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CURRICULUM VITAE

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CURRICULUM VITAE

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   - **1996-1999 -** PhD in Public Health, University of Medicine and Pharmacy, Carol Davila, Bucharest and Nuffield Institute for Health, University of Leeds, UK
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PRESENT POSITION

- Professor in Public Health and Health Services Management, University of Medicine and Pharmacy Victor Babes, Timisoara, Romania.

9. PROFESSIONAL AFILIATION

- Member of Guidelines International Network (GIN), Berlin, Germany, 2003-present
- Member of Fellow Policy Council of OSI Budapest - 2000
- Member of the Commission of Public Health of the Ministry of Health, 1997-present
- Member of Association Latine Pour L'Analyse Des Sistemes de Sante (ALASS), 1996-present ; Member of the ALASS Executive Council between 2002-2004
- Visiting Professor in Public Services and Health Policy, Wagner School for Public Services, New York University, 1994.
- Fellow in Health Policy, Salzburg Seminar, 1995

EDITORIAL BOARDS

- Member of the Editorial Board of the Romanian Health Services Management Journal, 1998 - present
- Member of the Editorial Board of the Ministry of Health Newsletter, 1997-1998.

- Scientific Adviser of the Romanian Edition of the British Medical Journal, 1998-1999

KEY QUALIFICATIONS:
- Health Policy and Planning
- Public Health
- Comparative Analysis of Health Systems
- Health Management
- Medical Sociology

12. EXPERIENCE RECORD (Selected)

A. EMPLOYMENT HISTORY
- President of the National Health Insurance House, Romania 2005 - 2007
- Executive President, Center for Health Policies and Services, 1999-2005
- Professor of Public Health and Management, Head of Department, University of Medicine and Pharmacy, Timisoara, 2002 - present
- Associate Professor in Health Policy and Health Services Management, University of Bucharest, Romania, 1996 - present
- General Director, Department for Health Programs, Reform and Accreditation, Ministry of Health, 1997-1998
- Senior Consultant in Public Health and Management, Institute of Health Services Management, Bucharest, Romania, 1991-1998

B. SPECIFIC CONSULTANT SERVICES

International
- Expert in Public Health and Health Policy Projects for WHO, Copenhagen, Denmark, 1997-2001
- Consultant for World-Bank on "Development of a Case Study on Output-Based Aid - Health Reform in Romania Project, 2001
- WHO Liaison Office Moldova, Consultant for the Moldavian Ministry of Health on the implementation of health insurance strategy, 2001
- Expert in Health Policy for the Council of Europe, Strasbourg, 1998 –2001
- Country Coordinator for the Overseas Development Institute (UK) funded Project "Health Policy in Developing Countries", 1996-1997
- Moldova – Adviser to the Ministry of Health, 1998 and 2001 Expert for Reform of the Moldova Health Care System

Local
- Supervisor for PhD students, since 2004
- Coordination of over 10 dissertation papers of students from undergraduate and postgraduate level
- Member of over 10 evaluation commissions for awarding different scientific degrees in public health and health management
- Adviser for the Romanian College of Physicians, 1999-2003
- Coordinator of several Opinion Surveys on the satisfaction of medical professionals with the Romanian health system reform, 1999 - 2002

- Health Policy Adviser to the Health Commission from the Romanian Parliament, 1998-2000
- Country Coordinator for the World Bank funded Project "National Strategy for Sectoral Reform of Romanian Health Care System", Jan.-June 1998
- Team Leader for the World Bank funded project "Financing the Romanian Health Care System", 1997-1998
- General Secretary of the National Council of Health Reform, 1997 – 1998
- Coordinator on behalf of the Ministry of Health of the Committee of the International Organizations Financiers of the Romanian Health Sector, 1997 - 1998
- Country Coordinator for the development of the PHARE funded Project "Romanian Health Care Strategy", 1997
- National Coordinator for the development of the White Paper of the Romanian Health Care Reform, 1997
- Project Coordinator for UNICEF Mission in Romania for the development of the "Global Policy on Child Care" Project, 1995-1997
- Consultant in TEMPUS program on curriculum development for the Department of Public Health and Health Management, Joint Project between the School of Public Health from Madrid, and University of Medicine, Bucharest, 1994-1996
- Expert in PHARE programme "Soutien Structurel pour les Services Socio-Sanitaires en Roumanie" 1994-1995
- Consultant on the World Bank Project of Decentralization of the Romanian Health System, 1992 -1994

C. RESEARCH PROGRAMMES/GRANTS

Director / Coordinator for national and international programmes

- **Development of the National Public Health Strategy, World Bank/Ministry of Health, 2004**
- **Analysis of the Reform of the Health Services in Romania, LGI Budapest, 2003 - 2004**
- "Channelling the Outrage" Project on support for signing the Framework Convention on tobacco control, WHO, Copenhagen, 2004
- **Reproductive Health in Romania - Romanian Ministry of Health/UNFPA/UNICEF/ USAID, 2004 - 2005**
- Mass media campaign on the promotion of voluntary and non-paid blood donation among the young population in Romania, H1O1A11 Global Fund to fight HIV/AIDS, Malaria and TB, 2004
- Training of family doctors and the medical staff involved in diagnosis, treatment and monitoring of Sexual Transmitted Diseasis (STD), in order to enhance the STD monitoring system, H 3102A13 Global Fund to fight HIV/AIDS, Malaria and TB, 2004
- Rising to the challenges of HIV/AIDS: a comprehensive, coordinated multi-sectored response in Romania, Promotion of the safe sexual behavior in the general population, especially 15-25 years old, regarding HIV/AIDS/STI's, H37O1A1Global Fund to fight HIV/AIDS, Malaria and TB, 2004
- Support for the Decentralization of the Health Services at the District Level, Humana Inc., USA/Ministry of Health Romania, 2003 – 2004

- Development of Evidence Based Guidelines, World Health Organization Copenhagen & OSI New York, 2003 – 2004
- Evaluation of the Health Status and the Access to Health Care of Rroma Population in Romania, Open Society Institute, New York, 2002 – 2003
- **Cervical Cancer screening - needs assessment and strategy, PO3/2003 JSI/ USAID, Romanian Family Health Initiative, 2003**
- The rights of Insured People in the Social Health System in Romania, EIDHR B7-700-102, European Community, European Initiative for Democracy and Human Rights, 2001
- Vocational Training of Romanian Students in Health Management, Health Administration, Health Financing and Public Health, RO/2001/PL87159/S/AS, European Community, Leonardo da Vinci/Mobility/Second Phase, 2001
- Information, Monitoring and Re-socialization Centre of the Marginalized Persons from Sector 2 of Bucharest, Access B7-300-098, European Community, Access – Micro Projects Scheme, B7-300, 2001
- Analysis of informal payments in health within the regional context, Harvard School of Public Health, 2001
- Formulation of a Regional Study on HIV/AIDS and the Rroma, 32/3001UNDP RER/01/001, 2001-2002
- **Information campaign regarding cervical cancer and the involvement of the NGO sector in raising the awareness of the population concerning important problems of public health RO0004.02.01/03-01, European Community, Phare, Development of Civil Society, 2000**
- Bridging services for Romania's underserved population, EuropeAid/ 113091/D/G /RO European Community, R0008 - Access Macro Projects Facility, 2000
- Medical Practice Management, RO.0007.02.01.02.0532, European Community, Phare, 2000
- Fighting against tabacco by rising awareness of the population on the pasive smoking and its effects on health, ONG2000-117, European Community, Phare, Development of Civil Society, 2000

Consultant/expert for national and international programmes

- Romanian-European eUniversity- RE2U, 100693-CP-1-2002-1-Ro-MINERVA-M, European Community, Socrates Programme -Minerva -Promotion of Open and Distance Learning - Information and Communication Tecnologies in the field of Education, 2002-2004
- „Asssesssment of the National Surveilance System for Infectious Diseases" Programme, WHO, 2001
- GRANT 149 CNFIS – Development of a Master Programme on Socio-medical Services, 1999-2001
- TEMPUS, JEP 12087/1997 Programme – European Social Policies, "Child welfare and antipoverty strategies", 1997
- TEMPUS C.M.E. Programme – O3022-97, "Development of a pilot distance learning programme", 1997
- TEMPUS JEP 7094. Programme "Development of public health and management training", 1997

- Romanian health system reform Project, World Bank, 1997-1998
- REPEDE Programme, Technical Assisteance for the Ministry of Health in the Fields of Decentralization, Financing Reform and Restructuring of Health Care Services in Romania, 1997

13. OTHERS (SELECTED PAPERS AND PUBLICATIONS)

Unpublished papers/presentations

Vladescu, C., *Decentralization of Health Systems; the Romanian case study*, Swiss Development Agency Meeting, October 12-14, 2005, Iasi**,** Romania

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Vladescu, C., *Reforma in asistenta primara din Romania*¸ Conferința internationala Reforma sistemelor de sănătate: actualităti şi perspective, O.M.S. si Schweitzer Institute, Sinaia,1-2 Sept. 1999.

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4. **Vladescu, C. (coord),** *Sisteme de Sanatate*, Ed.Exclus, Bucureşti, 2004
5. **Vladescu, C. (coord),** *Starea de sanatate si accesul populatiei Roma la serviciile sanitare din Romania***,** Ed. Exclus, Bucuresti 2003
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20. **Vladescu, C.** *Managementul Serviciilor de Sănătate* (Health Services Management), Ed. Expert, Bucureşti, 2000
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25. **Vladescu, C.** Politici de Sanatate in Romania dupa 1989: continut, proces, actori (Policy and Politics in the Romanian Health Care Sector after 1989), in "*Romanian Social Policy after 1989"*, coord. C. Zamfir, ed. Expert, Bucuresti, 1998.
26. **Vladescu, C.** The Role of the Government in the new Social Health Insurance System in Romania *in Health Policy in Central and Eastern European Countries*, eds. Zarcovic, G, and Enachescu, D, ed. Infomedica, Bucharest 1998.
27. **Vladescu, C.** Characteristics of the Law on Social Health Insurance in Romania in *Recent Evolutions and Perspectives of the Health System in Romania*, coord. Enăchescu, D., Editura Universitară Carol Davila, Bucureşti , 1998
28. **Vladescu, C.** Health Policy for Mother and Child in *Advocacy for a Child Centred Society*, cord. Catalin Zamfir, ed. Alternative, Bucuresti, 1997.
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30. **Vladescu, C.,** Politici sociale de sanatate (Social Policies for Health), in *Politici sociale. Romania in context european* (Social Policies. Romania in European Context), coord. Elena si Catalin Zamfir, ed. Alternative, Bucuresti, 1995.

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1. **Vladescu, C.,** Scîntee, S.G (2006), Recent issues of the Romanian health financing system, in *European Journal of Public Health,* Vol.14, No.4, Aug.2006
2. **Vladescu, C.,** Stoicescu, E., Enachescu, D. Necesarul de medici în Romania din perspectiva Uniunii Europene, in *Management în Sănătate*, nr.2, Iunie 2002.
3. **Vladescu, C.,** Radulescu, S. Primary Health Services: Output-Based Contracting to Lift Performance in Romania, in *Public Policy for the Private Sector*, No. 239, Sept.2001, The World Bank Group, Washington, D.C.
4. **Vladescu, C.** Privatizarea serviciilor sanitare intre ideologie si practica (Privatization of health care services between ideology and practice), in *Management în Sănătate*, nr.9, Bucharest, Septembrie 2001.
5. **Vladescu, C.** Privatizarea serviciilor sanitare, de la teorie la implementare, in *Medicina Moderna*, nr.6, p. 329-332, Iunie 2001, Bucuresti
6. **Vladescu, C.** Legislaţie şi Reforma in SASS din Romania, in *Management în Sănătate*, nr.2, p.2-6, Iunie 2000.
7. **Vladescu, C**., Fărcăşanu, D. Integrarea Europeană, organismele internaţionale şi reforma serviciilor de sănătate din Romania (European Integration and the reform of health care services in Romania), in Management în Sănătate, nr.5, Martie 1998.
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9. **Vladescu, C**., Fărcăşanu, D. Integrarea europeană şi sectorul sanitar: asistenţa tehnică externă, in *Management în Sănătate*, nr.1, Martie 1999.
10. **Vladescu, C**., Fărcăşanu, D. Integrarea Europeană şi sectorul medical, in *Management în Sănătate*, nr.4, p.2-7, Decembrie 1998.
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12. Pop, S., **Vladescu, C.** et al. (1998) Acreditarea unităţilor medicale (The accreditation of medical facilities in Romania), in *Management în Sănătate*, nr.1, p.15-17, Martie 1998, Bucureşti.
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COMMON CONTACT ALLERGENS IN DENTAL MATERIALS

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ABSTRACT

US National Library of Medicine describes as allergens over 4.000 chemical substances. Some of them can be associated with mutagenic processes. It is estimated that 15-20% of the adult population of Europe presents sensitivity to at least one allergen. Dentistry is one of the professions that presents a high risk in developing reactions to common or specific allergens. The body response to allergens consists in: immediate allergic reactions (rhinitis, asthma, conjunctivitis, generalized eruptions) and tardive allergic reactions (contact dermatitis.) Among the patients, the allergic reactions manifest predominantly at the oral cavity level, being caused more frequently by certain metals which the dental alloys are made of. We used the patch-test on a lot of 30 dentists in order to indentify the main substances responsible for producing immediate and tardive allergic reactions, then on a lot of 30 patients to determine the allergen potential of the typical compounds in dental alloys. Regarding the dentists, the testing offered us the following data: tardive allergic reactions to 2-HEMA (2 hydroxi-ethyl methacrylate)-52%; EGDMA (ethyleneglicol dimethyl methacrylate)-40%; nickel-32%; MMA (methyl methacrylate)-26%; 2-HPMA (2 hydroxi propil methacrylate)-20%; EMA (ethyl methacrylate)-17% and immediate allergic reactions to eugenol-32%; latex-19%, antiseptics-3%. Regarding the lot of patients, on the other side, the patch-testing led us to the following results: sensitivity to gold-5%; palladium-7%; nickel-30%; cobalt-2%. Due to the high percentage of reactions following the patch-testing, the identification of the allergic reactions in patients and practitioners as well, has a major importance for prevention of the possible mutagenic effects of the above-mentioned materials and the possibility of launching specific public health programs according the results obtained.

