness. Several studies affirm that immersing polyethers and addition silicones in glutaraldehyde encourages distortion when submitted to prolonged periods of disinfection; other studies however affirm that disinfecting these materials in glutaraldehyde does not produce important variations in the size and humectancy of silicon and polyether.

Rinsing after disinfection is also necessary to eliminate remains of the disinfectant which can affect the surface area of plaster models. Recent information indicates that oral bacteria can remain viable in set gypsum materials for periods up to 7 days.

Table 3. Recommended concentration and disinfection time for impression materials

Alginate	Reversible hydrocolloids	Polyethers	Polysulfures	Silicones
Sodium Hypoclorite 0,5 % 10 min	Altering it's surface	Glutaraldehyde 2% 20 min	Altering it's surface	Glutaraldehyde 2% by immersion or spray

CONCLUSIONS

The risk of interaction between impression material and disinfectant means that compatibility tests and experimental protocols must be drawn up for the new impression materials and chemical disinfection products[9,11]. All this promote appropriate hygiene conditions for the patient and clinic personnel along with obtaining optimum clinical results.

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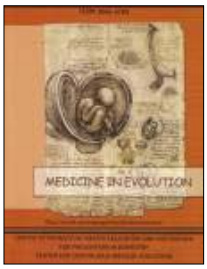
CORRELATIONS BETWEEN THE BLOOD VALUE OF C-REACTIVE PROTEIN AND THE CLINICAL COURSE OF ORO-MAXILLO-FACIAL INFECTION



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ABSTRACT

C-reactive protein (CRP) is an acute phase protein, synthesized by the liver, whose levels in blood increase in response to various infectious processes.

This study sought to establish a correlation between the blood concentration of C-reactive protein (CRP) and different clinical stages of oro-maxillo-facial odontogenic infections.

Before the medical and surgical treatment was applied, the blood CRP concentration was increased, high above the biological reference value.

These values have decreased with the remission of the infections symptoms.

We don't reported cases of oro-maxillo-facial infection where CRP is proved to be absent.

***Key words**: C reactive protein, odontogenic infection, surgical treatment*

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INTRODUCTION

C-reactive protein (CRP) is an acute phase protein found in blood, whose levels increase in response to various infectious processes in the body. It is a member of a family of proteins called pentraxins and is a pentameric disc in shape. CRP is synthesized by the liver and is a protein that normally does not exists in human serum. It is synthesized only in pathological conditions. CRP was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute infections, which reacts with the C polysaccharide of pneumococus. Initially it was thought that CRP might be a pathogenic secretion (as it was elevated in people with a variety of illnesses including cancer), however discovery of hepatic synthesis demonstrated that it is a native protein. CRP is used mainly as a marker of infection with other tests such as erythrocytes sedimentation rate (ESR) and fibrinogen and is the most sensitive marker of acute phase (better then ESR). Apart from liver failure, there are few known factors that interfere with CRP production. Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments. Various analytical methods are available for CRP determination, such as ELISA, immunoturbidimetry, rapid immunodiffusion, and visual agglutination. Normally, C-reactive protein is absent in healthy human serum. However, it is accepted as normal values below 5 mg/l. This values increase slightly with age. Elevated CRP values occur in acute and chronic infections, severe trauma, after surgery, myocardial infarction, tuberculosis, neoplastic proliferations, etc. For an accurate result for lower concentrations of CRP, hs-CRP test is used (high sensitivity C-reactive protein). It provides the result in 25 minutes with accuracy up to 0.04 mg/l. During pregnancy, mild and viral infections CRP value is approximately 10-40 mg/l. In severe infections, CRP concentration value reached 40-200 mg/l.

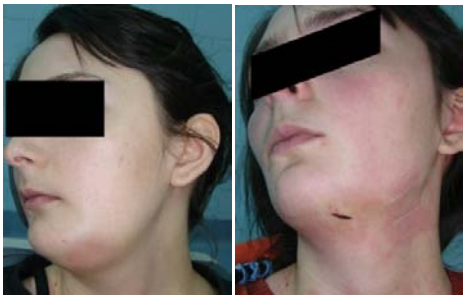
Objectives

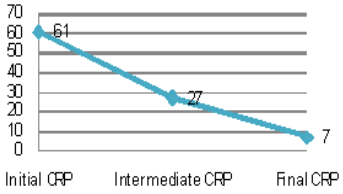
This study aims to monitor the values of CRP concentration and their oscillations in different stages of surgical and medical treatment of the maxillo-facial odontogenic infections. The study also tries to determine how the concentration of CRP in blood can provide information about the disease stage and the effectiveness of surgical and antibiotic treatment.

MATERIAL AND METHOD

The study included 20 patients, 13 women and 7 men aged between 5 and 51 years, who were hospitalized within Timisoara's Oro-Maxillo-Facial Surgery Department with different odontogenic infectious pathology. All the patients underwent surgical treatment followed by related antibiotics. During established time intervals, in relation to the stages of the treatment, blood samples were collected and the CRP concentration was determined, from an initial value in the beginning of the hospitalization, before establishing any kind of treatment, to a final value, obtained after the symptoms were resolved. The value of CRP concentration was obtained in a specialized laboratory, by the help of "Architect ci8200" apparatus (produced by Abbott Diagnostics), using the Abbott turbidimetry method. The determined values were compared to the biological reference value (5mg/l).

Case 1:
Left perimandibular abscess, odontogenic etiology. Treatment: incision, drainage, tooth extraction and antibiotics. Resolution in 5 days.





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LABORATOR CENTRAL-TM

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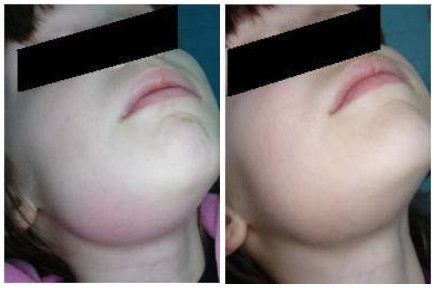
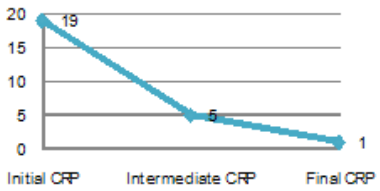
PROTEINA C REACTIVA..	7 mg/l	(< 5)	26/03/2010	27

(ser, Architect ci 8200, Metoda turbidimetrie Abbott)

Case 2:
Odontogenic periapical abscess 4.6. Treatment: tooth extraction, drainage and antibiotics. Resolution in 5 days.





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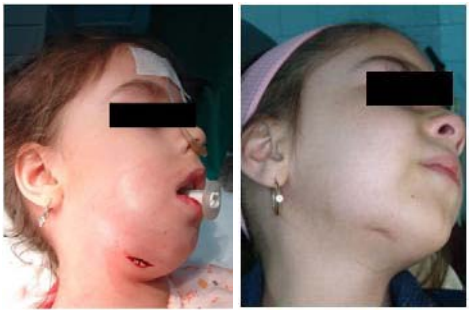
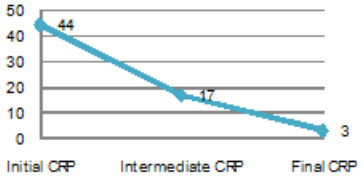
(ser, Architect ci 8200, Metoda turbidimetrie Abbott)

Case 3:
Right perimandibular abscess, odontogenic etiology. Treatment incision, drainage, tooth extraction and antibiotics. Resolution in 6 days.





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[redacted], 5 ani
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			VAL.BIOL.REF.	ANTECEDENT
PROTEINA C REACTIVA..	3 mg/l	(< 5)	11/03/2010	44

(ser, Architect ci 8200, Metoda turbidimetrie Abbott)

RESULTS

Before the medical and surgical treatment was applied, the blood CRP concentration was increased, high above the biological reference value. These values decreased gradually with the improvement of the clinical symptoms of infection. (Table 1)

There were no reported cases of oro-maxillo-facial infection where CRP is proved to be absent. In 15 (75%) patients of the 20 included in the study, CRP concentration value at the end of the treatment returned to normal levels, below the biological reference value of 5 mg/l. In 5 (25%) patients CRP concentration decreased, but not lowered below the biological reference value (Figure 1). This can be explained by the combination of other untreated general diseases, known or unknown in the patient's medical history, which can lead to a pathological increase of blood CRP concentration.

Table 1.

Initial, intermediate and final value recorded in 20 patients included in the study compared with the reference value of 5 mg/l.

Patient	Sex	Age	Initial CRP value	Intermediate CRP value	Final CRP value	Reference value
1	F	22	**56 mg/l**	**23 mg/l**	**4 mg/l**	**<5 mg/l**
2	F	21	**90 mg/l**	**43 mg/l**	**5 mg/l**	**<5 mg/l**
3	F	25	**35 mg/l**	**20 mg/l**	**2 mg/l**	**<5 mg/l**
4	F	24	**50 mg/l**	**25 mg/l**	**5 mg/l**	**<5 mg/l**
5	F	36	**21 mg/l**	**12 mg/l**	**13 mg/l**	**<5 mg/l**
6	F	22	**61 mg/l**	**27 mg/l**	**7 mg/l**	**<5 mg/l**
7	F	39	**85 mg/l**	**32 mg/l**	**4 mg/l**	**<5 mg/l**
8	F	51	**97 mg/l**	**45 mg/l**	**7 mg/l**	**<5 mg/l**
9	F	41	**70 mg/l**	**30 mg/l**	**4 mg/l**	**<5 mg/l**
10	F	28	**54 mg/l**	**22 mg/l**	**3 mg/l**	**<5 mg/l**
11	F	6	**20 mg/l**	**4 mg/l**	**1 mg/l**	**<5 mg/l**
12	F	7	**19 mg/l**	**5 mg/l**	**1 mg/l**	**<5 mg/l**
13	F	5	**44 mg/l**	**17 mg/l**	**3 mg/l**	**<5 mg/l**
14	M	20	**108 mg/l**	**37 mg/l**	**5 mg/l**	**<5 mg/l**
15	M	30	**102 mg/l**	**35 mg/l**	**6 mg/l**	**<5 mg/l**
16	M	24	**60 mg/l**	**23 mg/l**	**3 mg/l**	**<5 mg/l**
17	M	22	**61 mg/l**	**25 mg/l**	**5 mg/l**	**<5 mg/l**
18	M	31	**78 mg/l**	**36 mg/l**	**7 mg/l**	**<5 mg/l**
19	M	8	**20 mg/l**	**12 mg/l**	**2 mg/l**	**<5 mg/l**
20	M	10	**34 mg/l**	**16 mg/l**	**5 mg/l**	**<5 mg/l**

Another explanation may be a very short period of time from symptom remission until the final determination, which not allowed full adjustment of CRP concentration in the blood.

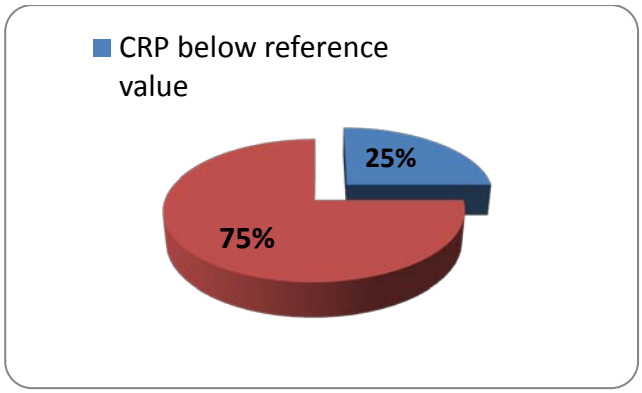

Fig. 1. Final results showing that 75% of patients are below the reference value of CRP and 25% of patients are above reference value of CRP at the end of the treatment.