Key words: *patch-test, allergic reaction.*

INTRODUCTION

US National Library of Medicine describes over 4.000 chemical substances as allergens. Some of them can be associated with mutagenic processes. It is estimated that 15-20% of the adult population of Europe show sensitivity to at least one allergen. The allergic reaction is an excessive reaction to an antigen, well-tolerated by another person.

The immune response can be divided in:

a) Immune response with humoral mediation of 3 types: type 1-immediate anaphylactic response, type 2-cytotoxicity, type 3-obtaining of immune complexes
b) Immune response with cellular mediation: type 4-tardive hypersensitivity (24-72 hours).

According to the European Union, the allergens are divided in the following categories: metals; plastic materials and chemical rubbers; preservatives and dyes;

perfumes. Dentistry is one of the professions which present a high risk in developing reactions to common or specific allergens.

Table 1 The mutagenic potential of chemical substances

CATEGORY 1	Substances about which it is known to induce or which can be considered that they might induce mutations of the stem cells.
CATEGORY 1A	Substances about which it is known to induce mutations of the stem cells.
CATEGORY 1B	Substances which can be considered that they might induce mutations of the stem cells.
CATEGORY 2	Substances the researchers are concerned about due to their possibilities of generating mutations in cells.

The response of the body to allergens consists in: immediate allergic reactions (rhinitis, asthma, conjunctivitis, generalized eruptions) and tardive allergic reactions (contact dermatitis.)

The mutagenic potential of chemical substances can be structured as follows: (table 1).

MATERIAL AND METHOD:

We used the patch-test (fig. 1) on a lot of 30 dentists in order to identify the main substances responsible for producing immediate and tardive allergic reactions, and on a lot of 30 patients to determine the allergen potential of the typical compounds the dental alloys are made of.

The patch-testing was performed for the chemical substances with allergen potential by applying separately on skin several samples of these substances which remained in contact with the skin for 48 hours.

After this period of time, the results were interpreted by a dermatologist.

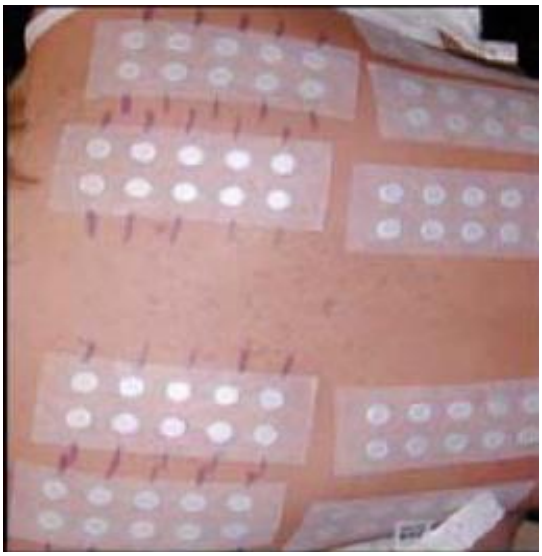

Fig.1 Patch test.

RESULTS:

Regarding the dentists, the testing offered us the following data: tardive allergic reaction at 2-HEMA (2 hydroxiethyl methacrylate)-52%; EGDMA (ethyleneglicol dimethyl methacrylate)-

40%; nickel-32%; MMA (methyl methacrylate)-26%; 2-HPMA (2 hydroxi propil methacrylate)-20%; EMA (ethyl methacrylate)-17% and immediate allergic reactions to eugenol-32%; latex-19% (fig.2), antiseptics-3%.

Regarding the lot of patients, on the other side, the patch-testing led us to the following results: sensitivity to gold-5%; palladium-7%; nickel-30%; cobalt-2%.

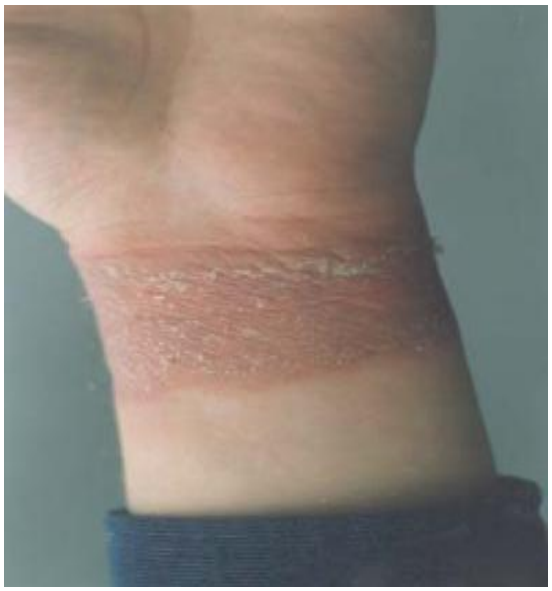

Fig.2 Allergic reaction to latex.

DISCUSSIONS

In dentistry, so far, the bibliographical research at a medline level does not indicate any information referring to coherent studies of the allergenic or mutagenic potential of the dental materials. 2-HEMA and EGDMA are the prototypes for methacrylates used in dentistry, which requires light activation. 2-HEMA and EGDMA have the most allergenic potential of the methacrylic monomers group. According to existing studies, the allergizing features of these substances are proved by the chain reaction of the 16 carbon atoms in their composition, which also reduces the cutaneous penetration [1]. The contact dermatitis on hands, with severe irritation, apperas more frequently than the allergic eczema type, the differential diagnosis of the two diseases being quite difficult to reveal [2]. In a survey on a lot of 37 volunteers who kept wearing powdered latex gloves for 6 hours a day for two weeks, 16% of them developed irritiation phenomena, manifested by erythema and pruritus (severe itching) predominantly located on the palmar side of hand and interdigital [3]. Other substances leading to allergic reactions are the additives: hydroquinone, pigments, dimethyl-para-toluidine and others such as colophony, eugenol, local anesthetic, antiseptics, and metals [4]. In the medical literature many cases of allergic reactions are described as being produced by the components of dental materials [5, 6]. A well-documented example is the one of an alleged sensitivity to mercury in a patient who presented endo-oral lichen lesions [7, 8, 9, 10] in the vicinity of a restoration made of amalgam [11, 12, 13]. Later, it was demonstrated that the manifestation was caused by other metals or allergens, the existence of amalgam restoration being only a pure coincidence. The final conclusion was that the patient was allergic to amalgam too, but the lichen planus was caused by the sensitivity to other substances [14, 15, 16, 17, 18, 19].

CONCLUSIONS:

The identification of allergic reactions in patients and practitioners as well, has a major importance through the light of prevention of the possible mutagenic effects [20, 21] to the above-mentioned materials and the possiblities of launching specific programs for public health according to the obtained results.

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THE EVALUATION OF MUSCLE WASTING IN COPD PATIENTS

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ABSTRACT

Introduction. *Decreased skeletal muscle mass, with metabolic and functional consequences is one of the most frequently extra-pulmonary features in COPD. Muscle wasting is negatively associated with exercise capacity, quality of life and mortality. There is many assessment methods of muscle wasting, some of them expensive (The dual energy X-ray absorptiometry DEXA, biopsy), and some of them cheap: fat free mass (FFM) measured by bio-electrical impedance analysis (BIA), effort testes, dynamometry etc.*

Objective. *To evaluate on practice the muscle wasting and effort capacity in COPD patients for better and correct management of disease. Design A comparative randomize study at 168 COPD patients (all ♂, age 62.7 ± 8.9), divided in 4 lots staged: I(27, FEV1 80.5 ± 10.6), II(43, FEV1 64.2±9.5), III(46, FEV1 39.5±5.8), IV(53, FEV1 24.4±7.5) and one healthy lot (32 ♂, age 59.6 ± 6.7). At all of these it was determined body composition and bioresistance by BIA, muscle force at the hand (using dynamometry), inspiratory and expiratory pressure (PI, PE), effort capacity (6 MinuteWalkTest), inflammatory level (C Protein), Quality of Life (ST.Georges Questionaire), depression status (TDI Questionaire).*

Results. *FFM decreased with a rate of 2.7±1.6/ lot from healthy to COPD IV, muscle force at the hand decreased with a rate of 0.17±0.05 /lot, distance at 6MWT decreased with 29.76%(from 561.81 to 394.57m), and QL it constantly impairment:17.8→24.2→41.0→70.2→81.0%. All these was high corerelated (r>0,7). C protein was greater at COPD patients versus healthy, but direct uncorrelated with disease severity.*

Conclusion It is possible and important to establish with simples methods muscle wasting and effort capacity in clinical practice before implementing the COPD treatment and pulmonary rehabilitation program.

Key words: *muscle wasting, weight loss, effort tolerance, COPD.*

INTRODUCTION

If initial COPD was defined as a strictly pulmonary affection characterized by progressive and irreversible obstruction and inflammation of the airways, in the last decade more studies proved the apparition/association of some extrapulmonary effects that impose the necessity to approach COPD as a multisystemic affection1. Besides the respiratory disorder, COPD is now generally accepted as a systemic disease.[2]

The systemic effects reviewed above are likely to have a profound clinical impact on the management of COPD. First, weight loss and skeletal muscle dysfunction clearly limit the exercise capacity of these patients and, therefore, have a direct negative effect on their quality of life.[3] Second, weight loss is a

prognostic factor in patients with COPD that, importantly, is independent of other prognostic indicators, such as FEV1 or PaO2, that assess the degree of pulmonary dysfunction [4,5] Thus, weight loss identifies a new systemic domain of COPD not considered by the traditional measures of lung function. [6]

The musculoskeletal system is among the extra pulmonary organ systems most frequently affected by COPD [7,8] Indeed, an abnormal low muscle mass is present in about 40% of the patients with moderate to severe COPD entering pulmonary rehabilitation.[5]

Initially described as weight loss and casexia, the involvement of the musculoskeletal apparatus in COPD is now better understood as a loss of fat-free mass (FFM) and bone mineral density (BMD) [9,10] Previous studies have described these processes separately and established the body mass index (BMI) as a predictor of loss of FFM and BMD.[4]

Increasing severity of COPD is found to be associated with decreasing FFM and BMD that includes progressive deconditioning and inactivity, greater number of exacerbations, increased use of corticosteroids, and increasing systemic inflammation.

Objective. To evaluate on practice the muscle wasting and effort capacity in COPD patients for better and correct management of disease.

Design A comparative randomize study at 168 COPD patients (all ♂, age 62.7 ± 8.9), divided in 4 lots staged: I (27, FEV1 80.5 ± 10.6), II (43, FEV1 64.2±9.5), III (46, FEV1 39.5±5.8), IV (53, FEV1 24.4±7.5) and one healthy lot (32 ♂, age 59.6 ± 6.7). At all of these it was determined body composition and bioresistance by BIA, muscle force at the hand (using dynamometry), inspiratory and expiratory pressure (PI, PE), effort capacity (6 Minute Walk Test), inflammatory level (C Protein), Quality of Life (ST.Georges Questionaire), depression status (TDI Questionaire).

Quantification of the quality of life, rated by St George's Respiratory Questionnaire (SGRQ) 11 elaborated by PW Jones et al represents now the most utilized questionnaire in assessing the quality of life in chronicle respiratory diseases. Assessment of SGRQ might surprise changes of the quality of life without significant changes of FEV1. Studies shown that it is: reproducible, valid and sensitive. SGRQ scores correlate significant with various parameters: symptoms score with frequency of wheezing ($r = 0.32$, $p < 0.0001$), activity score with 6 minutes walking distance. [11]

Quantification of dyspnoea grade imposed the description and validation of scales from which most utilized is MRC (Medical Research Council) scale12. MRC dyspnea scale is a validated instrument of quantification, easy to use.

Effort tolerance proved to be very well evaluated by 6 minutes walking test13, a simple test, accessible and very well correlated with peripheral muscular dysfonction. This way it was validated and entered in the clinical routine.

Body mass losses and body composition changes was evaluated by bio-electrical impedance analysis (BIA).[14]

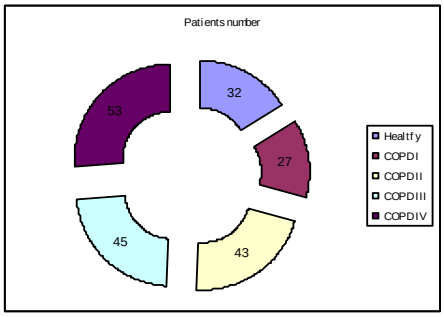
Results FFM (lean body mass) decreased with a rate of 2.7±1.6/ lot from healthy to COPD IV, muscle force at the hand decreased with a rate of 0.17±0.05 /lot, distance at 6MWT decreased with 29.76% (from 561.81 to 394.57m), and QL is constantlyimpairment: 17.8→ 24.2→ 41.0→ 70.2→ 81.0. All these was high corerelated (r>0, 7).