RESULTS

Before the medical and surgical treatment was applied, the blood CRP concentration was increased, high above the biological reference value. These values decreased gradually with the improvement of the clinical symptoms of infection. (Table 1)

There were no reported cases of oro-maxillo-facial infection where CRP is proved to be absent. In 15 (75%) patients of the 20 included in the study, CRP concentration value at the end of the treatment returned to normal levels, below the biological reference value of 5 mg/l. In 5 (25%) patients CRP concentration decreased, but not lowered below the biological reference value (Figure 1). This can be explained by the combination of other untreated general diseases, known or unknown in the patient's medical history, which can lead to a pathological increase of blood CRP concentration.

Another explanation may be a very short period of time from symptom remission until the final determination, which not allowed full adjustment of CRP concentration in the blood.

CONCLUSIONS

1. Although it was first describe in 1930, very few studies analyze the relationship between CRP and inflammatory and infectious diseases in the human body.

2. The odontogenic oro-maxillo-facial infections increase CRP values, normally the protein not being found in the human serum. Following a correct treatment of odontogenic infections, the values of CRP come back to normal together with the remission of the clinical symptoms.

3. C-reactive protein may be an important acute phase marker of odontogenic infections, providing useful information about disease stage and efficacy of specific medical and surgical treatment. All these makes C-reactive protein a more sensitive marker than erythrocytes sedimentation rate, which

is used on a larger scale due to a simple measurement method and a lower cost.

4. Probably, in the future, after more information will be known and the determinig costs will decrease, C-reactive protein will become a common marker of inflammation and infection.

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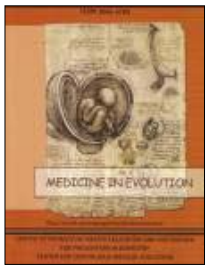
CORRELATIONS BETWEEN RED CELL DISTRIBUTION WIDTH AND CARDIOVASCULAR EVENTS AT PATIENTS WITH CORONARY HEART DISEASE



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ABSTRACT

***Aim and objectives**: Red cell distribution width (RDW) is a quantitative measure of variability in the size of circulating erythrocytes determined by modern analyzers, with higher values reflecting greater heterogeneity in cell sizes. The study tries to demonstrate a link between higher levels of RDW and the risk of cardiovascular events in this case, at patients with coronary heart disease free of heart failure.*

***Methods**: We included in our retrospective study a number of 60 patients with a coronary angiography revealing significant CAD, being reported the cardiovascular events or cardiovascular death that occurred.*

***Results**: The median values of RDW were 14.6%. There have been reported 2 cardiovascular deaths and 10 patients suffered a cardiovascular event with a higher incidence in the group with RDW levels over the median value. After adjustment for other cardiovascular risk factors we used Cox proportional hazards models to examine the association between RDW and adverse clinical outcomes, RDW proving to be a strong and independent predictor of cardiovascular death ($p<0.004$).*

***Conclusions**: RDW routinely reported parameter, so inexpensive, is a strong predictor of cardiovascular events.*

***Key words**: coronary artery disease, secondary prevention, RDW*

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INTRODUCTION

In the present we are looking for easier and inexpensive ways to determine the risk of cardiovascular events especially at patients with coronary heart disease. Besides exploring the lipid profile, the markers of inflametion, proteinuria and echocardiogramphic parameters we search for indicators that are easy to determine, that could underline the risk group. Red cell distribution width (RDW) is a quantitative measure of variability in the size of circulating erythrocytes determined by modern analyzers, with higher values reflecting greater heterogeneity in cell sizes. It is a numerical measure of anisocitosis, computed as the standard deviation of the distribution of red cell widths divided by the mean corpuscular volume. RDW is often elevated in clinical practice by nutrient deficiencies, which lead to heterogeneous red cell populations. A large number of reticulocytes can also increase the RDW, as can lab errors from red cell clumping or counting of large platelets or schistocytes. Recently, data from the CHARM study of heart failure patients reported an association between elevated RDW and mortality among heart failure patients [1]. In a randomized controlled trial of heart failure patients, Felker and colleagues showed that patients with RDW >15.8% had nearly a 2-fold increased risk of CVD death or hospitalization as well as death from any cause compared to those with RDW <13.3%. As a validation, Felker et al. also showed a 2-fold increased mortality risk comparing the highest RDW quintile (>15.5%) to the lowest (<13.0%) in a separate clinical cohort of heart failure patients. Even when analyses were restricted to nonanemic participants or to those in the reference range of RDW (11%-15%) without iron, folate, or vitamin B12 deficiency, RDW remained strongly associated with mortality. The prognostic effect of RDW was observed in both middle-aged and older adults for multiple causes of death [3], data demonstrate that elevated RDW is a strong and independent predictor of all-cause mortality in an unselected population of male patients across a broad spectrum of risk referred for coronary angiography[2]. There are studies that demonstrate that elevated RDW is a strong and independent predictor of all-cause mortality in an unselected population of male patients across a broad spectrum of risk (including ACS) referred for coronary angiography [2]. Red cell distribution width (RDW) has been shown to be an independent predictor of mortality in patients with coronary artery disease and heart failure [1].

Aim and objectives

The study tries to demonstrate a link between higher RDW levels and the risk of cardiovascular events, in this case, at patients with coronary heart disease free of heart failure.

MATERIAL AND METHOD

We included in our retrospective study a number of 60 patients with a coronary angiography revealing significant CAD (lumen reduction ≥70%) aged 44 to 78 years. The group included 15 women (25%) and 45 men (75%). They have been followed up for a period of 3 years being reported the cardiovascular events (unstable angina, resuscitated cardiac arrest, ischemic stroke and transient ischemic attacks) or cardiovascular death that occurred.

Clinical evaluation, EKG, ecocardiography, serum hemoglobin, Ht, RDW, fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and hs-PCR were determined. We included patients with the diagnosis of coronary heart disease with the RDW levels range 11.6-16.5% that had not developed heart failure, anemia, and diabetes, did not have iron, B12 vitamin or folic acid deficiency and did not consume alcohol. RDW values were divided in quintiles 11.6-13%; 13.3-14%, 14-14.8%; 14.8-15.8; 15.8-16.5%. Cox Proportional Hazard Model was used.

Table 1.

QUINTILES	RDW
I	11.6-13%
II	13.3-14%
III	14-14.8%
IV	14.8-15.8%
V	15.8-16.5%

Table 2. Baseline characteristics of patients

	I	II	III	IV	V
Nr of patients	8	12	10	14	16
Age (years)	57	58.2	59.4	61	64
Male (%)	55	57	58.6	59	60
Obesity (%)	28	30	31	34	35
Current smoker (%)	19	21.5	24	25.8	26.7
Diabetus melitus (%)	4	6	7.8	10	11.9
Hemoglobin (g/dl)	14.3	14.2	14.1	13.6	13.2
Hypertension (%)	70	70.5	71.4	72.1	74
Hyperlipidemia (%)	80.1	81	82.6	83	84

RESULTS

The median values of RDW were 14.6%. Median RDW in the subgroup that presented a cardiovascular event was 15.2% compared with the non-event subgroup with RDW median value of 14.4%. Participants with higher RDW values were more likely to be older, obese; currently smoking compared to those with lower RDW values. Hemoglobin levels decreased with higher RDW but hs-PCR increased with higher RDW. There have been reported 2 cardiovascular deaths and 5 patients suffered a cardiovascular event (unstable angina, resuscitated cardiac arrest, ischemic stroke and transient ischemic attacks) with a higher incidence in the group with RDW levels over the median value. After adjustment for other cardiovascular risk fac-

tors (smoking, obesity, hs-PCR, dyslipidemia, hypertension) we used Cox proportional hazards models to examine the association between RDW and adverse clinical outcomes, RDW proving to be a strong and independent predictor of cardiovascular death ($p<0.004$).

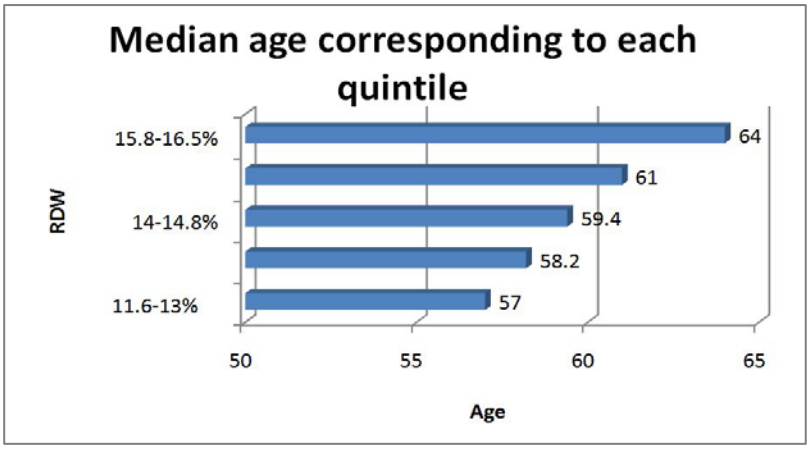

Fig. 1.

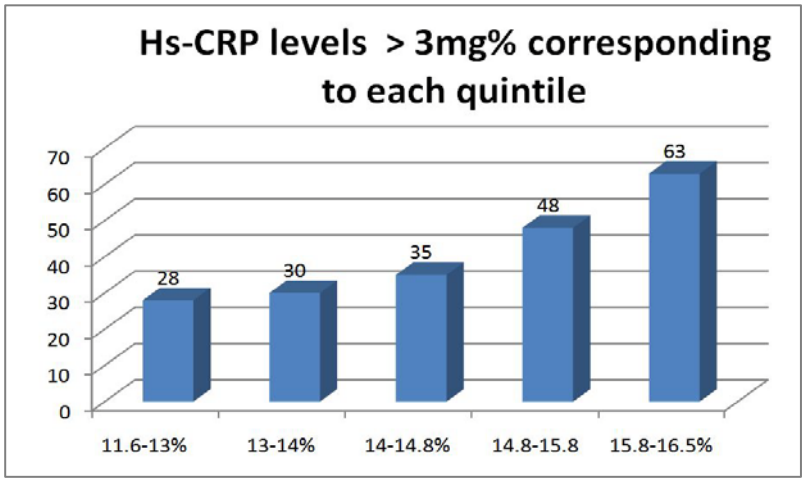

Fig. 2.

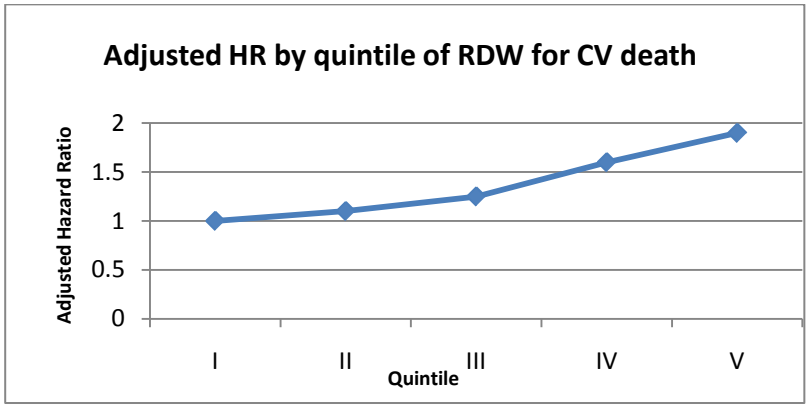

Fig. 3.