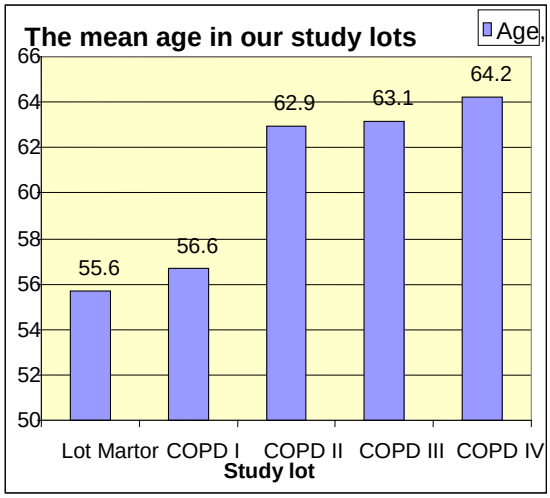
C protein was greater at COPD patients versus healthy, but direct uncorrelated with disease severity. Bioresistance increase from healthy to COPD IV (from 386.34 to 445.67ohms), methabolic rate decreasing in backward (1940.4→1728.0), but these was low correlated with severity of COPD (affected by the concomitant diseases).

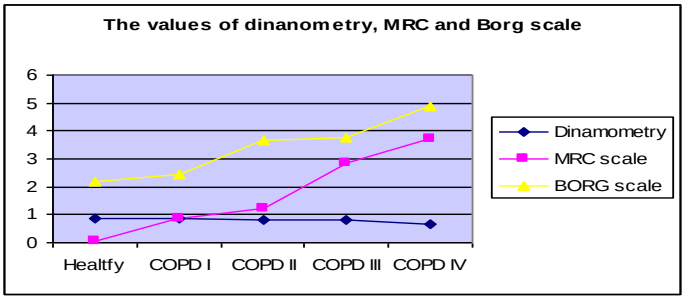
The best indicators we founded 6MWT, FFM, scale MRC and Borg, QL side by side to classical FEV1.

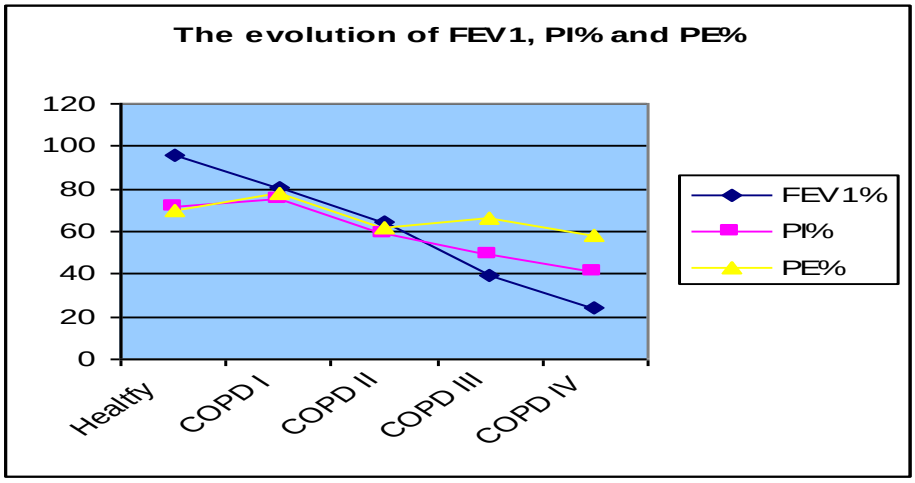
Table 1 The results of study (average values)

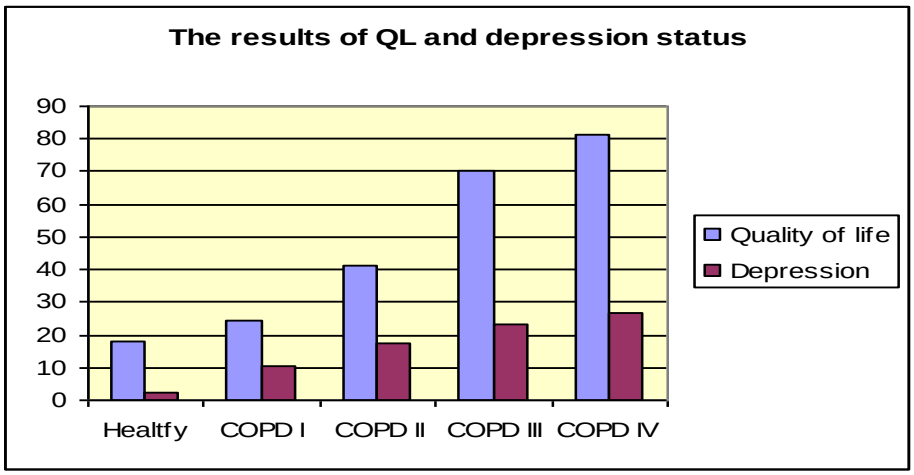
	Lot Martor n=32	COPD I n=27	COPD II n=43	COPD III n=45	COPD IV n=53
Age, years	55.6	56.6	62.9	63.1	64.2
BMI, kg/m2	27.5	26.1	25.9	25.5	25.1
%Body Fat	18.7	17.6	19.8	20.3	19.4
Lean body weight,kg	63.8	59.6	57.9	57.5	56.4
Total body water,l	62.9	62.5	61.8	62.5	63.0
Bioresistance,ohms	386.3	417.8	437.8	420.4	445.6
Methabolic rate	1940.4	1812.7	1764.8	1817.6	1728.0
Dinamometry	0.865	0.846	0.823	0.82	0.675
6 minute walk test,m	561.8	515.5	467.1	421.8	394.5
BORG scale	2.1	2.4	3.6	3.7	4.8
MRC scale	0.031	0.888	1.214	2.863	3.698
Quality of life%	17.8	24.2	41.0	70.2	81.0
C Protein,ug	4.01	5.79	14.12	8.91	11.78
FEV1%	96.2	80.5	64.2	39.5	24.4
FEV1/FVC	101.6	91.3	85.9	67.2	64.5
PI%	71.6	75.2	59.3	49.6	40.8
PE%	70.1	77.7	61.8	66.1	57.8
Depression	2.5	10.6	17.5	23.3	26.6








The evolution of FEV1, PI% and PE%
120
100
80
60
40
20
0
Healtfy
COPD I
COPD II
COPD III
COPD IV
FEV1%
PI%
PE%


The results of QL and depression status
90
80
70
60
50
40
30
20
10
0
Healtfy
COPD I
COPD II
COPD III
COPD IV
Quality of life
Depression

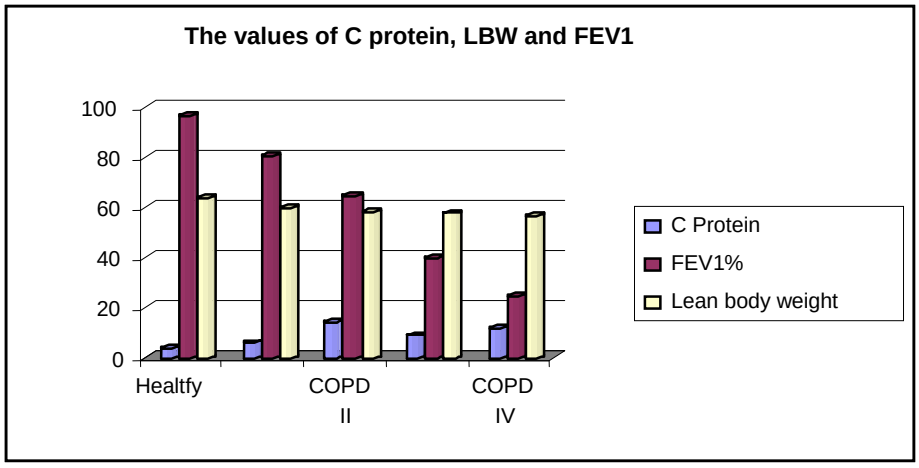

The values of C protein, LBW and FEV1
100
80
60
40
20
0
Healtfy
COPD II
COPD IV
C Protein
FEV1%
Lean body weight

Table 2 It was a strong correlation between:

LeanBodyMass and 6MWT	0.93512
MRC and Borg scale	0.926393
Dinanometry and Borg scale	0.89002
FEV1 and PI%	0.959677
FEV1 and PE%	0.730382
QL and Depression	0.956861

Table 3 It was a moderate correlation between:

C protein and FEV1	-0.66008

Table 4 It was a low correlation between:

Body fat % and byoresistance	0.396852

Conclusion

COPD must be considered a systemic disease, and the extra pulmonary manifestations must be considered in the evaluation of its severity. These investigations are very simple, cheap, accessible and good predictors for patient's evolution. The treatment of these manifestations could modify the prognosis of these patients. Pulmonary rehabilitation, recomended by GOLD in COPD starting with stage II proves to have a special value, especially through global assesment and early intervention on pulmonary as well as on systemic effects caused by the disease.

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PAGES 25 -34

ROMANIAN POPULATION KNOWLEDGE, ATTITUDES AND PRACTICES REGARDING TUBERCULOSIS AFTER 15 YEARS OF INTERNATIONAL FUNDED PROJECTS IN TUBERCULOSIS CONTROL FIELD

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ABSTRACT

Since 1994 various international institutions and organizations funded several projects in the field of tuberculosis control and prevention. Among these are worth mentioning World Health Organization, Soros Foundation, World Bank, USAID and the most recent and substantial the Global Fund to fight AIDS, Tuberculosis and Malaria. These projects included population information, education and communication campaigns, training for medical personnel and roma health mediators, provision of second line drugs and support for policy elaboration (the national tuberculosis programme, national strategy for tuberculosis control, and others). A measure of these projects success is the population knowledge, attitudes and practices regarding tuberculosis. These were estimated using opinion questionnaires applied in 2007 and 2009. The article presents the 2009 study results and discusses comparatively some essential aspects from 2007 and 2009. Both studies show a reasonable level of tuberculosis knowledge and also the attitudes and practices are in a positive register. These studies can not reveal the causal link between the international funds and the population knowledge, attitudes and practices but can measure these dimensions to which without doubt the international programmes along with the national government contribution and the effort of the tuberculosis network had a sizable contribution. Unfortunately similar data from the early 90s are missing, but the high tuberculosis incidence of that time suggests a low level of them.

Key words: *Tuberculosis, international programmes, knowledge, attitudes, practices, population.*

Abbreviations
GFATM – Global Fund to fight AIDS, Tuberculosis and Malaria
TB – Tuberculosis

INTRODUCTION

Since 1994 various international institutions and organizations funded several projects in the field of tuberculosis (TB) control and prevention. Among these are worth mentioning World Health Organization, Soros Foundation, World Bank, USAID and the most recent and substantial the Global Fund to fight AIDS, Tuberculosis and Malaria. These projects included population information, education and communication campaigns, training for medical personnel and roma health mediators, provision of second line drugs and support for policy elaboration (the national tuberculosis programme, national strategy for tuberculosis control and others).

The Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) – the

most recent and substantial international donor for TB control in Romania – is an international funding instrument established in 2002 with the aim to provide resources through which the countries affected by these three devastating epidemics to be able to develop proper response mechanisms. The decision to create GFATM was taken in 2001 during the General Extraordinary Session of United Nations. Romania applied till now to two funding rounds – second and sixth – and obtained four grants: two for TB component (second round: $16,743,641 and sixth round $4,695,694 for the first two years of five) and two for HIV/AIDS.

The objective of the study was to illustrate the population knowledge, attitudes and practices regarding TB in the context of international funded projects and to compare the results of two similar studies from 2007 and 2009.

MATERIAL AND METHOD

The volume of the sample was 1213 persons with age over 15 years from urban and rural areas of Romania. The sample was probabilistic and multistage stratified. The criteria for stratification were the development region, the residence area and type of locality. The research method was face to face interview based on a questionnaire administered by the interview operator. The sampling was done by probabilistic selection of the locality, household and respondents. The sample is representative for the Romanian population over 15 years old with an accepted error of ± 3 % and a trust level of 95%. In the first stage the sample was stratified in the eight development regions: North-East, South, South-West, West, Nord-West, Center and Bucharest. In the second stage for each region were selected randomly 3-4 counties. In the third stage, in each county the localities were stratified according the urbanization degree/type of locality in four categories: 1. peripheral village; 2. village center of commune; 3. small and medium town (under 50,000 inhabitants and between 50,000 and 200,000 inhabitants); 4. big towns, county capital (over 200,000 inhabitants). Two rural localities were randomly selected (a village center of commune and a peripheral village) and two urban localities and there the interviews took place. The selection chances of each locality were directly proportional with the locality's size (number of inhabitants), in order to provide each county inhabitant equal chances to be included in the sample. In the fourth stage, in each selected locality, a sector of households were randomly selected (cluster, succession of households, selected based on a certain statistic pace, staring from a randomly selected starting point).

The interviews were done in the clusters. In each cluster the households were selected successively, starting with the starting point (randomly selected), respecting the rule of the right side of the street, using various rules for following the path based on the situations encountered. Based on the required number of households calculated in this way and based on the sector visiting rules the lists of sampling were elaborated. These included the addresses that have to be visited beginning with the starting point, following the right side of the street rule.

In each household a person over 15 years was selected. If the selected household included more eligible persons, only one was selected, using a table of random numbers correlated with the questionnaire code and number of eligible persons in the household. If the selected person was not home a re-visit was scheduled. The interview operator visited three times the household in order to get the selected person (the "principle of three visits"). The interview operator registered for each visited household the total number of eligible persons and the main socio-demographic characteristics (sex, age, education level etc.). In this way the sample included 1213 persons.