CONCLUSIONS

RDW predicted mortality among participants who were clearly non-anemic. Mortality rates were graded across the entire distribution of RDW and were particularly elevated in participants with RDW greater than 14%. Older age as well as elevated hs-CRP, was strongly associated with higher RDW levels. Systemic factors that alter erythrocyte homeostasis, such as inflammation and oxidative stress, likely play a role. Inflammation might contribute to increased RDW levels by not only impairing iron metabolism but also by inhibiting the production of or response to erythropoietin or by shortening red blood cell survival. Studies made so far stated that higher RDW levels could reflect an inefficient eritropoiesis that may be another factor involved in the underlying inflammatory state [6]. RDW routinely reported parameter, so inexpensive, is a strong predictor of cardiovascular events.

DISCUSSIONS

Studies had also observed an association between RDW and metabolic syndrom [5]. A possible explanation for the observed association between RDW and MetS is that high RDW reflects an underlying inflammatory state that leads to impaired erythrocyte maturation and anisocytosis. The association between high RDW and MetS is weaker than the observed association between RDW and cardiovascular events in high-risk populations. It can be speculated that the inflammatory state induced by MetS is not as strong as that induced by established cardiovascular disease. Given that RDW rises with age and strongly predicts mortality, it is conceivable that anisocytosis might reflect impairment of multiple physiologic systems related to the aging process or is caused by inflammation and age-associated diseases. While further research is needed to elucidate the mechanisms, RDW provides prognostic information that can be used to improve risk stratification.

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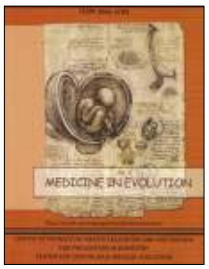
MOTIVATIONAL ASPECTS CONCERNING THE PRESENCE OF PREGNANT WOMEN IN THE DENTAL PRACTICE



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ABSTRACT

The presence of the pregnant woman in the dental practice during the first months of pregnancy is a particularly important aspect for the prophylaxis of oral-dental diseases in pregnant women. In order to familiarize the pregnant woman with dental check-up examinations, motivational mechanisms may be addressed.The need to change habits and behaviours is obvious and it implies a profound motivation.

This is achieved by a personal professional endeavor from the part of the dentist, as well as by the use of specific informative materials offered to the pregnant woman as early as possible.

Most oral-dental diseases may be prevented by fighting the causes.

This is why practicing oral-dental hygiene is primordial and it must become a habit.

***Key words**: motivation, informative materials, pregnancy, oral-dental diseases*

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INTRODUCTION

Pregnancy is a specific physicological state characterized by multiple hormonal, metabolic and psychological changes. The adaptation of the organism to pregnancy is achieved through physiological mechanisms associated to certain psycho-somatic changes. The psychological component has a very important role in the way a pregnant woman perceives her situation. The emotional balance is achieved by perceiving all pregnancy-specific manifesttations as perfectly normal phenomena. The importance of pregnancy surveyllance is equally focused on pregnancy as a whole as well as on psysiopathological changes in the oral cavity. The presence of the pregnant woman in the dental practice during the first months of pregnancy is a particularly important aspect for the prophylaxis of oral-dental diseases in pregnant women.

In order to familiarize the pregnant woman with dental check-up examinations, motivational mechanisms may be addressed. Motivation constitutes one of the imperatives of the physician-patient relationship. The first step in creating motivation is information by sustained campains in familiy medicine as well as in gynecology practices. The dentist must be interested in the psychological preparation of patients which may stimulate their behaveiour towards the intended direction.

The dentist's speech must reach the deepest places of the unconscient in order to determine the occurence of some reasons which resonate with this specific state. Obtaining oral-dental health and limiting some specific diseases may be achieved only by a close and periodic collaboration with the pregnant woman.

Specific Aims – The aim of the present paper is to show motivational aspects which may bring the pregnant woman to the dental practice. The dentist must achieve collaboration with the patient, facilitating a harmonious relation based upon psychological connection. As such, we cannot ignore the psychological aspects of their behaveiour. Moreover, in the dental practice, the patient's personality is influenced by stress which affects the knowledge of true behavioural trends. Under these circumstances, the dentist must establish cooperation with the pregnant woman based upon imperative motivational aspects. Most oral-dental diseases may be prevented by fighting the causes. This is why practicing oral-dental hygiene is primordial and it must become a habit. The need to change habits and behaviours is obvious and it implies a profound motivation. This is achieved by a personal professional endeavor from the part of the dentist, as well as by the use of specific informative matherials offered to the pregnant woman as early as possible. The doctor-patient relationship is based upon a series of defining aspects which address the following:

- *establishing a good connection with the patient*
- *keeping a pleasant psychological climate during treatment*
- *permanent self-control regarding aggressive trends as well as their expression*
- *empathic capacity, being able to see the other's side of the problem*
- *education by conversation on the investigation and therapy by explaining the need for an intervention.*

MATERIAL AND METHODS:

The study included two groups of women:

- the first group of 50 pregnant women
- the second group of 50 women without pregnancy.

The following criteria were considered regarding the motivation for visiting the dentist:

1. The main motivation for visiting the dentist is represented by dental pain. Its emotional component causes an increased addressability of patients, pregnant or not. The alteration of general health due to dental pain alerts the patient even more considering that the possibility of affecting her pregnancy represents one of the main reasons for visiting the dentist.

2. Gingival bleeding causes a discomfort and it also affects the function of the dental-maxillary apparatus, complicated by avoidance of a proper brushing leading to a vicious circle which augments the initial disease.

3. Gingival hypertrophy, of hormonal etiology or not, causes a mastication discomfort further complicated by a series of diseases which may widen the area of oral-dental pathology, inherently complicating long term treatment.

4. Fetide halitosis represents another reason for addressing the dentist, augmented by the social component involved.

5. Esthetic changes represent subjective and objective causes. The discomfort caused by absent frontal teeth or by carious lesions in this area may lead to social and professional insertion problems, as well as to severe behavioural changes.

6. Functional changes caused by more or less expanded edentations are felt by the patients as elements which affect dental-maxillary functions, also possibly leading to major digestive problems.

7. A relatively restricted category of patients come to the dentist by habit and for prophylactic reasons, at regular intervals (every 6-12 months).

8. The recommendation made by the family physician may be a necessity when general pathology occurs or an extremely important aspect in preventive programmes for general or oral-dental health diseases.

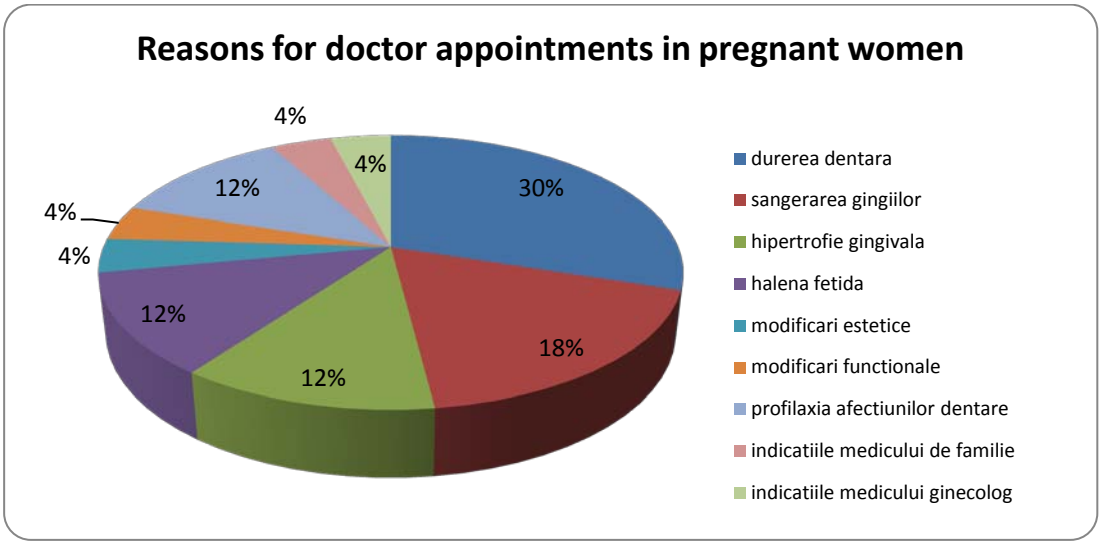
9. Recommendations from the gynecologist represent esppecially in the case of pregnant women, an important advice for both the health of the future child and for the evolution of pregnancy and of the pregnant woman's health.

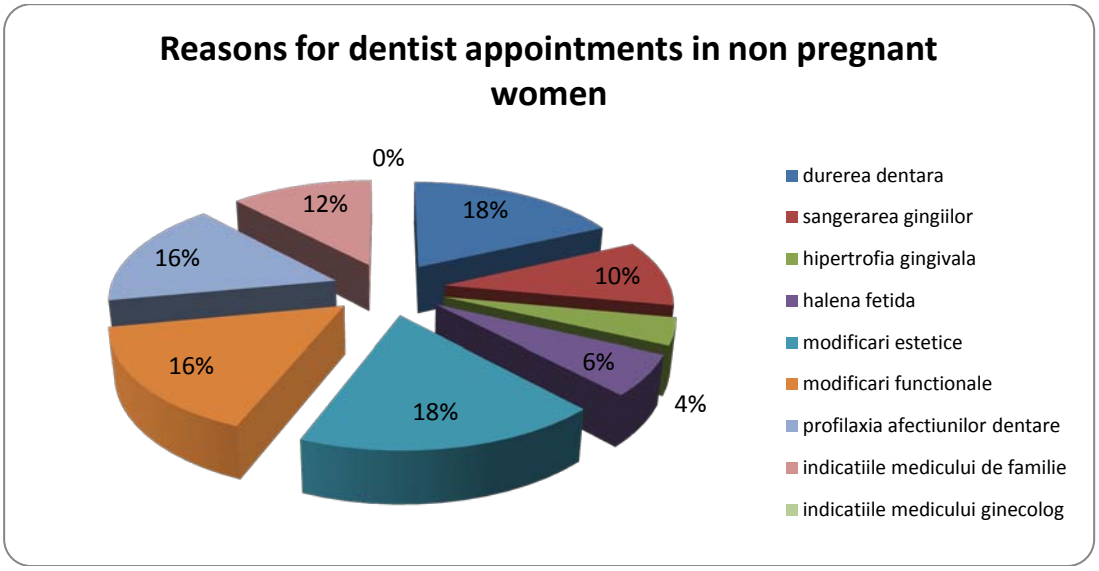
Considering the above mentioned criteria, specific charts were filled in for the two studied groups.

RESULTS

The results analysis shows that the main reason for which pregnant patients come to the dentist is dental pain. The absence of dental education programmes causes a decrease of the interest for oral health, as well as the absence of mechanisms to prevent diseases during pregnancy. Prevention of oral-dental diseases in pregnant women is a completely unapproached area. Oral-dental complications (gingival hypertrophy, gingival bleeding and halitosis) represent a high percent of the causes for which pregnant women visit the dental practice. As a consequence, oral-dental preventive programmes in pregnant women might respond to some imperative needs caused by general and local chanages during pregnancy. In such programmes, better coordination and cooperation between dentist, family physician and gynecologist might be addressed. The need for dental follow up visits before pregnancy might represent an important component of general health evaluation in women, together with other complementary examinations. Prevention of oral-dental

diseases in pregnant women might stop or at least decrease more or less manifest and unpleasant symptoms which may occur during pregnancy.





MOTIVATION FOR VISIT	PREGNANT	NONPREGNANT
dental pain	30%	18%
gingival bleeding	18%	10%
gingival hypertrophy	12%	4%
fetide halitosis	12%	6%
esthetic changes	4%	18%
functional changes	4%	16%
prevention of dental diseases	12%	16%
refered by family physician	4%	12%
refered by gynecologist	4%	0%

CONCLUSIONS

The reasons for pregnant women visiting the dental practice must be analyzed in the context of specific medical education during this period. Realizing the importance of a good oral-dental health in this period implies a better implementation of oral prevention programmes, thus preventing the occurence of acute diseases. Pain, as well as certain pregnancy specific diseases, are the main reasons for which pregnant women visit the dentist. Preventing acute diseases by prophylactic programmes and monitoring women, even before pregnancy occurs, represent major necessities. The presence of pregnant women in the dental practice during the first months of pregnancy reduces the amplitude of inflamatory phenomena through preventive and therapeutic programmes.