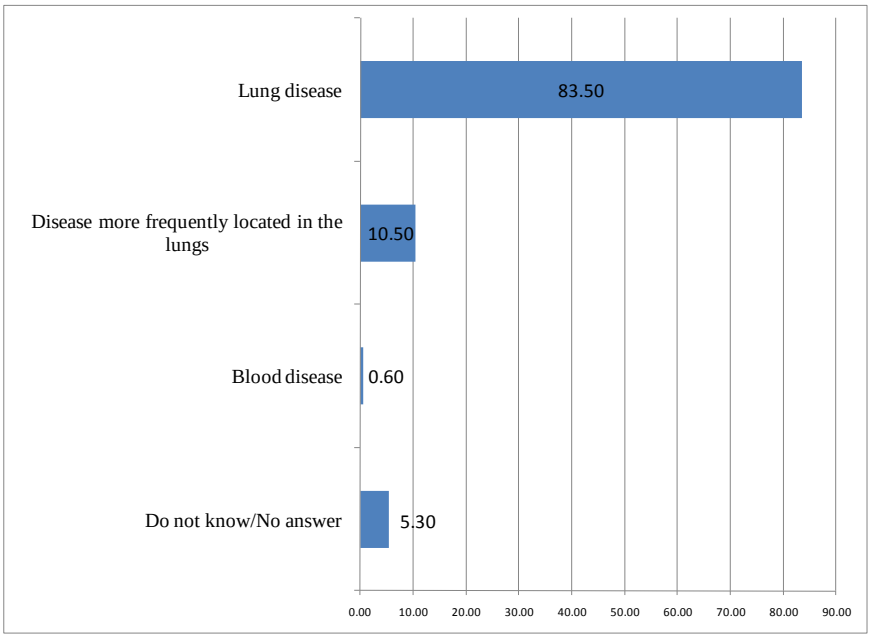
The data validation was done based on the data from the National Statistics Institute.

RESULTS

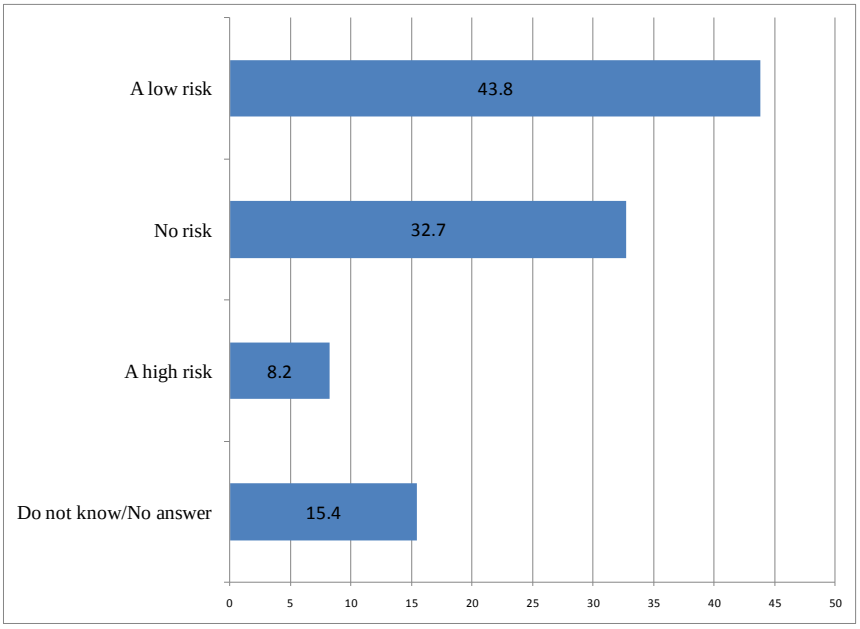
Knowledge

Of the persons interviewed, the vast majority (90.2%) heard of TB, under this name or TBC or waste. Only one of ten respondents (9.8%) declares that never heard and does not know about a disease under any of these names.

For most of the interviewed persons (83.5%), TB represents a lung disease or, in 10.5 percent of cases, a disease more frequently located in the lungs. A percentage of 5.3 declare that even if they heard of TB they do not know what kind of disease it is and 0.6 believe it is a blood disease (Graph 1).



Graph 1: Knowledge regarding TB (%) (Number of cases: 1094 persons in the total sample)



Graph 2: Knowledge regarding the risk to contract TB (%) (Number of cases: 1029 persons in the total sample)

Almost half of the interviewed persons (43.8%) consider that the risk of contracting TB is low and almost one third (32.7%) does not fear of getting this disease. Only 8.2% consider that they have a high risk to get the disease and 15.4% cannot estimate this risk (Graph 2).

The main reasons for not fearing contracting TB are in decreasing order the following: the fact that there is nobody from whom to catch the disease (32.5%), the fact that they consider themselves resistant to diseases (31%) and the fact that they do not smoke (18.5%). Also, among the reasons mentioned we found 29.7% the fact that they avoid sick persons, 22.5% the fact that they maintain a good hygiene or 22.1% that do not let the cold to advance.

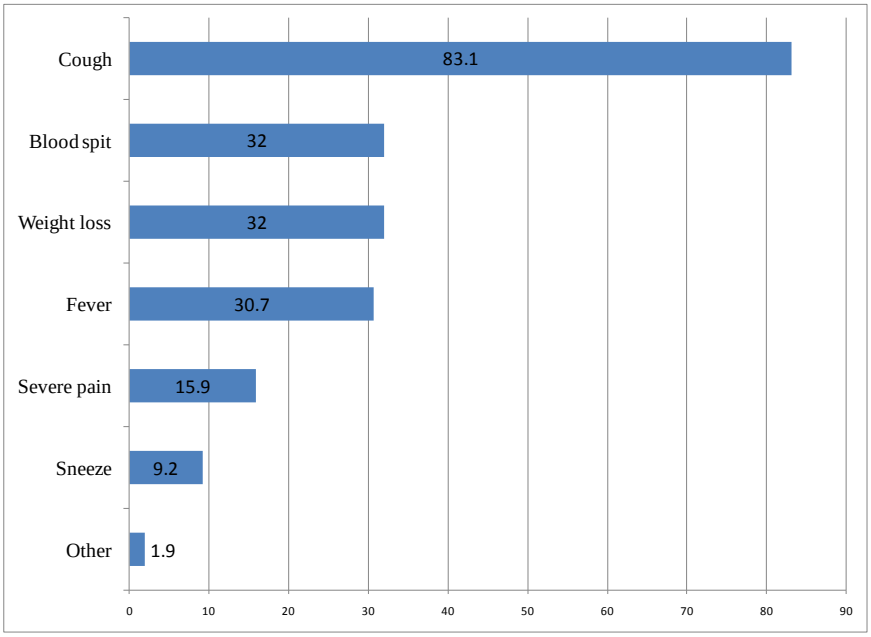
Most of the ones interviewed (62.8%) do not know the reasons for which they consider the risk of getting TB high. Only 11.6% declare that the main factor is the favoring environment conditions, 7% the fact that there are sick persons around them, 6.6% declare they have sensitive lungs and 6.6% think that they are very weak.

Almost two thirds of the interviewed persons (62.3%), considers that there are categories of people more exposed to the risk of getting TB. Less than a quarter of the population (16.5%) considers that there are no categories with a higher risk.

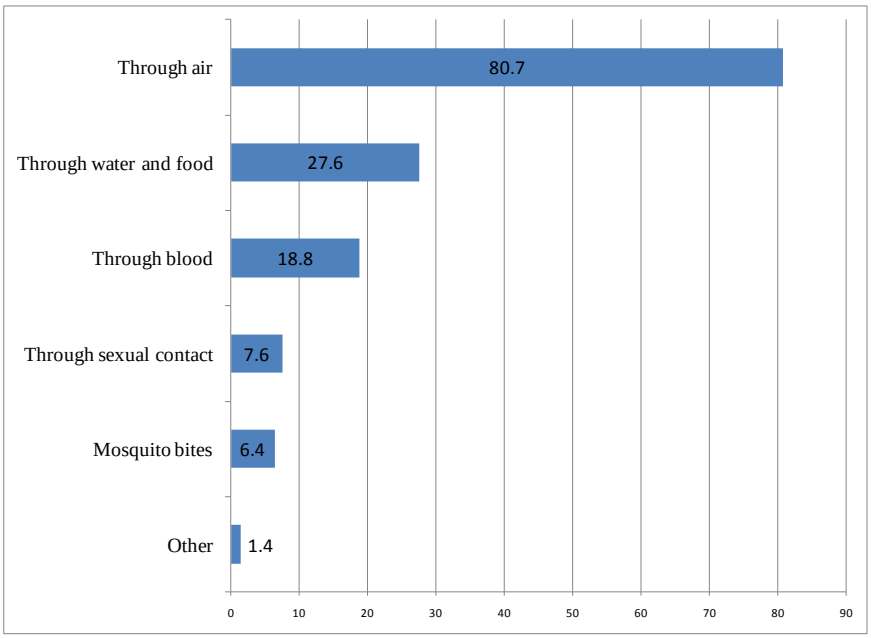
The categories indicated by the respondents as having a higher risk to get TB are: the ones with sensitive lungs (56.5%), poor people (45.3%) and the heavy smokers (44.3%).

About half of the population (51.4%) considers that it is not possible to have TB without obvious signs of disease. Less than a quarter of the interviewed persons (21%) consider that this is possible and 27.6% recognize the fact that they do not know if this is possible or not.

The most important sign of disease is the cough for more than three quarters of respondents (83.1%) that were able to answer without being presented options of answers. Relatively equal percentages were registered of persons indicating: weight loss (32%), blood spitting (32%) and high fever (30.7%) (Graph 3).

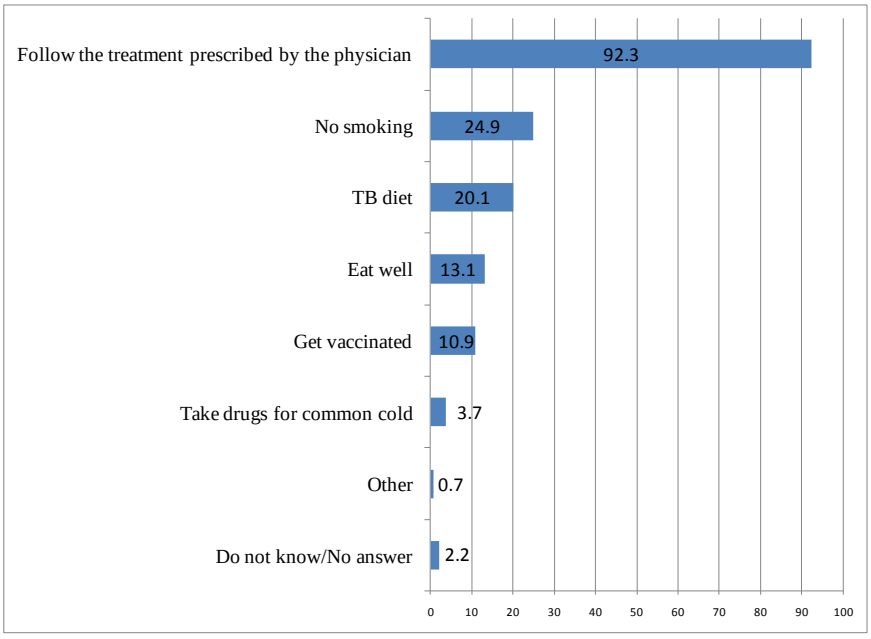


Graph 3: Knowledge regarding TB signs (spontaneous answer) (%) (Number of cases: 629 persons in the total sample)



Graph 4: Knowledge regarding TB contracting methods (%) (Number of cases: 565 persons in the total sample)

When the interviewees were in the situation to select answers from a list presented by the interview operator, most of them (67%) indicated cough as main sign of disease, about half indicated weight loss (54.5%), blood spitting (44.6%) and fever (59.1%). Less than half of the population (37.6%) was able to provide the correct answer spontaneously (without being presented the answer options), declaring that TB is transmitted through the air – this being the way of transmission for most of the ones spontaneously answering this question (80.7%) (Graph 4).

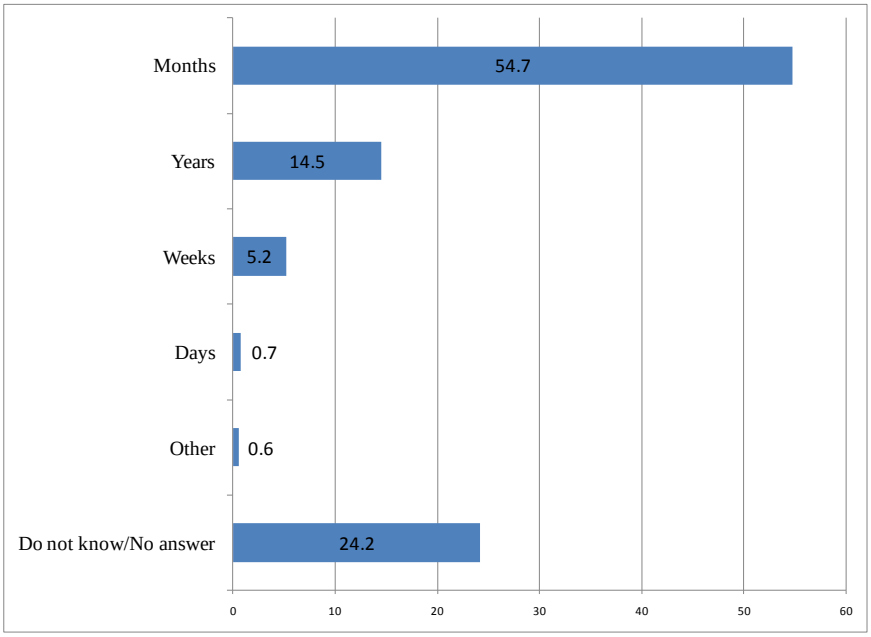


Graph 5: Knowledge regarding TB curing requirements (%) (Number of cases: 807 persons in the total sample)

When provided the answering options, more than half of the population in the study (51%) indicates the correct answer – the fact that TB is transmitted through the air. Among the wrong answers there were 40.4% considering that TB is transmitted through blood, 32.6% through food, 17.6% through sexual contact and 16.6% through mosquito bites.