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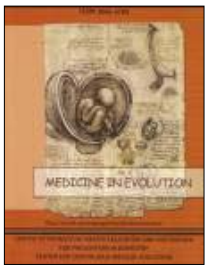
ANALYSIS OF RISK FACTORS FOR DISTANT METASTASIS IN SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY



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ABSTRACT

***Aim**: Our study evaluated some clinical and histopathologic factors to predict distant metastasis in patients with squamous cell carcinoma of the head and neck.*

***Materials and Methods**: A total of 206 patients with histologically proven squamous cell carcinoma of the head and neck were studied. The relationships of tumor stage, primary site, clinical growth pattern, tumor differentiation, regional node status, and extranodal spread tumor with metastastatic disease were evaluated.*

***Results**: 20% of the patients developed distant metastasis ss the initial treatment failure. The incidence was significantly higher in patients with neck metastasis than in those without neck metastasis (P < 0,001). There was no statistical difference in the incidence based on location, stage of the disease, and clinical growth pattern. On multivariate analysis, only histopathologic nodal status and extranodal spred proved to be independent cofactors of distant metstases.*

***Conclusion**: The presence of pathologically positive nodes is the most critical factor to influence the eventual development of distant metastasis.*

***Key words**: distant metastasis, squamous cell carcinoma, neck dissection*

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INTRODUCTION

Patients with distant metastasis from squamous cell carcinoma of the head and neck have a poor prognosis. In the past, uncontrolled or recurrent locoregional disease was the main cause of death in patients with carcinoma of the head and neck, but recently the use of conservative multimodal treatment approaches to locoergional treatment, a higher percentage of patients have died of second malignancies [1]. An analysis of the factors leading to distant metastasis is important in predicting prognosis and serves in elucidating possible mechanisms underlying this process. In literature the predictors of neck node metastasis have been largerly shown [2,6]. However, factors predictive of distant metastasis have not been well descrybed. The main aim of our study was to evaluate several Impact of clinical and histopathologic parameters on outcome in predicting distant metastasis in patients with squamous cell carcinoma of the head and neck.

MATERIAL AND METHODS

The subjects consisted of 206 previously patients selected from casuistry of Oro-Maxillofacial Surgery Clinic, UMF „Carol Davila" Bucharest. All those patients underwent resection of primary lesions and neck dissections in a number of cases for squamous cell carcinomas of the oral cavity. In all the cases were showed no evidence of persistent or recurrent disease. Postoperative radiation therapy was administered in every patient. The clinical features examined included age, sex, primary tumor site, TNM staging, and gross appearance of the tumor. The histopathologic features selected for the analysis were: the degree of tumor differentiation, pathologic nodal status, and extranodal spread of tumor. Follow-up evaluation consisted of physicccal examination, biochemical studies, and chest radiographs performed at 3-month intervals for the first year after treatment and then every 6 months the two years after. Statistical analysis was performed by univariate dispersion analysis of clinical and histopathologic factors to identify potential prognostic factors in the occurrence of secondary determinations. Multivariate analysis to assess the interdependence of differrent variables influence the distant metastasis incidence used to estimate the distance logistic regression analysis. Were considered statistically significant results for which the value is <0.05. Data integra-tion was carried out using the *JMP Start Statistics* software.

RESULTS

The age of the patients ranged from 36 to 78 years, with a mean of 57 years. There were 169 men and 37 women, with a male-to-female ratio of 4,5:1. The clinical stage at presentation was determined according to the TNM classification recommenddded by the *UICC* and *AJCC* [7]. There were 18 patients (9%) with stage I, 44 patients (21%) with stage II, 77 patients (34%) with stage III and 74 patients (36%) with stage IV disease. Histopahological results showed that were 42 (20%) poorly differentiated / undifferentiated tumors (G_3 and G_4), 102 (50%) moderately differentiated tumors (G_2) and 62 (30%) well differrentiated differentiated tumors (G_1).

Prophylactic neck dissections were performed in 88 patients and therapeutic neck dissection was performed in 59 patients. Metastatic disease was confirmed histologically in 72 (61%) of patients that underwent therapeutic neck dissections patients and 27% (24 cases) of patients who underwent prophylactic neck dissections. Of the 206 patients, 96 (47%) had metastatic lymph nodes, and extranodal spread of tumor was confirmed histologycally in 42 patients (45%). There were no statistical differences in the incidence of distant metastasis based on sex, location, stage of the disease and clinical growth pattern of the tumor. Distant metastasis were present in 10 T_4 patients (20%), 12 T_3 (30%), 18 T_2 patients (20%) and 2 T_4 patients (7%). Of 88 patients who had undergone prophylactic neck dissections, 24 (27%) developed distant metastasis and 14 (16%) of them had metastatic disease. Of patients who had undergone therapeutic neck dissections, 10 N_1 patients (13%) and 18 N_2 patients (43%) developed distant metastasis. Thus, N-stage was not related to the development of metastatic disease. However, histopatologically, the incidence of distant metastasis was best related to the neck node status. Of the 42 patients with metastatic disease, four patients were node negative and other 38 patients were node positive. The incidence of distant metastasis was statistically different between neck-positive and neck-negative patients. Patients with extranodal spread of tumor were more likely to develop distant metastasis than patients who had neck metastasis without extranodal spread of tumor (P <0,05) (Table 1). Therefore, the presence of positive neck nodes was the most critical factor to influence the eventual development of distant metastasis. On multivariate analysis, histopathologic nodal status (P = 0, 04) and the presence of extranodal spread of tumor (P = 0, 03) were correlated with the development of distant metastasis (Fig. 1).

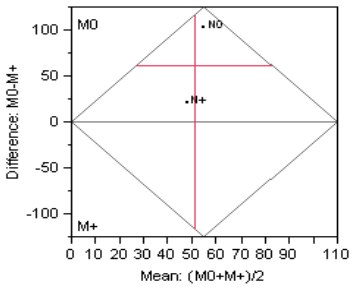

Fig.1. Contingency Analysis of the presence of extranodal spread tumor with development of distant metastasis has statistical significance

Table 1: Incidence of distant metastasis according o histopathologic factors (Univariate analysis)

Factori	Nr. pacienți	Nr. cazuri M+	Nr. cazuri M0	Dif. statistică
G1	62	4	58	
G2	102	20	82	p < 0,01
G3 / G4	42	18	24	
N0	110	4	106	p < 0,001
N+	96	38	58	
Fără ruptură capsulară	54	14	40	
Cu ruptură capsulară	42	24	18	p < 0,05

DISCUSSIONS

The incidence of distant metastasis from squamous cell carcinoma of the head and neck is reported to range from 10% to 40% [8,9]. The variation may

be due in part to the nature of the manner of detecting distant metastasis (clinical or pathological) and the selection of patients. In our study, distant metastasis was related to the histopathologic nodal status, histologic grade, and extranodal spread of tumor. Among them, the nodal status had the strongest association with distant metastasis, with 40% of neck-positive patient's exhibitting secondary tumors vs. 4% for N_0 patients ($P < 0,001$). Is known that there are two main potential routes for hematogenous dissemination: 1) access through regionnal lymphatics via the thoracic duct and 2) direct release through tumor invaded blood vessels [10]. It is clear that distant metastasis by the second route can be confirmed only in patients who do not exhibit positive neck nodes. This type of DMs was found in only 4 patients in our series. We can consider that the lymphatic system is the common route of access to the venous system for systemic dissemination. Our findings are consistent with this hypothesis. It has been suggested that measurement of DNA content in oral carcinomas may be useful in predicting of lymph node metastasis and perhaps risk of distant metastasis, because higher DNA content was associated with greater lymph node metastasis [11]. As locoregional control of head and neck squamous cell carcinomas seems to have reached a plateau, further effort should be directed to prevent distant metastasis with systemic therapy in a high-risk group of patients.

CONCLUSIONS

Neck metastasis act as a clinically readily available predictor and are intimately and directly related to the possibility of distant metastasis in head and neck squamous cell carcinomas patients. Eradication of micrometastasis is crucial for improvement of survival, especially for patients with nodal disease. We believe that patients with a high risk of lymph node metastasis should undergo prophylactic neck dissection followed by locoregional radiation therapy, if histopathologic evidence of nodal metastasis is obtained.

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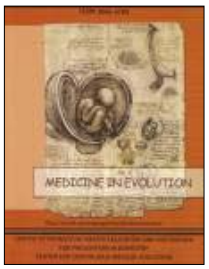
ANTIAGREGANT PLATELET TREATMENT – BENEFITS / RISKS



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ABSTRACT

This article brings proof regarding the benefits of antiplatelet therapy which definitely exceed the risk of haemorrhagic complications in a certain category of patients' with different clinical manifestations of cardiovascular conditions.

The association of certain risk factors (age over 60, smoking, the presence of Helicobacter Pylori) increases the rate of side effects, especially gastrointestinal ones, after the administration of antiplatelet medication.

***Key words**: platelet antiagregants; aspirin, clopidogrel; Helicobacter Pylori, gastrointestinal complications; major cardiovascular events*

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INTRODUCTION

The role of aspirin and in general that of antiplatelet agents in the treatment and prevention of atherothrombosis has been revised several times. There are over 300 studies of secondary prevention that provide updated information about the efficiency and safety of antiplatelet treatment.

The purpose of this paper is to integrate an understanding of the action of certain drugs into a definition based on proofs of patient categories to which the benefits of the antiplatelet therapy definitely exceed the risk of haemorrhagic complications.

MATERIAL AND METHODS

This study comprises a number of 526 patients observed on age groups (25-40 years old, 40-60 years old, over 60 years old) during January 2006 August 2008. The effects of certain antiplatelet drugs have been investigated in this study (aspirin and clopidogrel) on certain conditions of cardiovascular pathology, envisaging primary and secondary prevention aspects. For the elaboration of this paper I have taken into consideration my personal experience as a board certified physician in internal diseases with competence in digestive endoscopy, as well as a rich bibliographic material. The study comprises the clinical observation, EKG and periodic biological and investigation of patients. Biologically, the patients have been monitored by observing the coagulation tests and haemostasis (bleeding time, no. of thrombocytes, etc.) as well as the periodic superior digestive endoscopy every 6 months, highlighting the gastro-duodenal lesion secondary to therapy (superficial oesophagus, gastric and, less often, duodenal erosions, mucous petechia, asymptomatic and symptomtic ulcerations, and even the presence of digestive superior haemorrhage).

When the superior digestive endoscopy was performed, antral mucous biopsy was also performed to identify Helicobacter Pylori.

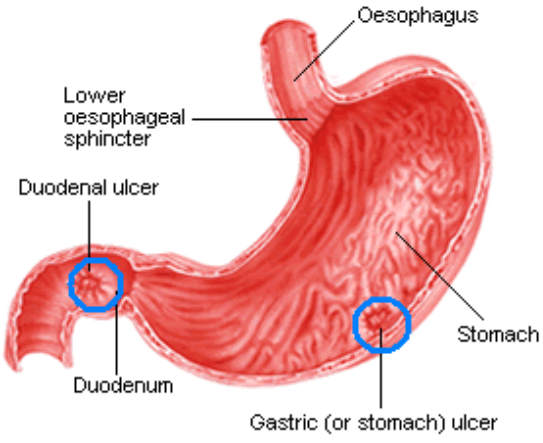

Fig 1. The stomach anatomy and the ulcer localisation.