About 8 of 10 people (78.4%) consider TB curable. Still, 8.7% think that TB is incurable and 12.8% do not know. Most of the ones considering TB curable (92.3%) consider that the condition for cure is to follow the treatment recommended by the physician. Also, about a quarter of these (24.9%) think that one should not smoke and 20.1% that a TB diet is required (Graph 5).

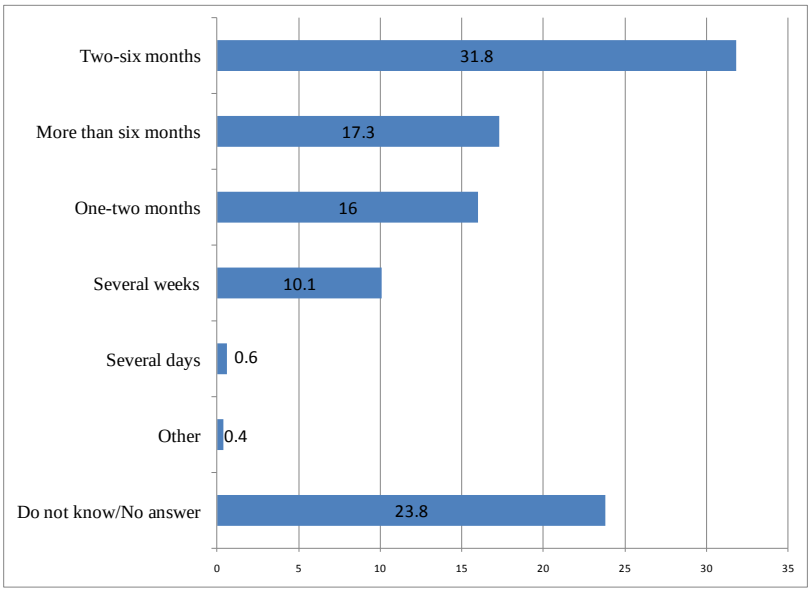
About a quarter of the people that believe that TB is curable declare that they do not know how long is the correct TB treatment, more than half (54.7%) provides the correct answer indicating a duration of several months (Graph 6).



Graph 6: Knowledge regarding TB treatment duration (Number of cases: 807 persons in the total sample)

Most of the people that believe that TB is curable (83.8%) think that hospital admission is required and 9.4% do not know. Among the persons considering hospital admission required, 31.8% indicate a period of 2-6 months. Almost a quarter (23.8%) declare that they do not know the hospitalization period (Graph 7). The risk faced if not treating TB is obvious for most of the population (79.8%), that they can die in this situation. Other risks less present among the ones interviewed are: 15.7% one gets weak, 15.2% think one risks developing associated disease and 12.4% think that the risk is to get cured becomes more difficult.

More than half of the interviewed persons (53.7%) know that in order to reduce the risk of getting the disease, the best method is to avoid contact with people having TB. Also, among the correct answers there were 27.3% – to maintain a proper hygiene and 23.1% – to eat well. There were also a high proportion of incorrect answers: 33% – to not smoke, 40.8% – to get a vaccine and 29.3% – to avoid getting a cold.

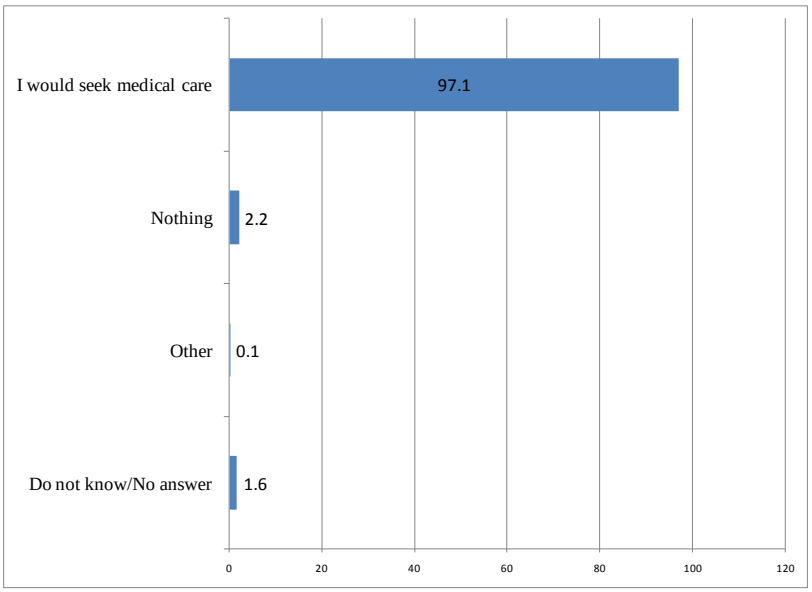


Graph 7: Knowledge regarding TB hospitalization length (%) (Number of cases: 676 persons in the total sample)

Attitudes

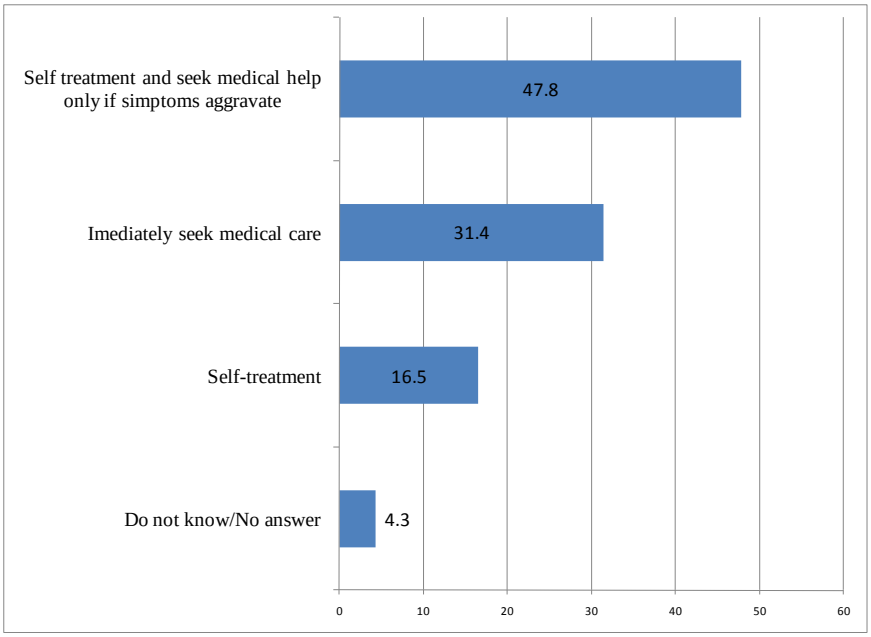
Compared with respiratory disease situation in which most prefer to treat themselves, we found that if it was suspected to be ill with TB, almost all respondents (97.1%) say they would go to the doctor (Graph 8). The overwhelming majority of the population (95.7%) believes that if suspecting having TB, they would go to the doctor immediately.

Starting from the fact that over half of those interviewed considered that the best way to prevent illness is to avoid the sick persons; it is interesting that only 23.7% say that they would avoid seeing a TB ill person from their entourage and only 19% would go to the doctor to see if they became ill.



Graph 8: Attitude in case of suspecting being ill with TB (%) (Number of cases: 1029 persons in the total sample)

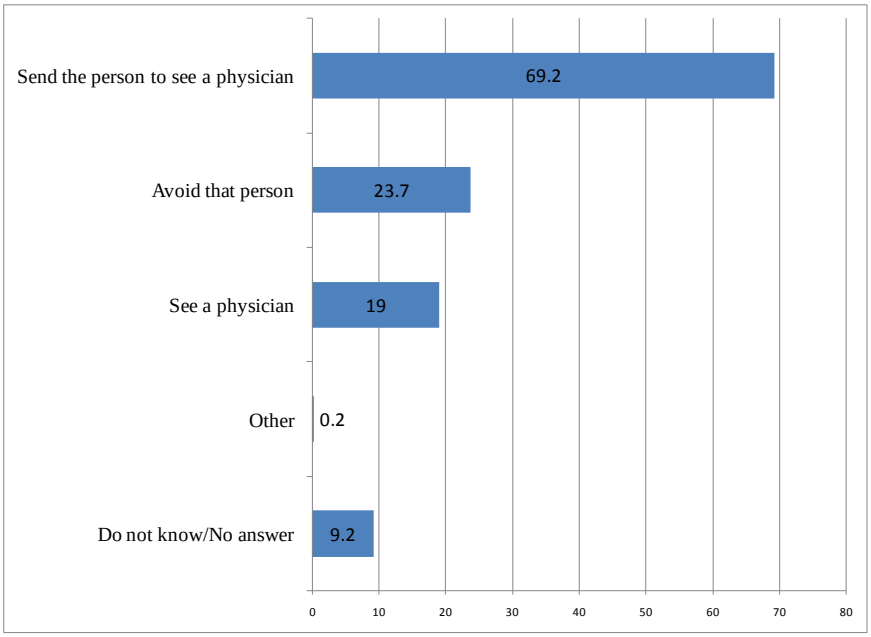
In this case, 7 of 10 people (69.2%) would send the sick person to the doctor but approximately one person out of 10 (9.2%) do not know what to do (Graph 9).



Graph 9: Attitude in case of suspecting that somebody close has TB (%) (Number of cases: 1029 persons in the total sample)

Practices

More than half of the interviewed persons (64.3%) admit that when they have symptoms of a respiratory disease they prefer to treat themselves and taking the decision to go to the doctor only if the disease gets worse (47.8%) or they continue to treat themselves till healed (16.5%). Only one third (31.4%) of the population goes to the doctor immediately if symptoms appear (Graph 10).



Graph 10: Practices in case of respiratory disease symptoms (%) (asthma, bronchitis, viral disease etc.) (Number of cases: 1213 persons in the total sample)

About 4 in 10 people in the population (33.7%) made at least once a test for TB. Almost two thirds of the population (63.7%) never made any tests for TB. Among those who were investigated for TB, in most of the cases (92.5%), lung X-rays were performed and for 9.2% a sputum examination was made.

More than half (59.1%) of those who were investigated for TB, the reason was the requirement of such analysis for employment, admission in schools or moving abroad (45.7%). Suspicion of TB was the reason for investigating a quarter (26.8%) of those investigated, while 4.9% do not know the reason of such analysis. Among those who made at least once tests for TB, we find that 4.6% had tuberculosis (on average every 18 persons investigated for tuberculosis, a person had the disease). More than 95% say they never had tuberculosis. Two of five people (40%) responded that for diagnosis they would address the family doctor, 20% a TB dispensary and 22.5% a TB hospital. Few people interviewed had experienced the situation of suffering from TB or have such a person in their entourage, 93.6% stating that they had no such situations in the past 2 years in the family, among friends, neighbors or colleagues.

DISCUSSIONS

A similar study was conducted in 2007. Some major aspects were observed by comparing the data from the 2 studies. Most persons continue to not consult a doctor when they have symptoms of a respiratory disease (64.3% in 2009 versus 64.9% in 2007). If the symptoms appear, only one third of population address to the doctor (31.4% in 2009 versus 34% in 2007).

Most of the respondents (90.2% in 2009 and 96.6% in 2007) heard about tuberculosis under this name or under the name of TBC or waste. Most of the respondents (94% in 2009 and 96% in 2007), consider TB a lung disease or a disease more frequently located in the lungs. When suspecting that they have TB most of the people responding to the questionnaire (97.1% in 2009 and 98.2% in 2007) declare that they would schedule a doctor visit.

The high percentage of people not recognizing the risk of contacting TB is still high – about half of the population declaring that they cannot contract TB (32.7% in 2009 and 31.6% in 2007). The percentage of people that consider that they do not have from whom to catch TB is on the rise from 27.1% in 2007 to 32.5% in 2009. It is decreasing from 76.2% (in 2007) to 62.3% (in 2009), the percentage of people considering that there are categories of people that are more exposed to the risk to catch TB. Among these are mentioned the one that smoke but less than in 2007 (decreasing percentage from 61.2% in 2007 to 44.3% in 2009). About half of the population (51.4% in 2009 and 46.7% in 2007) considers that it is not possible to have TB without obvious signs of disease. The percentage of people considering the cough is the most important sign of TB is increasing significantly, from 37.3% in 2007 to 83.1% in 2009. Comparing with 2007 the percentage of the ones that know the way TB is spread is increasing, through air (from 46% in 2007 to 51% in 2009).

The vast majority of the population (95.7% in 2009 and 96.5% in 2007) considers that when suspecting that a person might have TB should consult a physician immediately. The percentage of the people that considers TB a curable disease is increasing (from72% in 2007 to 78.4% in 2009) and the percentage of population considering TB an incurable disease is decreasing (from 14.4% in 2007 to 8.7% in 2009). The high percentage, 92.3% in 2009 and 92% in 2007 is maintained – representing the persons that think that in order to cure TB they have to follow the treatment prescribed by the physician. About a quarter of the population continues to think that they have to quit smoking and follow a diet in order to cure TB. Most of the persons considering TB a curable disease (83.8% in 2009 and 85.6% in 2007) think that hospital admission is required. It is decreasing from 89.4% in 2007 to 79.8% in 2009, the percentage of

people thinking that they can die if not receiving TB treatment.

More than half of interviewees (53.7% in 2009 and 53% in 2007) know that in order to decrease the risk to catch the disease, the best method is to avoid contact with people that have the disease and about half of the population (40.8% in 2009 and 42.9% in 2007) still consider vaccination a TB prevention method. When suspecting that somebody from their entourage has TB, most of the people (69.2% in 2009 and 70.6 in 2007) would send the sick person to a physician.