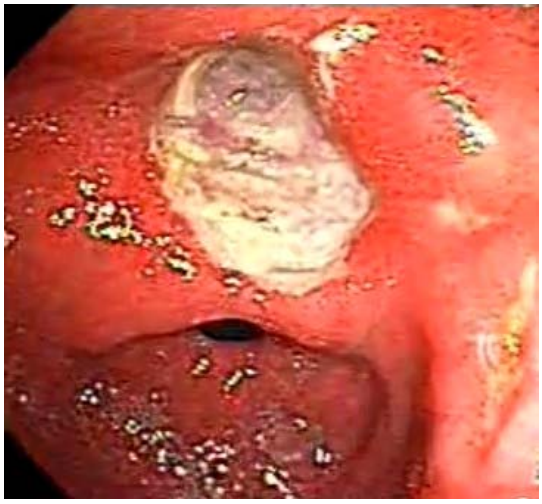

Fig 2. Endoscopic video image post-treatment with aspirin.

Table 1: The repartition of patients on age groups and factors that foster the appearance of side effects (smoking and the presence of Helicobacter Pylori

CV conditions		Drug	Erosive Esophagitis	Erosive Gastro-Duodenitis	Gastric Ulcer	
Stabilized Effort Angor	76 patients	Aspirin	1 (0.19%)	1 (0.19%)	-	-
		Clopidogrel	-	-	-	1case HDS, 1 case EVM
Atrial Fibrillation	100 patients	Aspirin	1 (0.19%)	5 (0.95%)	4 (0.76%)	2cases HDS, 1 case EVM
		Clopidogrel	-	-	-	-
Peripheral Arteriopathy	50 patients	Aspirin	-	7 (1.33%)	4 (0.76%)	2cases HDS, 2 cases EVM
		Clopidogrel	-	-	-	-
Unstable Angina	70 patients	Aspirin	-	-	-	-
		Clopidogrel	3 (0.57%)	6 (1.14%)	4 (0.76%)	2cases HDS, 2 cases EVM
HTA	155 patients	Aspirin	2 (0.38%)	22 (4.18%)	4 (0.76%)	3 cases HDS
		Clopidogrel	-	-	-	-
Old Myocardial Infarction	75 patients	Aspirin	4 (0.76%)	8 (1.54%)	4 (0.76%)	1case HDS, 1 case EVM
		Clopidogrel	1 (0.19%)	2(0.38%)	2(0.38%)	1case HDS

Table 2: Side effects of the antiplatelet treatment and treatment efficiency of by quantifying possible major vascular events

CV conditions		Drug	25-40	40-60	>60	M	F	Smokers	Non-smokers	Positive	Negative
Stabilized Effort Angor	76 patients	Aspirin	15	25	36	46	30	40	36	35	42
		Clopidogrel	-	-	-	-	-	-	-	-	-
Atrial Fibrillation	100 patients	Aspirin	5	40	55	60	40	55	45	30	70
		Clopidogrel	-	-	-	-	-	-	-	-	-
Peripheral Arteriopathy	50 patients	Aspirin	-	2	48	35	15	45	5	5	45
		Clopidogrel	-	-	-	-	-	-	-	-	-
Unstable Angina	70 patients	Aspirin	-	-	-	-	-	-	-	-	-
		Clopidogrel	-	29	41	52	18	40	30	30	40
HTA	155 patients	Aspirin	2	45	88	97	58	95	60	50	105
		Clopidogrel	-	-	-	-	-	-	-	-	-
Old Myocardial Infarction	75 patients	Aspirin	-	20	45	55	10	40	25	25	40
		Clopidogrel	-	10	-	8	2	9	1	2	8

RESULTS

The two tables presented below (table 1 and 2) show, for the cardiovascular conditions under discussion, both the direct and indirect benefit of the treatment through the appearance or non-appearance of major cardiovascular events, and also the risks of the antiplatelet therapy administered, by outlining complications and side effects, especially hemorrhagic ones in some of the patients (results comparable with [5]). Thus, 155 patients with arterial

hypertension were monitored, in fact primary prophylaxis with aspirin being under scrutiny. The majority of patients are around 60 years old and over, most of them being male and smokers. It can be noticed from the table that the risk of atherothrombosis in these patients is relatively low but there is a high risk of complications (esophagitis, erosive gastroduodenitis, gastric ulcer and even 3 cases of superior digestive haemorrhage). Thus, the benefit-risk ratio for this category of patients is not conclusive. The 76 patients with stabilized effort angor, most of whom male and smokers had few secondary gastro intestinal manifestations at the clinical monitoring and only one case of superior digestive haemorrhage, as well as only one major vascular event during the monitored period. The 100 patients with chronic atrial fibrillation, most of whom 60 years old and over, male and smokers, had a relatively small number of side effects and 2 cases of superior digestive haemorrhage and only one major vascular event. 50 patients with peripheral arteriopathy were monitored, most of whom over 60 years old, male and smokers, the side effects of the antiplatelet therapy being relatively more numerous, 4 cases of gastric ulcer and 2 cases of digestive haemorrhage, but also two major vascular events.

Table 3: The benefit/risk ratio of the antiplatelet prophylaxis with aspirin in different clinical situations

CLINICAL SITUATION	Benefit (no. of patients for whom a major vascular event is avoided	Risk (no. of patients to whom a major gastrointestinal event is caused per 1000/year)	
Men with cardiovas cular risk from low to high	1 –2	1 –2	The benefits and the risks are similar
HTA	1–2	1–2	
Stable chronic angina	10	1 –2	The benefits do not exceed the risks significantly
Myocardi al heart attack history	20	1 –2	
Unstable angina	50	1 –2	

The 70 patients with unstable angina were treated with clopidogrel, most of whom over 60 years old, male and smokers, with relatively frequent side effects: gastro-duodenitis, gastric ulcers and 2 cases of superior digestive haemorrhage, but also 2 major vascular events. The lot of 75 patients with old myocardial heart attack, treated with aspirin 75mg/day or clopidogrel 75mg /day presents differences: the ones treated with clopidogrel presented slightly more side effects for a relatively small lot of patients without major vascular events. Sometimes, even for small doses of aspirin gastric and/or duodenal ulcers may appear as side effects (shown also by [7] and [9]). Comparing the results obtained with the ones in table 3 (the benefit-risk ratio of the antiplatelet prophylaxis with aspirin in different clinical situations in the specialist literature [5]), they are similar, the exception being the number of major vascular events in unstable angina, where an improvement can be observed. Although for either the primary or secondary prophylaxis with aspirin or clopidogrel

small doses of 75mg/ day were used, the gastrointestinal haemorrhagic effects could not always be avoided due to the fact that these drugs also have antiplatelet effect apart from the one of direct irritation of the gastro-duodenal mucous. For this reason, the administration of tamponated concentrates or enteral release ones (see Aspenter, TromboAss) did not avoid completely the gastrointestinal side effects.

CONCLUSIONS

The benefits of therapy with aspirin and clopidogrel exceed the risks of haemorrhagic complications, especially gastrointestinal ones, in numerous clinical situations characterised by medium or high risk of vascular or occlusive events. In people with low cardiovascular risk the benefit/risk ratio of the antiplatelet therapy is not conclusive. The administration of aspirin and clopidogrel in minimum therapeutically efficient doses prevents major vascular events (myocardial heart attack, cerebral vascular accident, death by vascular cause) and has a small rate of side effects, especially gastrointestinal ones, that is why these platelet antiagregants must be used on a large scale for people who have predictable benefits.

The association of risk factors (age over 60 years old, smoking, the presence of Helicobacter Pylori) increases the rate of side effects, especially gastrointestinal ones, after the administration of antiplatelet medicine, sometimes wrong conclusions being taken regarding the side effects generated by them.

According to our study, clopidogrel has modestly better results if compared with aspirin; for this reason, its administration is not always justified taking into consideration especially the fact that this treatment is quite expensive. Of course, this will not prevent the administration of clopidogrel, alone or associated with aspirin, as indicated in the consecrated treatment protocols.

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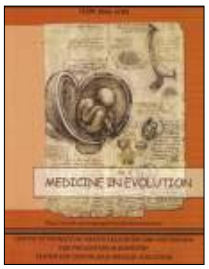
GIANT CELL BONE TUMORS - CLINICAL AND THERAPEUTIC ASPECTS



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ABSTRACT

Giant cell bone tumors (osteoclastoma, myeloplax tumor) are benign tumors, although they are locally aggressive. They represent between 5% and 7% of primary bone tumors. The most common occurrence sites are near joints (commonly the knee joint) involving the ends of long bones: proximal tibia, distal femur, distal radius. The onset age of the disease is between twenty and thirty years, with a slight predominance of the female gender. The diagnosis is based on clinical examination, X-rays of the bone, CT and MRI. Some authors suspected an angiogenetic origin of the tumor and another possible factor in the etiology is genetic predisposition. Giant cells arise by transformation of circulating monocytes, many of them later becoming active osteoclasts.

A rare complication of these tumors, but with high lethal potential, is the malignant transformation (primary and secondary malignancies). The best treatment is surgery, with or without area reconstruction. Another therapeutic method is cryosurgery. In the treatment of tumor metastasis (commonly occurring in the lungs), chemotherapy and surgery are indicated.

***Key words**: bone tumor, giant cells, locally aggressive, metastasis, circulating monocytes, surgery.*

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INTRODUCTION

Giant cell tumors of the bone (osteoclastoma, myeloplax tumor) are generally regarded as part of the benign neoplasia, although they are locally aggressive. They represent between 5% and 7 % of primary bone tumors and approximately 10% of primary malignant bone tumors [7, 10]. Sometimes, these tumors can metastasize, although this is not a common feature. Most often these metastases occur in the lung (1-9% of cases) [16]. There are data in the literature [16] reporting metastases in various places, such as mediastinal and para-aortic lymph-nodes, bones, skin and breasts. The most common occurrence sites of these bone tumors (over 80% of cases) are in the vicinity of joints of mature bones (75% of cases occur around the knee joint), involving the ends of long bones: proximal tibia, distal femur and distal radius [7, 10]. Increasingly rare localizations are the sacrum (10%) and spine (2-5%). Also, extremely rare is the multicenter giant cell bone tumor (less than 1% of cases) [7, 10]. The age of onset is between the second and third decades of life [10]. Some authors [7] increase this time period until the age of 55 years, with a peak incidence in the third decade of life. Regarding gender distribution, there is a slight predominance of females (1.2: 1 ratio) [7].

Clinical manifestations - the disease onset is insidious, with rheumatic type local pain that lasts between four and eight months. Functional impotence of the adjacent joint, local warmth, presence of collateral circulation and a significant joint effusion are also found. Pathological fractures may occur in advanced forms.

The origin of giant and stromal cells - The majority of giant cells are derived from macrophages and formed after repeated cell divisions, but unaccompanied by divisions of the cytoplasm, with the result of conformational and enzymatic changes. These processes require an increased telomerase activity and some gene rearrangements [15]. The cause of these divisions could be the exposure to some infectious agents and/or endogenous and exogenous foreign substances. Enzyme deficiency can lead to increased cell size by excessive, unprocessed endogenous substances accumulation. It seems that giant cells arise from the transformation of circulating monocytes, a majority of them subsequently becoming active osteoclasts [15]. The other predominant cell type in this kind of cancer, the stromal cells, seems to be activated fibroblasts. Stromal cells can release chemokines (e.g. macrophage chemoattractant protein 1 and IL 8) which can attract other monocytes in the tumor area, with subsequent transformation into mature osteoclasts [15]. Some authors suspected the angiogenic origin of tumor, with an important role of the Stromal Derived Factor 1 (SDF-1) which is a chemoatractant involved in attracting osteoclast precursors (monocytes) during tumor induced osteoclastogenesis. However, intraosseous hemorrhage caused by defective collagen in the matrix and /or in the vascular wall, locally brings new monocytes and plasma proteins. Activated stromal cells in the tumor facilitate tumor giant cell conversion into active osteoclasts. [15] Another likely factor in the etiology of these tumors is genetic predisposition. Among the characteristic changes in cancer (e.g. lack of telomere shortening, increased telomerase activity, karyotype aberrations) the increased telomerese activity and telomere fusion are more typical for giant cell bone tumors. Increased telomerase activity is not only a tumor specific factor, but it also

occurs in rapidly proliferating tissues (e.g. endometrium, epidermis, lymphocytes) and in a series of non-neoplastic bones diseases, such as: osteochondroma (exostosis) and hystiocitic fibrous reaction [15].

Disease diagnosis - The disgnosis of giant cell bone tumor is made through clinical examination combined with bone radiography, although in some cases, computed tomography (CT) and magnetic resonance imaging (MRI) may be necessary. The diagnosis is easily made for typical sites and ages. However, there are difficulties in the preoperative diagnosis of tumors occuring in unusual locations and in advanced ages [12]. Mc Carthy EF and KL Weber [8] showed that tumors occuring in elderly patients (62-78 years) have an identical behavior with typical disease, occurring in young people. For a confirmed diagnosis, the anatomopathological examination is necessary. The samples are obtained by tumor biopsy.

Macroscopic examination shows a reddish brown soft tumoral tissue, with internal foci of bleeding and necrobiosis. Also, there is cortical thinning or cortichal bone destruction and peritumoral bone lysis.

Microscopic examination shows predominantly small tall mononucleate and stromal cells with a poor cytoplasm. In the case of aggressive tumors, an increase in the number of stromal cells occurs, with different locations, accompanied by nucleotides and plasma monstrosities. Vasculature is rich, with numerous neoformation capillaries, vascular ectasia and hemorrhagic areas, and with hemosiderin deposits. Sometimes necrobiosis areas are found. The presence of high vascularization almost always indicates an evolution stage of giant cell tumor of the bone.

The differential diagnosis is made with:

- kidney and thyroid carcinoma metastasis
- hemophilic pseudo tumor, with hemorrhage
- large osteo-articular hydatid cyst
- telangiectatic osteosarcoma
- brown tumor in hyperparathyroidism
- pigmented villonodular synovitis – PVNS (in the elderly)

Staging giant cells tumors of the bone is based on tumor grade (G), their location (T) and on the presence or absence of metastasis (M). Using these elements, Enneking WF (1986) classified these tumors into three stages [5]. Stage I, with 2 forms - IA and IB (G1T1M0 and G1T2M0) is characterized by low tumor grade, intra-compartmental location, without metastases and low tumor grade, extra-compartmental location, without metastases, respectively. Stage II, also with two forms - II A and II B (G2T1M0 and G2 T2 M0) is characterrized by increased tumor grade, intra-compartmental location, without metastases, and increased tumor grade, extra-compartmental location, without metastases, respectively. Stage III, with metastasis, also with two forms - III A and III B (IIIA - G1T1M1 or G2T1M1 and III B - G1T2M1 or G2T2M1) is characterized by a low or high tumor grade, intra-compartmental location, with metastases and low or high tumor grade, extra-compartmental location, with metastasis, respectively. S. Viswanathan et al. (2010) conducted an extensive research over 20 years to see whether there is an association between clinical and histological parameters of giant cells tumors of the bone and their tendency to metastasize, although these tumors have a low percentage of metastases [16]. The average age of the 24 patients in the study was 26 years (within 16 and 76 years - age limits), and in terms of the ratio between the two genders, it was slightly tilted towards males (male / female ratio - 1.6 / 1). After making the initial diagnosis of giant cell bone tumor, metastases occurred

after a median period of 2 years (between 4 months and 11 years), the most common location was the lung, in agreement with existing literature data [16]. It is worth mentioning that none of the patients with metastases died during the study. Following this study no relationship between clinical and histopathological parameters and the occurrence of metastases was revealed. Another conclusion was that metastasectomy (whenever possible) is recommended, despite the generally positive evolution of these metastases [16]. A rare complication of these tumors is malignant evolution (1.8%), which may be primary (very rare) or secondary, after radiotherapy and/or surgery [2]. Primary malignancy is a lesion with a high degree of sarcomatous growth areas, with synchronous development of the tumor, situated near the benign giant cell bone tumor. Secondary malignancy is a developing high-grade sarcomatous process superimposed to a benign giant cell tumor of the bone, previously treated either by surgery (progressive form) or by radiotherapy (radiation-induced form) [2]. Frequent locations of these malignancies are the long bones near the knee (usually, distal femur), and the dominant symptoms are pain (80% of cases) and local swelling (40-45%) [2]. The differentiation between the two forms of malignant bone tumor and between the two subtypes of secondary malignancy is difficult. However, patients with primary malignant bone tumors have a more advanced average age, and patients with secondary malignancy, have more prominent radiological aspects of malignancy. Basically, these malignancies are high-grade sarcomas, such as osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma (MFH). The secondary malignancy time to onset is variable: between 1.8 and 36 years - post surgery and between 4 and 42 years, post radiotherapy [2]. Benign recurrence of giant cell tumors of the bone may occur after long latency periods, but most of them appear within two years after the initial treatment. Suspicion of secondary malignancy should be considered when tumors initially treated with surgery or radiotherapy has recurrences more than 3 years after the diagnosis [2].

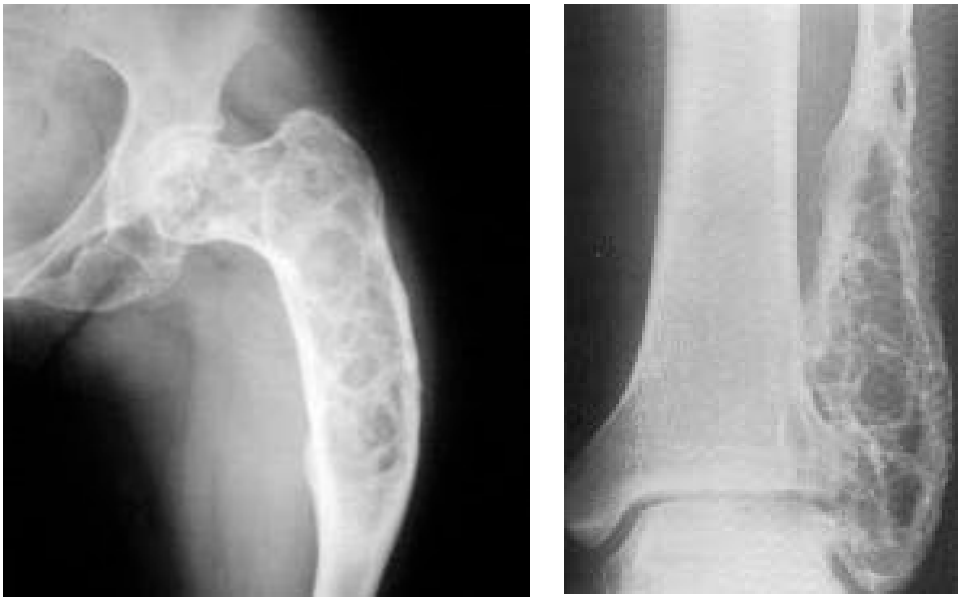

Fig.1. Radiological aspects of giant cell bone tumors.

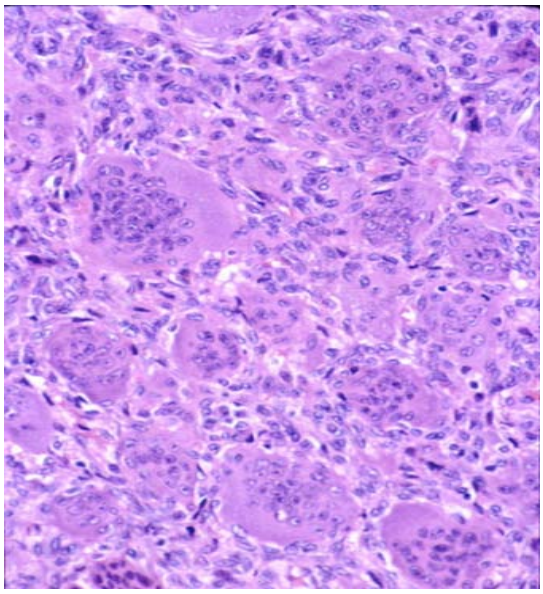

Fig.2. Typical histological aspect of giant cells tumors of the bone (hematoxylin-eosin stain).

TREATMENT

The best treatment for these tumors is surgery, followed or not by area reconstruction (wide resection, curettage without cement, curettage with cementation, bone grafting, total hip arthroplasty, bipolar hip arthroplasty). [10] Another treatment successfully used in this condition is cryosurgery, with benefits like lower local recurrence rate, compared with curettage alone and without any risk of malignancy (sarcomatous transformation) [7]. Cryosurgery consists of liquid nitrogen (-196 ^{o}C) insertion into the tumor cavity. To avoid thermal damage to the surrounding soft tissues, these are irrigated with saline solution at normal temperature. Two cycles of freezing and thawing are needed for treatment, each with 1-2 minutes duration; spontaneous thawing is expected after 3-5 minutes. After nitrogen evaporation, the tumor cavity is irrigated with normal saline solution and hemostasis is performed [7]. Sometimes, phenol may be used in combination with surgery and bone cementation. When treatment is correctly done it reduces the resection and amputation indications. Local recurrence rate after surgery is 15-26%. It was found that this rate is higher (27-41%) after intralesional curettage than after wide excision (0-7%) [10]. The best tumor treatment for stage III is wide resection. Multiple and asymptomatic lesions may remain locally stationary or even spontaneously regress without treatment. In the treatment of giant cell bone tumors, chemotherapy and surgical treatment of metastases is indicated. Radiotherapy, according to data from the literature, is questionable, with a sarcomatous transformation risk, particularly in symptomatic and unresectable lung metastases [6]. For metastases, the most appropriate therapy is metastasectomy (in the cases with lung metastases - splicing resection, lobectomy - to prevent progressive pulmonary dysfunction) [14]. It has been proven that the disease *prognosis* depends not on histological (Jaffe et al. cited by Ng ES, Saw A. et al.) [8] and radiological grading [3], the only predictor being the

appropriate tumor resection. The evolution is unfavorable in case of tumor malignant transformation with a slightly better prognosis for primary malignancies [9], so early diagnosis is very important, in order to ensure appropriate intervention by surgery and / or chemotherapy [2].