CONCLUSIONS

It is clear that in 2009, the level of population knowledge, attitudes and practices regarding tuberculosis is at an encouraging level and reflects the significant investments made by Ministry of Health and international projects on information, education and communication regarding TB. However, even if the TB incidence is decreasing, the level is still high and imposes to support the efforts to consolidate these achievements.

Acknowledgements

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PAGES 35 -40

PROPOSED STRUCTURE OF PERSONAL HEALTH RECORD FOR PREGNANT WOMEN

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ABSTRACT

Few studies, have dealt with PHR needs of families. No studies have specifically targeted pregnant women regarding PHR systems design despite increased interest in health matters exhibited by pregnant women. The aim of this study is to elaborate the functional specifications of the pregnant woman personal health record and to create and propose a functional prototype.

Key words: *Personal Health Record, Pregnancy.*

INTRODUCTION

The Personal Health Record (PHR) is an Internet-based set of tools that allows people to add, maintain, access and coordinate their lifelong health information and make appropriate parts of their own medical and health-related information available to those who need it (specialists, doctors, nurses, family members, etc). Some doctors and hospitals keep computerized medical records, but most personal health information's are stored in thick paper files that line office walls. There is no coordinated system, no standardized, no structured, private and secure way to integrate an individual's health information in one place. A visit to a new doctor means new forms to complete, new tests to run and new conversations reviewing your personal medical history. Those conversations depend almost entirely on memory alone and those tests involve costs. People need effective tools to help them manage their health and their care. Interest and research in personal health record (PHR) systems has recently increased, leading to the availability of a variety of PHR systems on the market that targets everyone from the general public to disease-specific patient groups. For individuals, having a PHR can have a lot of benefits like: helping understand consulting physician instructions, improving prevention of medical mistakes, helping person to ask physician better questions or just give more control over own care. PHR systems currently available on the market target a variety of patient and consumer groups and vary considerably with respect to what information the records may contain and how that information is presented.

AIM AND OBJECTIVES

Production and experimental PHR systems and PHR research have targeted a diverse variety of demographic groups as well as more general audiences. To date, systems that address the needs of pregnant women have received relatively little

attention. During pregnancy, time, or the stage of pregnancy, is an important factor in the management and communication of information for health care providers and pregnant women and their families. Evidence that carrying personal health records during pregnancy helps women communicate with their health over their maternity care taken together with evidence that many women are motivated to seek health information from a variety of resources suggests that this is a demographic group that could benefit greatly from a comprehensive personal pregnancy health record system. The work we present here focuses on the pregnancy component of a family health record system, which we call Pregnancy Personal Health Record (PPHR). Records for pregnancy are an interesting focus because of both heightened attention to health information by the pregnant woman and because pregnancy, as a health condition, extends for a finite period of time, 40-41 weeks for most normal pregnancies. Moreover, pregnancies progress is monitored according to relatively well-defined developmental stages throughout the 40-41 week gestation period. This study is a result of explorations of possible interfaces for the PPHR as component of the family health record system.

Aim of study is to produce a model that:

- could record all antenatal care regardless of medical or/and antenatal complications;
- could be held by the pregnant woman;
- would contain pertinent information, tools and facilities for the woman and all her carers.

MATERIAL AND METHOD

We propose through this study to elaborate the functional specifications of the pregnant woman personal health record and to create and propose a functional prototype. As primary users we're targeting pregnant women and their family members. We intend to respond, as many as possible, to some of the specific needs of this life period. Secondary, especially through interactions modules, targeted users are doctors, pharmacists and other health care providers. In order to fulfill this proposed task, to understand pregnancy health information, we've started an content analysis of (a) medical pregnancy literature, (b) preexistent paper-based pregnancy documents and record forms, including online medical examination schedules, checklists or databases and (c) an overview of some of personal health record (PHR) systems or proposal of systems existent on the market (e.g. Google Health, Microsoft Health CUI, Oracle Healthcare Transaction Base). Review and analysis of temporal organization of popular pregnancy guides in monograph format and interfaces of PHR systems currently available on the market was performed. Monographic guides were chosen because they are a popular information resource for pregnant women. The monographic guides or systems which were included in our study resources were intended for a general audience and information regarding the organizational structure of the guide or system was readily accessible from the Internet. Reviews of a paper-based pregnancy record form set, a pregnancy organizer, and literature examining information-seeking and health record use as related to maternal care and pregnancy were taken into consideration when interface was designed. Temporal visual metaphors were reviewed with respect to time-based factors of pregnancy and pregnancy records. Information derived from these resources was applied to the development of an experimental PHR pregnancy system interface design.

Design principles that we tried to followed are: (1) to promote information sharing among women, health professional's hospitals and diagnostic services, (2) to provide a guideline for evidence based practice, (3) to promote documentation of care, (4) to promote coordinated antenatal care, (5) to discourage transcribing, (6) to protect the integrity and security of the record. Five

facets have we identified: <Appointment>, <Diary>, <Health Data>, <Finance>, and <Resources and Tools> and were selected as major organizational elements in the user interfaces.

RESULTS:

The pregnant women Personal Health Record can become part of the woman's hospital obstetric record at the time of birthing. That's why we propose following structure:

(A)Personal details:

(A1) Contact general information – this includes expectant woman's name, age, address, phone, marital status, religion, ethnicity, spoken language -if an interpreter is needed, occupation, etc.

(A2) Partners details - information about the expectant woman's partner;

(A3) Midwife information's – information about expectant woman preferred midwife;

(A4) Contact Person – a list of preferred alternative contact person if this is not the partner

(A5) Appointment information – provides scheduling information's about medical examination terms, other health care related activities, social events and personal events;

(A6) Birth Preferences - provides the woman with the opportunity to articulate her birth preferences.

(A7) Other information - allows expectant women to add some information's which are important from his point of view.

(B)Personal medical history:

(B1) Medical history – provides a collection of relevant information's:

(a) gynecological (like date of last pap smear, fertility problems, gynecological disease, prenatal diagnosis counseling, etc.) history,

(b) medical (like childhood illnesses, blood disorders, asthma, chest disease, heart disease, diabetics, gastrointestinal disorders, high blood pressure, kidney disease, epilepsy, thyroid diseases, psychiatric diseases, etc.) history,

(c) surgical (like blood transfusions, surgical history, previous anesthetics, etc.) history, (d) about used medication/drugs (like current medications, alcohol, smoking, other drugs, etc.)

(e) about family health history (like presence of following diseases in family: asthma, diabetes, heart disease, high blood pressure, postnatal depression, psychiatric illness, genetic disorder, etc);

(B2) Alerts – for known allergies;

(B3) Previous pregnancies- information on previous pregnancies. Important information's for each previous pregnancy are included like: date and place of birth, mode of delivery, duration of labour, outcome type, complications, newborn child name, sex and weight, APGAR score, feeding method and length of breastfeeding.

(C) Current pregnancy:

(C1) Best estimate due date

(C2) Contraception: - provides a picture of the contraceptive used methods (previous contraception method and date of ceased, assisted conception and method)

(C3) Current scans:

(a) Laboratory results - this section provide a guide to the types (like blood group, antibody screen, hemoglobin, syphilis serology tests RPR/TPHA, hepatitis B, rubella titre, urine dipstick and mid stream specimen urine, glucose screen, early glucose tolerance test etc.) and timing (in 5-12 weeks, 28 weeks, 36 weeks, other if necessary) of laboratory investigations.

(b) Ultrasound results – provides imported information's and pictures from GP

(D) Birth plan:

(D1) Mobility an position for labour and birth – description of indented position (like walking, standing, squatting, sitting, kneeling, lying on floor mat/bed, etc);

(D2) Relaxation and personal comfort like massage oils, aromatherapy, bath, music, relaxation CD/tapes, shower, relaxation techniques, hot towels, etc.

(D3) Pain Relief – selected option like: entonox gas, epidural, pethidine (or other narcotic) injection, etc.

(D4) Contingency Plan – description of what women might want if things don't go

as planned, e.g. long and/or difficult labour, preterm baby. (More pain relief than anticipated, assisted delivery like forceps/ventouse-vacuum extraction, caesarean-operative delivery, episiotomy, other).
(D5) Cutting the cord – describes who suppose to cut the cord partner/supporting person or other person.
(D6) Placenta (afterbirth);
(D7) Infant Feeding – describes if women plans to breast/bottle feed baby soon after birth.

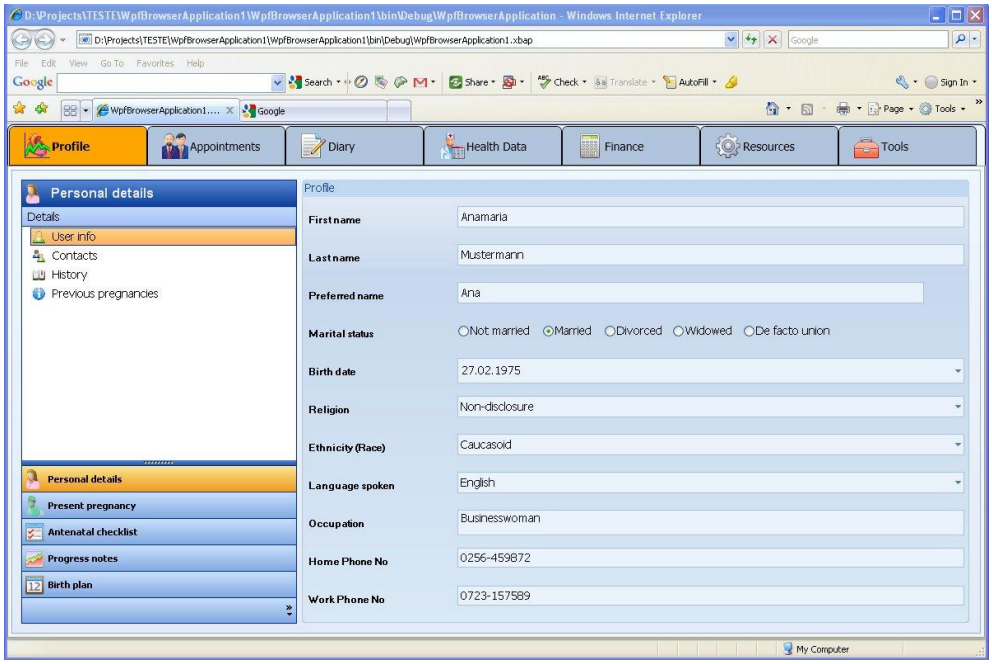

Fig.1. Snapshot from <Profile> view

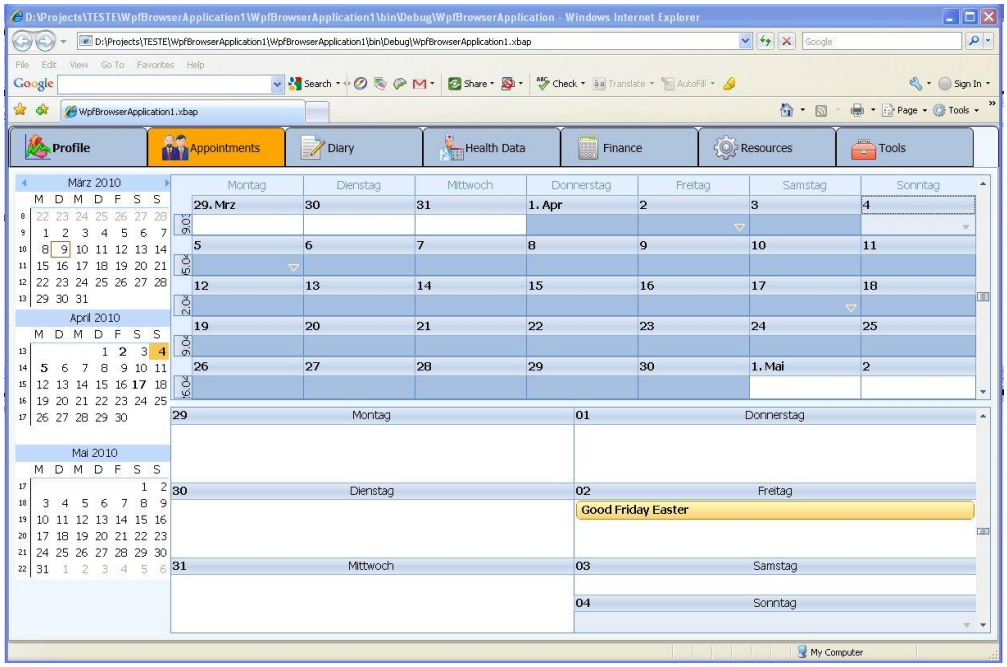

Fig. 2. Snapshot from <Appointment> view

DISCUSSIONS & CONCLUSIONS

The Personal Health Record (PHR) as an Internet-based set of tools that allow people to access and coordinate their lifelong health information and make appropriate parts of it available to those who need it, offers an integrated and comprehensive view of health information, including information people generate themselves such as symptoms and medication use, information from doctors such as diagnoses and test results, and information from their pharmacies and insurance companies. Individuals access their PHRs via the Internet, using state-of-the-art security and privacy controls, at any time and from any location. Family members, doctors or school nurses can see portions of a PHR when necessary and emergency room staff can retrieve vital information from it in a crisis. People can use their PHR as a communications hub: to send email to doctors, transfer information to specialists, receive test results and access online self-help tools. PHR connects each of us to the incredible potential of modern health care and gives us control over our own information.

The current generation of Internet-accessible PHR-like tools is almost exclusively owned, controlled and maintained by large integrated health care delivery networks for the exclusive use of the patients they serve in an effort to reduce their overall costs.

In the future PHR must be able to be integrated with a standardized, interoperable network of electronic medical record (EMR) systems. Successful PHR efforts will have to build upon standards and protocols that are adopted and fully implemented by community providers, insurers and other key data suppliers.