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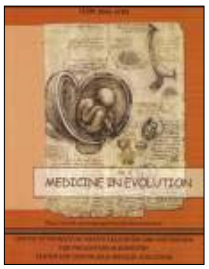
DENTAL DEVELOPMENT IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA – CASE REPORT



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ABSTRACT

Background. *Acute lymphoblastic leukemia is defined as a clonal proliferation of the lymphoid cells with the stop of the development of normal hematopoiesis, having as result anemy, trombocytopenia and leukemic infiltrations that lead to the patient's death if no effective curative treatment is administered. Chemotherapy and radiotherapy, as treatment methods in the pediatric oncology, interfere with the processes of tooth formation and maturation (odontogenesis). Odontogenesis starts in the first weeks of intrauterine life and continues until around the age of 14-15 years.*

Case report. *The paper presents the clinical case of a boy aged 10 and a half years diagnosed with acute lymphoblastic leukemia from the age of two with multiple complications and CNS relapse. The patient followed the cytostatic treatment according to protocol ALL-BFM-95, ALL-REZ-95 and therapeutic cranial irradiation. The clinical examination of the mouth emphasised several anomalies of dental development and problems of tooth erruption.*

Conclusion. *The clinical case presents a peculiar interest because the the cytostatic curative treatment and the cranial irradiation extended over a long time span, in which in the child's life the process of odontogenesis finished.*

Key words: *children leukemia, dental development, chemotherapy, radiotherapy.*

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INTRODUCTION

The acute lymphoblastic leukemia (ALL) is a severe hematological condition determined by the uncontrolled spread in the bone marrow of malignant and immature cells called lymphoblasts, forerunners of lymphocytes [5]. Leukemias are the most frequent forms of neoplasias in children, in Romania they constitute a percentage of 45% from the malignant conditions in the child under 16 years of age: a percentage of 25% corresponds to the acute lymphoblastic lekemia, a percentage of 15 % to the acute myeloblastic leukemia, while the chronic myelocitic represents 5 % from the total cases of leukemia in children [9,10]. The incidence of the acute lymphoblastic leukemia on a world-wide level is considered to be at 1:25000 children/year with a top at the age of 4, 85% of cases being diagnosed between the age of 2 and 10, when the processes of development, maturation and mineralisation of the dental formations is at the height of its activity. The physiological process of odontogenesis starts in the first weeks of intrauterine life and continues until the age of 14-15. The effective curative treatment of acute lymphoblastic leukemia in children, through chemotherapy and radiotherapy, overlaps with the important stages in odonotgenesis [4]. The aim of this paper is to emphasise the anomlaies of dental development in a child in the phase of mixed dentition, with acute lymphoblastic leukemia, over a time span of eight years from the diagnosis of the neoplasia and from the start of the specific therapy. The peculiarities of the clinical case presented are related to the interference of specific protocols of chemotherapy and radiotherapy with the physiological processes of odontogenesis over a very long period and to the fact that in this time span, from the diagnosis of acute lymphoblastic leukemia (2 years) until the moment of appreciating the evolution of dentition (10,5 years), the development and mineralisation of an important number of dental germs was done.

CASE REPORT

We report the case of a boy aged 10, 5 who was examined in the Integrated Centre of Dental Medicine of the University of Medicine and Pharmacy Tg. Mures, he being sent for investigations and stomatological treatment by the physician from the Hemato-Oncopediatrics of the Pediatrics Clinic I Tg. Mures.

History: The male child, coming from the rural environment, is investtigated at age 2 years and 4 months in Pediatrics Clinic I Tg. Mures, the discharge reason being the joint and bone pains that started approximately two months before, the fever for two weeks, and also adynamics. Based on the hematological picture and the peripheral smear, the examination of bone marrow and the immunephenotypical examination through cytometrics in flow supposes the identification with specific antibodies of certain proteins present on the surface of the lymphoblasts or in their cytoplasm, the patient was ***dignosed*** with acute lymphoblastic leukemia with B cells. The laboratory data are given in tables 1 and 2, the morphological aspect of the lymphoblasts (lymphoblasts L1) in picture 1, and the immunophenotypical profile of the lymphoblasts determined through in flow cytometry is given in picture 2.

Table 1.

Hgb	**Htc**	**Leucocytes**	**Neutrofiles**	**Trombocytes**	**VSH**	**PCR**	**LDH**
7,5 g/dl	22,5%	4500/mm	400/mm	120000/mm	60/1 h	pozitive	527 U/ l

Table 2.

Peripheral smear: atypical lymphocytes 9%	**Examenation of bone marrow:** 74% cells with aspect of lymphoblasts	**Immunophenotyping from the bone marrow:** ALL with pre B cells

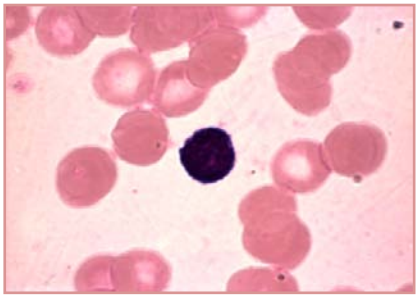

Fig.1. Lymphoblast L1 in the peripheral blood

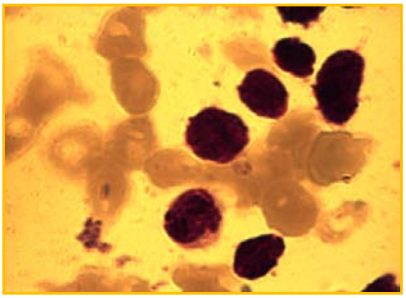

Fig.2. Bone marrow infiltrated with pre B lymphoblasts

We start the **cytostatic treatment** according to protocole ALL-BFM-95. After 1 year and 4 months we start the mainatenance treatment, but under this medication the patient presents the first isolated relapse in CNS for which he follows treatmnent according to protocole ALL-REZ-95 and therapeutical **cranial irradiation.** After a time span of 2,5 years he presents the second systemic relapse that was treated according to this protocole, and after other 3 months presents the third CNS relapse. The cytostatic treatment is stopped due to the severe hepatotoxicity: the patient developed hepatic cyrrhosis, oesophagian varices of degree II that were ligatured, portal hypertention and hypersplenism, at the moment he is on palliative treatment.

Upon **clinical examination of the mouth** we noticed: insufficient oral hygiene and the presence of generalised gingival inflamations; mixed dentition phase II with tooth replacement in the support areas, the presence of temporary molars 54, 64, 65, 75, 84, 85; physiological mobility of temporary molars 54 and 64 affected by the radicular resorption; the presence of permanent inferior canines and the eruption in progress of the superior canines; the first permanent molars are present, the incisive replacement is finished; the microdontion of 34; the presence of certain problems of the eruption order: the right superior canine errupted before the first premolar, and the left superior canine errupted before premolars I and II; the precocious erruption of 23 and 33 before the age of physiological replacement; complicated caries and important coronary distruction at incisive 22 as well as the presence of other eight simple carious lesions. The radiological examination on orthopantomogram also indicated other anomalies of dental development: the agenesis of second premolars 35 and 15, the microdontion of the first four premolars, the presence of certain thin, well built and short roots at the level of the all the permanent first molars, the lack of wisdom teeth (picture 3).

The complex parodontal, pedodontical, ethiological **diagnosis** is synthesised in table 3. The patience benefited from the treatment of simple carious lesions, endodontic treatment, radicular opturation and physionomical restauration in the left side incisive, of training regarding the mouth hygiene and its importance, of professional brushing.

Table 3. Complex oral diagnosis

PARODONTAL DIAGNOSIS • Chronical Gingivitis induced by the microbian dental plaque
PEDODONTIC DIAGNOSIS • Multiple carious lesions, simple and complicated, untreated • Microdontion of first premolars • Agenesis of second premolars • Insufficiency of radicular development of the permanent first molars • The troubling of erruption order • Precocious erruptions
ETIOLOGICAL FACTORS • Chemotherapy • Radiotherapy • Bacterial dental plaque

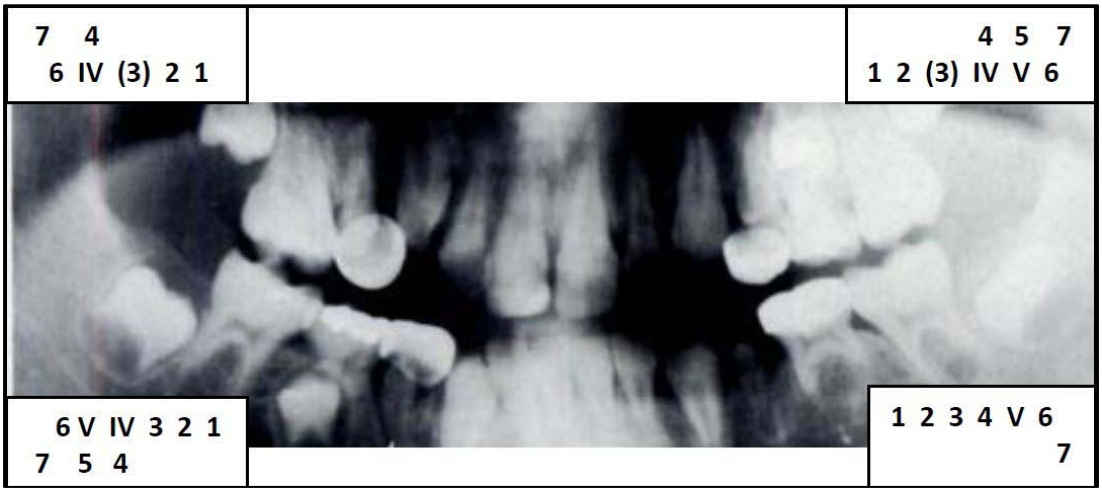

Fig.3. Boy aged 10 with acute lymphoblastic leukemia: dental formula and orthopantomogram.

DISCUSSIONS

The mineralisation (calcifiation, dental maturation) represents a complex process that is performed over a long period of time and includes a series of important stages that each dental bud experiences in its evolution. Vasconcelos and coop. [13] indicated the fact that there would be eight distinct development stages and they appreciated the drgree of dental maturation on a cohort of 92 children with acute lymphoblastic leukemia, who fo-

llowed a curative treatment according to protocole ALL-BFM-95, through comparing the chronological age of the children included in the study with the dental age, appreciated according to the stage of teeth development. The authors noticed that there are significant inconsistencies between the chronological ages and the dental ages as indicators of dental maturation, in children who followed the cytostatic medication and radiotherapy. The presentation of our clinical case emphasised the fact that the child's chronological age does not coincide with his or her dental age, as there are severe problems of erruption order as well as the precocoius erruption. The cytostatic treatment and the therapeutical cranial irradiation interfered with the processes of radicular building of the temporary teeth from the support zones (canines, first molars and temporary second molars), so that the roots of these teeth presented stressed resorption, before the physiological age. The consequences consisted in premature losses of these teeth and precocious erruption of the permanent replacement teeth.

Minicucci and coop. appreciated the frequency of dental anomalies on a cohort of 76 children with acute lymphoblastic leukemia who followed specific chemotherapy with or without cranial radiotherapy [8]. Of all the 76 children, 13 didn't present any anomaly of dental development, but 8 of them were only at the formation age of dental germs; the rest of 82,9 % presented at least one dental anomaly. The most frequent anomalies diagnosed in this study were hypolasias, microdontion and late erruption. The patient described by us presented microdontion in all the four first premolars and stressed erruption of the permanent teeth due to the premature loss of successional temporary teeth. The radiosensitivity of teeth in formation was also proved by other authors [3, 6, 12] who showed that the nature and effects of the potential negative effects of therapeutical irradiation upon dental development varies according to the child's age at the moment of diagnosis with acute leukemia and start of the specific therapy, the stage of tooth development, the treatment protocole and the irradiated anatomical region. The secondary effects of radiotherapy upon the dental buds in formation, including upon the processes of amelogenesis and dentinogenesis, are represented by the destruction of the dental bud, the block of the erruption potential of the tooth, troubles of mineralisations (hypoplasias), insufficient coronary or radicular development, radicular agenesis, the occurence of short, well built and dull [7].

In the present case, the formation of the first and second premolars started around the age of 2, life stage that coincided with the diagnosis of the acute lymphoblastic leukemia pre B and with the establishment of the cytostatic treatment according to protocole ALL-BFM-95. Practically the whole process of mineralisation and development of first and second premolars interfered with the cytostatic medication and the therapeutical cranial irradiation. The influence of the cytostatic treatment and radiotherapy upon odontogenesis manifested through the insufficient development of all the first premolars (microdontion) as well as the lack of development of the second premolar buds 15 and 35 (agenesis). The erruption of the first molars in the mouth started at age 6, and their radicular building continued posterruptively until the age of 10, what explains the presence of well built, thin and short roots of these.

Another important aspect is the high number of simple and complicated carious lesions present in this child aged 10: the alteration of dental structures in the formative phases of the odontogenesis explains the increased

tendency towards the carious incidence. The dental structures formed in parallel with the specific mediation are very vulnerable towards the cariogene attack, to this aspect also contributes the extremely poor oral hygiene, very frequently met in children with leukemic affections [1,2,11]. Due to the high risk of bleeding (trombocytopenia), the children avoid the dental brushing what determines accumulation of bacterial plaque and gingival inflamation, etiological factors accused in the occurence of carious lesions and the chronical gingivitis.

CONCLUSIONS

The clinical case presents a particular interest because the curative cytostatic treatment and the cranial irradiation extended on a long time span, while the stages of odontogenesis were fulfilled in the child's life. The multidisciplinary approach of the child with acute lymphoblastic leukemia implies a team formed from a pediatrician oncologist, pathologist, hematologist, radiologist, pediatrician dentist, surgeon, nutritionist and psychologist for the growth of life's quality and the prevention of these children's suffering. From the point of view of pediatrician dentistry, this case proves on the one hand the need to monitor the children with leukemic conditions under cytostatic treatment and radiotherapy, especially the ones undegoing long term treatment, with the aim of improving the state of orodental health, and on the other, emphasises the impact of the curative treatment upon the processes of dental development and mineralisation.

Acknowledgments

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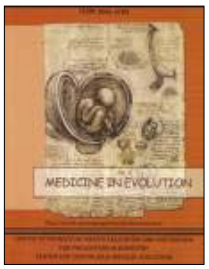
CLINICAL AND BIOMECHANICAL ASPECTS IN ADULT LINGUAL ORTHODONTICS



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ABSTRACT

Adult treatment is considered one of the most challenging parts in contemporary orthodontics. These patients are highly motivated and show excellent compliance to doctor's instructions. The demand for orthodontic treatment in adults had led to a higher need for esthetic appliances. Therefore, the introduction of lingual appliances in the world of orthodontic appliances has provided the ultimate in aesthetics. This article attempts to review the current clinical and biomechanical principles of lingual orthodontics.

***Key words**: lingual orthodontics, adult treatment, biomechanics.*

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INTRODUCTION

The decision of adult patients to undertake orthodontic treatment is a more complex matter than in younger group, as they are influenced by their professional and social activities [1,2,3]. The introduction of lingual orthodontics in clinical therapy has revolutionnised the clinical aspects in orthodontics. Since its introduction more than 30 years ago, a lot of work has been done in order to improve the technology and clinical aspects of lingual orthodontics. Nowadays, lingual appliances are available from many producers, in standard sets of brackets and wires, or in more recent customised devices. Among problems that are associated with lingual appliances are bracket debonding, difficulties in correct positioning and patient discomfort [4,5,6]. Therefore, and of course as a result of increased time and effort required, not all the orthodontist are routinely using this technique in their offices. Case selection is very important in lingual orthodontics. Theoretically, this technique can be applied in the treatment of all types of malocclusion. The results can be fast achieved in ideal cases like deep bite, low angle, medium crowding. Difficulties can be seen in patients with high angle, open bite, in surgical cases or in patients with short clinical crowns [7,8]. Previous difficulties had been eliminated by the ultimate technology in orthodontics and engineering, which has lead to the development of a totally customized treatment. The Incognito customized orthodontic appliance offers a modern alternative through CAD-CAM technology that improves bracket positioning, the predictability of results and patient comfort [9].

Aim

The objective of this study was to evaluate the clinical and biomechanical effectiveness of lingual orthodontic appliances in adult patients.

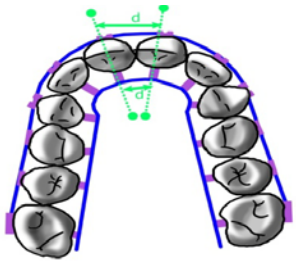


Fig. 1. Interbracket distance is lower in lingual than in labial technique (4).

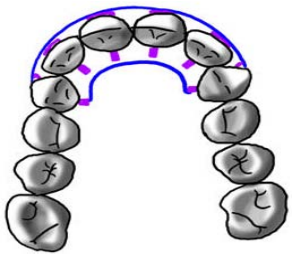


Fig. 2. The arch dimension is shorter in lingual technique (4).

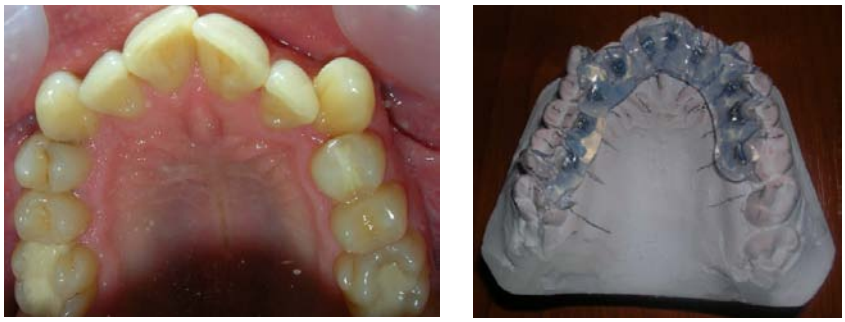
Comparative biomechanical aspects between labial and lingual orthodontics

It is a general rule that anchorage values are better for lingual treatment than in labial one. As brackets are placed on the lingual surfaces of the teeth, it makes easier to control the vertical height of molars through the application of labial root torque, which tips molars lingually. The vertical dimension in lingual orthodontics is dictated by the intrusive forces that are applied on the frontal area and by the disoclussion in the posterior zone. In sagital direction, during "en masse" phase of retraction, force should be minimized in order to prevent the bowing effect and a control of a palatal torque is required. The interbracket distance is lower in lingual than in labial technique (fig.1) and the dimension of the arch is lower (fig.2), which means that the archwire stiffness is also increased. In crowded cases, a lighter archwire sho-

uld be used, and the correction of rotations will be more difficult to achieve. The distalization of maxillary molars can be done with more translation than tipping movements, since the lingual brackets are situated closer to the molar center of resistance.

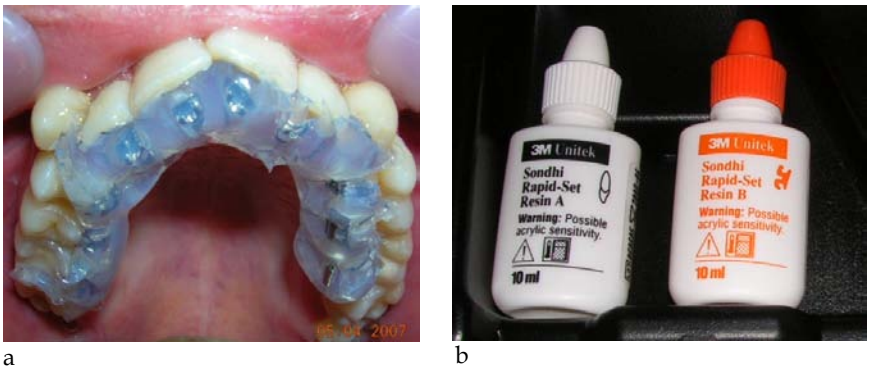
Case 1

This 25 years old patient was reffered to the orthodontist by the general dentist in order to solve the lack of space and to align the blocked out upper canines. Due to the professional esthetic demands of this patient, labial appliances were not considered, and the orthodontist started the treatment with lingual brackets. The system chosen was STB (Ormco), which has high clinical efficiency and can be successfully used in nonextraction cases. The indirect technique was used for bracket positioning and bonding. The Memosil silicone and a vacuum formed tray were used in order to apply the brackets on the lingual surface of the teeth. The bonding agent was Sondhi Rapid Set (3M).



a b

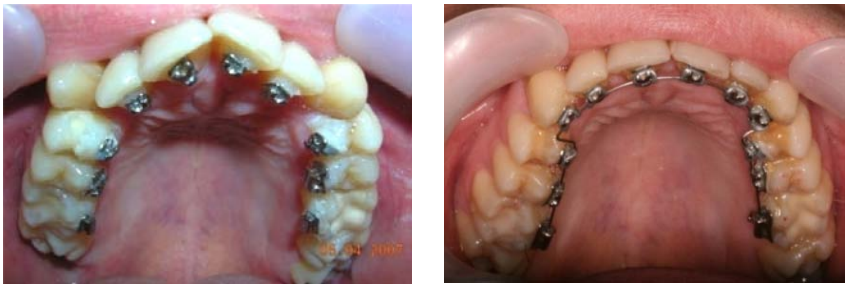
Fig.3. 25years old male patient with severe crowding and blocked out canines.a-initial situation, before bonding. b – Model positioning and the Memosil preparation for indirect bonding.



a b

Fig.4. Previous case.a – Indirect bracket positioning after removal of vaccum formed tray. b – the Sondhi adhesive system.

After the indirect bonding of STB system, a 0.012" NiTi lingual archwire was inserted in order to initiate the alignment phase. The normal archwire sequence has followed, and 11 months later, the upper arch was aligned. Lingual therapy has obvious advantages towards the labial technique in crowded cases, because it makes much easier to obtain expansion [3]. Therefore, in a borderline extraction/nonextractional case like this, lingual approach has made canine alignment much faster. It is possible that the shorter interbracket distance could play a role in this expansion effect.

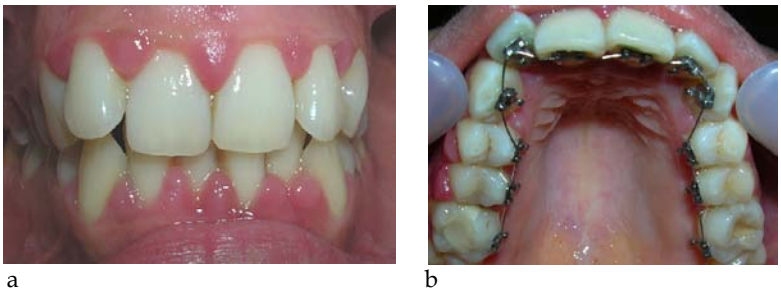


a b

Fig.5. a Start of treatment, before archwire insertion. b- results after 11 months of treatment.

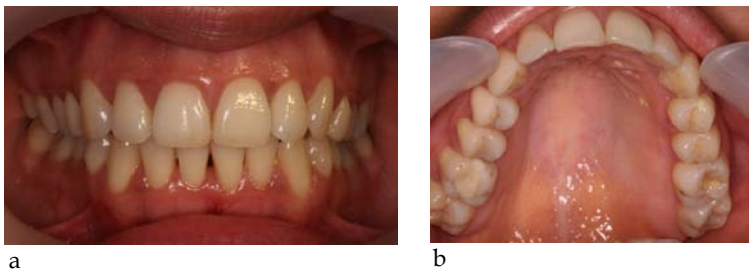
Case 2

This 24 years old female presented to the orthodontist with a moderate class II/2 malocclusion, upper and lower crowding and deep bite. The periodontal status was critical; therefore perio therapy was performed before the beginning of orthodontic therapy. In order to assure the patient comfort, the low profile 2D brackets from Forestadent and a progression of round NiTi wires were chosen. The 2D system is indicated for low to moderate types of malocclusion and cannot achieve complex movements as torque. Final result was achieved in 15 months and the retention recomended was permanent.



a b

Fig.6. 24 years old female patient, deep bite, upper and lower mild crowding, high esthetic demands. a – initial situation. b –start of orthodontic treament.



a b

Fig.7. Previous case. Final result.

CONCLUSION

Although lingual orthodontics requires special biomechanical knowledge, continuous training and good clinical skills, it has shown a high efficiency and represents an important part of the future in esthetic orthodontics.

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