Developers of data standards for PHR face several unique challenges. Standards developed primarily for electronic medical record (EMR) do not recognize or anticipate all of PHR potential benefits and objectives. For example, PHR users are likely to enter important health information that will gain value when interpreted alongside EMR data – such as self-administration of medications, monitoring of blood pressure or glucose levels, dietary or exercise information, or functional and symptom measures. Most of these concepts have not been standardized and algorithms for integrating, displaying or taking action on these data as they interact with EMR data are not available. Similarly, a standard way for people to note and communicate possible errors or conflicts in their record across the network will need to be developed.

In this direction our study proposes also an open source graphic interface for our model of Pregnancy personal health record.

To ensure widespread adoption and use of PHR, PHR-specific standards should be identified. Standardization efforts include the health data and functionalities specific to the needs of diverse individual users. Latest guidelines will need to be established for transmitting and maintaining information created by PHR users. Standards for sharing information will need to be developed for care settings inside and outside of traditional health care systems.

This will require that PHR data taxonomy, syntax, architecture and communications protocols result in relatively easy and secure transfer of information between people and their various health care providers.

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CORRELATIONS BETWEEN BIOLOGICAL AND ULTRASOUND DATA IN PATIENTS WITH METABOLIC SYNDROME AND LOW CARDIOVASCULAR RISK

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ABSTRACT

Metabolic syndrome (MetS) increases up to 3-fold the risk of cardiovascular disease (CVD). Interrelations between MetS components and parameters of subclinical expression of CVD as carotid intima-media thickness (IMT) and flow-mediated vasodilation (FMD) are poorly understood, especially in patients with low cardiovascular risk.

Objectives. We aim to study the relationship between biological markers (HDL-cholesterol, triglycerides) and ultrasound parameters (left ventricular diastolic function, IMT, FMD) in patients with MetS and low cardiovascular risk.

Materials and methods. We studied 49 patients with MetS and low cardiovascular risk, admitted in Internal Medicine Clinic of City Hospital of Timisoara between June 1, 2008 to September 1, 2009. All patients were performed: biological samples, echocardiography, carotid ultrasonography and determination of flow-mediated vasodilatation in the brachial artery.

Results. We did not find statistically significant correlations between biological and ultrasound data. The average IMT was 0.76 ± 0.16 mm. Atheromatous plaque was present in 14.28% of patients. The average FMD was 6.81 ± 3.92%. Impaired FMD was present in 79.58% of patients. Left ventricular diastolic dysfunction was present in 75.5% of patients.

Conclusions. The lack of correlations between biological and ultrasound data is due to minimal expression of disease in MetS patients of average age and low cardiovascular risk, difficult to detect with regular investigation means. FMD should be introduced in the evaluation of patients with cardiovascular risk because it diagnoses early endothelial dysfunction, the initial stage of CVD, and contributes to the primary prevention of CVD.

Key words: *metabolic syndrome, FMD, IMT, diastolic dysfunction, endothelial dysfunction, low cardiovascular risk.*

INTRODUCTION

Metabolic syndrome (MetS) is increasingly important in recent years due to the proven association with increased risk of developing coronary heart disease and type 2 diabetes mellitus. Multicenter randomised trials demonstrated that MetS is associated with a 2-3-fold increase in the risk of cardiovascular disease and 5-fold increase in the risk of type 2 diabetes mellitus. Cardiovascular risk conferred by MetS may exceed the sum of the risks incurred by each component. The major

clinical consequence of MetS is the atherosclerotic cardiovascular disease (CVD) and several components of MetS are known as risk factors for atherosclerosis.

OBJECTIVES

We aimed to study the relationship between biological and ultrasound data in patients with MetS associated with low cardiovascular risk:

- the relationship between serum lipids (HDL-cholesterol, triglycerides) and ultrasound data (left ventricular diastolic function, carotid intima-media thickness and flow-mediated vasodilation);
- the relationship between the various ultrasound parameters (left ventricular diastolic function, carotid intima-media thickness and flow-mediated vasodilation).

MATERIAL AND METHOD

This cross-sectional, observational study included 49 patients with MetS and low cardiovascular risk, admitted in Internal Medicine Clinic of City Hospital of Timisoara between June 1, 2008 to September 1, 2009.

MetS was defined according to NCEP 2005 criteria for the European population: abdominal obesity – waist circumference in men ≥ 94 cm, in women ≥ 80 cm; triglycerides (TGL) ≥ 150 mg/dL (1.7 mmol/L) or specific treatment; HDL cholesterol in men < 40 mg/dL and in women < 50 mg/dL or specific treatment; SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or antihypertensive treatment; fasting blood glucose ≥ 100 mg/dL (5.6 mmol/L) or hypoglycaemic treatment. Diagnosis of MetS was established in the presence of at least three criteria. We have considered the obesity mandatory criteria.

We excluded the patients with clinical manifest CVD (coronary heart disease, stroke, and peripheral arterial disease), the patients diagnosed with insulin dependent or non insulin dependent diabetes mellitus, chronic viral hepatitis, chronic consumption of ethanol.

The following laboratory investigations were performed in all patients: biological samples, echocardiography, carotid ultrasound (intima-media thickness) to assess early changes of vascular wall and determination of flow-mediated vasodilatation in brachial artery to assess endothelial function. The transthoracic echocardiogram was performed to identify the patients with left ventricular diastolic dysfunction and/or left ventricular hypertrophy (LVH). Vascular ultrasound was done in the morning, in fasting patients, with the reccommendation to avoid smoking and vasoactive medication since the previous evening. Carotid intima-media thickness (IMT) was assessed by the Kawamori method, the normal value being less than 0.9 mm. Atheromatous plaque is defined by a thickness greater than 1.5 mm. Evaluation of flow-mediated vasodilation (FMD) was performed by the method of Celermajer. Abnormal FMD is considered when the variation between the induced-ischaemia diameter of the brachial artery and the initial determinations is less than 10%.

Statistical Analysis

Parameter values were expressed as mean ± standard deviation or as average percentage values. For the analysis of correlation a Pearson linear analysis was used. A p-value < 0.05 was considered of statistical significance. For statistical analysis we used GraphPad InStat 3 program.

RESULTS

The average age of patients was 50.51 ± 9.17 years, with two peaks of incidence: between 40 to 50 years (32.65% of patients) and between 50 and 60 years (36.74% of patients). A percentage of 55.1% of the patients were males. Average waist circumference was 109 ± 14.5 cm in men and 103.4 ± 11.87 in women. Average blood pressure showed a pattern of systolic hypertension, with values slightly increased above the normal (SBP 140.1 ± 17.3 mmHg, DBP 81.42 ± 11.36 mmHg).

The average serum TGL value was 210.3 ± 148.52 mg/dL, including most patients in moderate hypertriglyceridemia. Average HDL-cholesterol value was 42.12 ± 12.43 mg/dL, with a gender difference: 39.07 ± 12.6 mg/dL in men and 50.4 ± 12.97 mg/dL in women. A percentage of 55% of patients met the HDL-cholesterol criteria to define MetS. The average E/A ratio, important criteria in diagnosing left ventricular diastolic dysfunction, were 0.89 ± 0.31. Left ventricular diastolic dysfunction was present in 75.5% of patients and left ventricular hypertrophy in 24.4% of patients. The average IMT was 0.76 ± 0.16 mm, below the cutoff value of 0.9 mm. Only 16% of patients had impaired IMT value. Atheromatous plaque was present in 7 patients (14.28%), 2 men and 5 women. The average FMD was 6.81 ± 3.92%, below the cutoff of 10%. A percent of 79.58% of patients had impaired FMD. We didn not find a correlation between serum levels of HDL-cholesterol/TGL and ultrasound parameters (diastolic dysfunction, IMT and FMD). The statistical significance was reached only for the relationship between TGL and IMT (p = 0.008), meaning that in this case is no reliable correlation (r =- 0.04). No statistically significant correlations were found by analysing the bilateral relationship between measured ultrasound parametres.

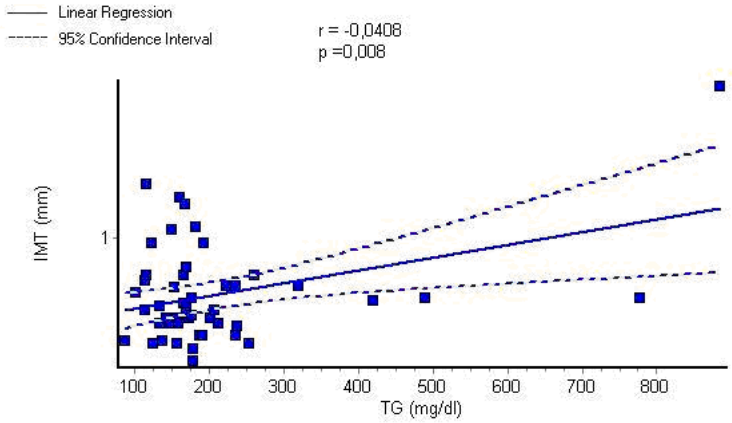

Fig.1. Correlation between serum TGL and IMT

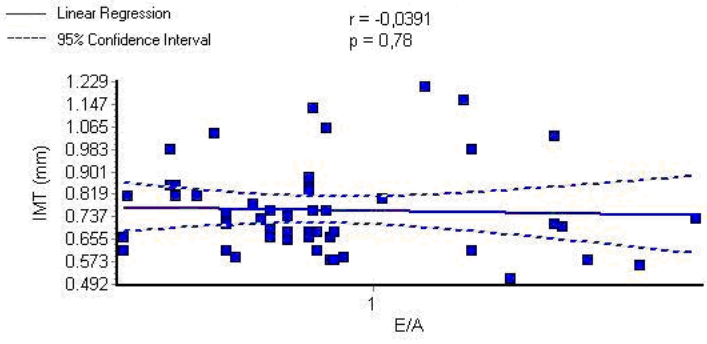

Fig.2. Correlation between E/A ratio and IMT

DISCUSSIONS

Nowadays the value of clinical diagnosis of MetS is controversial as there are a multitude of studies both for and against it. Our study includes patients without CVD, with low or intermediate cardiovascular risk, an average age of approximately 50 years, in whom the

pathological changes are at a subclinical level. This is the model patient in whom prophylactic measures have the most important outcome. We have analysed, from this point of view, the average age MetS patient to follow the presence of changes and correlations at initial stage of the disease. Our results show a relatively high value of average waist circumference in women, only 5.6 cm lower then in men, while the difference in threshold values for abdominal obesity for the two sexes is 14 cm.

The percentage of patients with low HDL-cholesterol (55%) is much higher then in literature (almost double compared to figures in the National Health and Nutrition Examination Survey), which may be a particular characteristic of MetS in our population.[1] One of the possible explanations of this high percent may be the higher proportion of smoking and inactivity in our population then in the Western population. HDL-cholesterol is significantly higher in women, due to the oestrogen protection in women before menopause. In one of his studies, Fuentes demonstrates that patients with MetS have diastolic dysfunction independent of the left ventricular mass [2].

In our study, ultrasound showed a high prevalence of diastolic dysfunction of the left ventricle in MetS patients (75%). Since blood pressure was only slightly increased in the studied patients, the cardiac injury, in this case the altered left ventricular relaxation seems not to be caused by the hypertensive cardiopathy and may have endothelial dysfunction as underlying mechanism.

In our study, carotid ultrasound showed a relatively high prevalence of atheromatous plaque – 14.28% (7 patients, 2 men and 5 women), confirming the subclinical stage of CVD, in contradiction with the low cardiovascular risk evaluated according to classical risk factors.

We did not find studies in literature showing correlations between serum levels of HDL-cholesterol /TGL and ultrasound parameters measured in MetS patients with average age and low cardiovascular risk.

Correlation between diastolic dysfunction and impaired IMT is controversial, many studies being carried out in a relatively small number of patients (hundreds) and with contradictory results. A study carried out by Parrinelo in 2001 in 105 patients demonstrates a negative correlation between IMT and the E/A ratio in young patients newly diagnosed with hypertension, but only in those with LVH, which implies an older hypertension. [3] Most patients in our study did not have LVH, so hypertension was more recently installed compared to the moment of diagnosis and the subclinical stage of the disease was in its beginning. This may be the explanation why we did not find this correlation, apart from the small number of patients.

On the contrary, other studies suggest that correlation between diastolic dysfunction and impaired IMT is independent of the presence of LVH, endothelial dysfunction being the morphophysiopathological mechanism for both the diastolic dysfunction as well as for the rise in IMT in MetS patients. This is also our opinion, and the possible explanation for the lack of correlation may be the small number of patients and the use of a single indicator (E/A ratio) and not the most sensitive one for the left ventricular diastolic dysfunction due to altered relaxation. Other indicators, isovolumic relaxation time and E-wave deceleration time have positively correlated with the increased IMT [4], independently of the presence or absence of LVH.

Relationship between FMD and left ventriculae diastolic dysfunction in MetS patients with low or intermediate cardiovascular risk has been less studied until today. Correlation between FMD and IMT could not be demonstrated in our study, as it is controversial in literature. Impaired FMD and IMT are surrogate markers for atherosclerotic disease and are considered predictors of cardiovascular events. Studies in patients with CVD or

high cardiovascular risk have shown negative correlations between IMT and FMD.[5]

Relationship between IMT and FMD was not adequately evaluated in patients without BCV with low or intermediate risk for acute cardiovascular events. An important result of our study is the lack of correlation between IMT and FMD in MetS patients without CVD. We consider that these results are due to the temporal dissociation between vascular functional and structural changes in patients with low cardiovascular risk. Probably endothelial dysfunction precedes detectable morphological changes of the arterial wall and it may be partially reversible.[6]

Among the limits of our study we mention: too small number of patients for statistically significant results in a low or intermediate risk population; for the diagnosis of the left ventricular diastolic dysfunction we have not used more sensitive indicators for altered relaxation such as isovolumic relaxation time and E-wave deceleration time, the E/A ratio being the most calculated parameter in clinical practice.

CONCLUSIONS

FMD does not correlate with carotid IMT in MetS patients without clinical manifest CVD and with low or intermediate cardiovascular risk, because endothelial dysfunction precedes morphological alterations of the arterial wall. The lack of correlations between biological and ultrasound data is due to the minimal expression of disease in MetS patients of average age, difficult to detect with regular investigation means.

FMD should be introduced in the evaluation of patients with cardiovascular risk, even low, because it diagnoses early endothelial dysfunction, the initial stage of CVD, and contributes to the primary prevention of CVD.

Our study has demonstrated the importance of MetS as a cardiovascular risk factor, identifying asymptomatic patients considered to have a low to intermediate cardiovascular risk according to classical scores and who showed an advanced subclinical stage of CVD (carotid atheromatous plaque), patients at risk for acute cardiovascular events and who will benefit from an adequate treatment and careful monitoring through targeted, specific explorations.

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THE ANALYSIS OF STATE OF TENSION AND STRAIN AT THE LEVEL OF LUMBAR VERTEBRAE THROUGH FINITE ELEMENT METHOD.

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ABSTRACT

Objective: the analysis of state of tension and strain at the level of lumbar vertebrae through finite element method.

Method and material: We started with CAD modelling of biomechanic structures, realising a model of sustainability of the lumbar vertebrae, after which we performed the analysis states tension and strain at the level of lumbar vertebrae using finite element method. For elaboration of the solid CAD model was used tomography scanning of a real human lumbar vertebrae. The model developed was subjected to different loads through successive iterations similar to those governing the spine in a car accident.

Results: Higher or lower incidence of certain injuries is not random, and can not be charged solely to the conditions of the accident occurrence, but is implicitly determined by the structural characters of the vertebrae and the size of the loading forces.

Key words: *lumbar vertebrae, tension, deformation, resistance*

INTRODUCTION

The achievement of CAD models of the lumbar vertebrae, which covers the four basic phases of reverse-engineering in the geometric modelling namely: data acquisition phase, stage of data pre-processing, the stage delimiting the areas and construction of the surfaces, construction phase of the solid geometrical model CAD. The phase of data acquisition treats the imagistic of the vertebrae transverse sections through the process of tomography scanning. The phase of data pre-processing sets in detail the geometric reconstruction of the vertebrae surfaces starting from cross section images obtained by tomography scanning. Reconstructed surfaces of the vertebrae form the triangulation network, obtained by the technique of bevelling modelling, this technique being described in full in the introductory chapter.

In this stage appear the itinerary realising the triangulation network using the program of MATERIALISE Mimics 10.01. It is important to mention that physical object surface detail fidelity, whose geometric reconstruction was performed after its tomography scanning, depends on the accuracy of the cross sectional images of self-performance and implicit on the performances of the tomography scanning equipment. Tomography equipment of the last generation is capable of very high performance in terms of achieving cross-sectional images of any physical object.

Therefore the use of performance tomography equipment in conjunction with the adoption of appropriate programs of geometric reconstruction leads to impressive results in the field. In general, following completion of the triangulation network, there may be defects of discontinuities (gaps) type, which necessarily must be removed by filling operations. These operations were performed under the Rapidform XOR program. After carrying out the operations of filling gaps and refining the triangulation networks it results a number of 811,186 facets for the lumbar vertebrae, the average size of 0.2 mm sides.

Within the phase of areas delimitation and surfaces construction, triangulation network is divided into a multitude of areas (regions) taking into account the variation of the curves as there are oriented the facets in space. Operation of delimitation of areas or regions is also called segmentation. On the basis of regions resulting from segmentation operation is performed the3D curved surfaces that mimic the geometry of the scanned object 3D, such areas are interconnected by criteria of continuity and tangency. The 3D curved surfaces may be of Bézier or NURBS type. In other words, within the stage, it is realised the transition from the multitude of flat triangular surfaces (facets) of the triangulation network to the multitude of 3D curved surfaces. In the case of the lumbar vertebrae, the stage of areas delimitation and creation of surfaces was conducted throughout the Rapidform XOR program. Basically, were obtained 2.732 surfaces for the lumbar vertebrae. In the future compatibility of Bézier surfaces with CAD platforms, they are saved in an IGES file.

The CAD solid geometrical model construction phase realises the compatibility at the level of representation and consistency of Bézier surfaces with CAD platforms. This compatibility depends entirely on the type of the file that stores information about the Bézier surfaces, file made at the completion of the earlier phase. Therefore, generally the surfaces of Bézier type are saved in IGES files, these files having 100% compatibility with most CAD platforms. Also during this phase it is realised the "hardening" of the geometrical model by taking into account the volume defined by the multitude of the Bézier surfaces and the possibility of linking this volume of some mass properties specific to a considered material. In case of the lumbar vertebrae, the operations afferent to the phase were realised in the CAD SolidWorks 2005 program.

Analysis of the stress and strain states at the level of the lumbar vertebrae with the help of the Finite Element Method (FEM) begins with a brief description of the method. The proximate character of the FEM results pursuant to the fact that the real geometry is always replaced with a network of finite elements seeking the real form, but it can not be exactly reproduced only for some particular geometry, due to finite number of elements, and the unknown measures of the problems are calculated only in structure nodes. It follows the conclusion that the accuracy of calculation increases with the increase of the number of finite elements.

In general, structures of resistance, whose geometric shape present a plane of symmetry (i.e. the structures may be considered at geometric level as two "halves" identical mirrored), it is analysed with FEM at the level of a single "half" of the considered structures. As to the conditions applied in the FEM analysis, one can say that the CAD solid geometric model on half of a symmetrical structure resistance is embedded in the absent part (the half in the mirror) not represented in the model. For these reasons, CAD models of the two vertebrae were analyzed with FEM taking into account only half of their geometry.

As main objective of the analyses with FEM it consists the distribution method of the total tensions throughout each vertebra in part, tensions due to forces developed in various impact situations on the vertebrae, based on the fact that maximum values of tension during spread

are known, respectively compression, supported by bone material. Also, as the main objective is to determine the values of the critical forces of impact that can cause fractures at the level of the lumbar vertebrae.

The Software package with which the analyses with FEM were made, within the CAD SolidWorks 2005 program, is entitled COSMOSWorks 2005. Initially it is specified the type of study to be conducted. The type „Static Analysis'' was chosen because it is considered that the forces that are developed on the vertebrae are applied in a static regime. Once the study defined, the material of which the assembly is made is declared. Because the SolidWorks 2005 and COSMOSWorks 2005 package do not include in the database of the material types the characteristics of the bone matter, a new sheet of material was created with the required characteristics (maximum tensions during stresses - compression, the longitudinal modulus of elasticity and the coefficient of Poisson's transverse contraction). It is noted that it was considered perfectly homogeneous and isotropic material, i.e its mechanical properties of resistance do not vary with the directions of application of forces. This fact was used as a simplifying assumption.

After declaring the type of study and specification of the material characteristics, it was chosen the type of discretization in the finite elements (operation called meshing). In this case it were used finite elements of the tetrahedral type with four nodes per element – TETRA 4 adopted for the FEM analysis of solid bodies. It was adopted a high accuracy of discretization of the two CAD models in half of the vertebrae, the average size of finite elements was 1 mm. The discretization of the lumbar vertebrae model gathered 285,570 finite elements with a total of 53,064 nodes.

Introducing the boundary conditions or conditions on the outline are materialized by declaring the bearings imposed on CAD models of the vertebrae (those areas considered fixed, that do not suffer of displacements or who suffer certain blocked displacements - displacements being targeted to the three fundamental axes: x, y and z). Also during this phase, over the CAD models of the vertebrae are applied external charges (external forces – direction of the force marked with the mauve shade on the figures) that take place after the appliance of some shocks (strokes) as effect of some situations encountered in various road accidents.

It was made a series of FEM analysis, each analysis taking into account a possible scenario as a result of a road accident. In each analysis, the adopted value of the external force applied was determined by successive iterations, so that the total voltage σvonMises to reach the maximum allowable value (133 MPa), case in which it is considered the danger of fracture occurrence – the red shade on the figures show the risk areas for fracture occurrence. The possible scenarios considered for the lumbar vertebrae are:

I) horizontally back bump (fig.1, fig.2, fig.3a, fig.3b)
II) vertically previous bump due to the compression of the lumbar vertebrae (fig.4, fig.5, fig.6)
III) vertically bump due to the lateral compression of the lumbar vertebrae (fig.7, fig.8, fig.9) and
IV) horizontal lateral blow (fig.10, fig.11, fig.12).

CONCLUSIONS

Issue I): in case of a horizontally back bump applied to the posterior side of the lumbar vertebrae, to the dorsum apophysis, the fracture risk is highest at this level and smaller to the articular apophysis, and while maximum deformation is to the dorsum apophysis, the site of action of force (fig.1, fig.2, fig.3a, 3b.).

Issue II): in case of a vertically previous bump due to the compression of the lumbar vertebrae, such as in the case of the forced flexion, the tension is highest to the vertebral corps and the maximum

deformation to the anterior place of the corps (fig.4, fig.5, fig.6.). Such a mechanism is involved in causing settling fracture type.

Issue III): in case of a vertically bump due to the lateral compression of the lumbar vertebrae, such as in the case of lateral forced flexion, the tension is highest to the vertebral spring and the maximum deformation at the anterior place of the corps (fig.7, fig.8, fig.9). Such a mechanism is involved in causing lateral settling fracture type.

Issue IV): in case of a horizontal lateral blow to the transverses apophyses, such as in the case of direct hit, the maximum tension same as the maximum deformation is to the shock place, respectively to the transverse apophysis (fig.10, fig.11, fig.12).

After conducting the analysis with MEF afferent to each scenario in hand, it can come off a first conclusion, perhaps the most important one, the one related to the resistance of the vertebrae, the maximum resistance being given by the highest value of the external load applied in various situations of possible scenarios. Also, the lumbar vertebrae presents the maximum resistance for a horizontal back stroke (836 N), and minimal resistance with a previous vertically back stroke due to the compression of lumbar vertebrae (383 N).

In terms of deformations (movements) for maximum results, we considered favourable the situations in which they recorded the minimum values. Thus, the lumbar vertebrae presents the resulting minimal deformation for a horizontally lateral stroke (0.144 mm) and the maximum resulted deformation in case of a previous vertically stroke due to the compression of the lumbar vertebrae (1.203 mm). Analyzing the results, it can be stated the fact that, generally, the lumbar vertebrae is more resistant, supporting higher external loads, this fact being a direct consequence of the higher dimensions of this vertebrae and of the different geometric construction of the cervical vertebrae.

The results of this study demonstrate that higher or lower incidence of certain injuries is not random, and can not be charged solely to the conditions of the accident occurrence, but is implicitly determined by the structural characters of the vertebrae and the size of the loading forces.

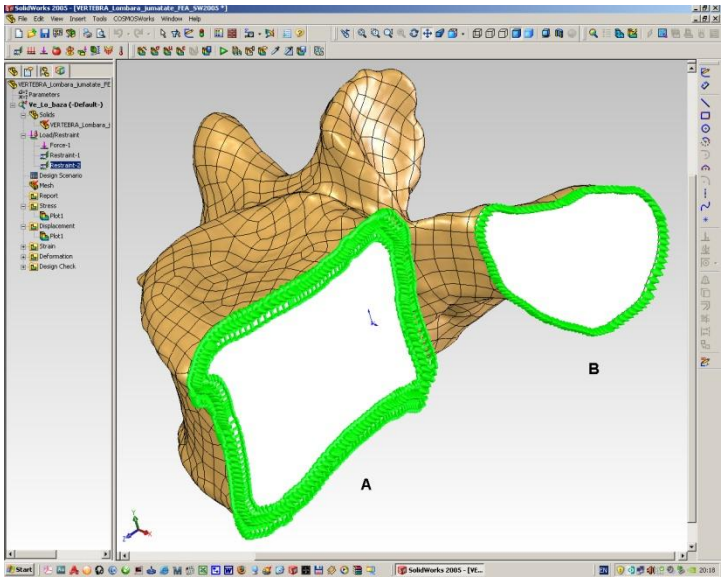

Fig.1 Lumbar vertebrae - horizontally back bump – leaning.

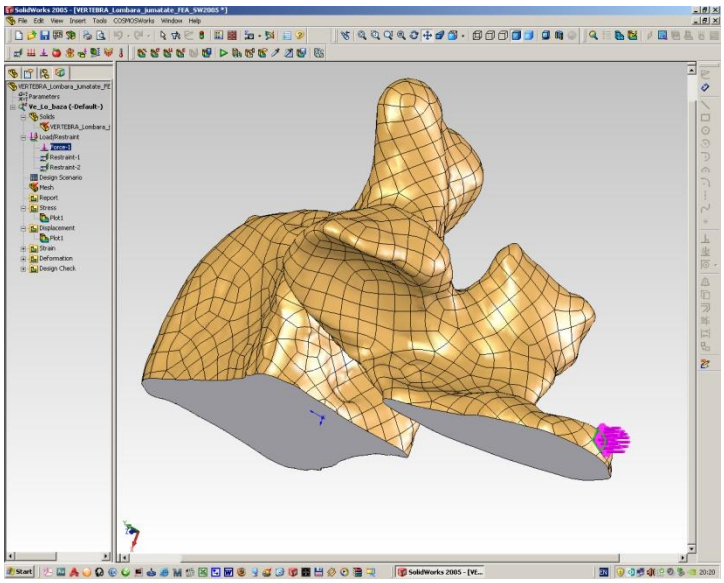

Fig.2 Lumbar vertebrae - horizontally back bump- charges.

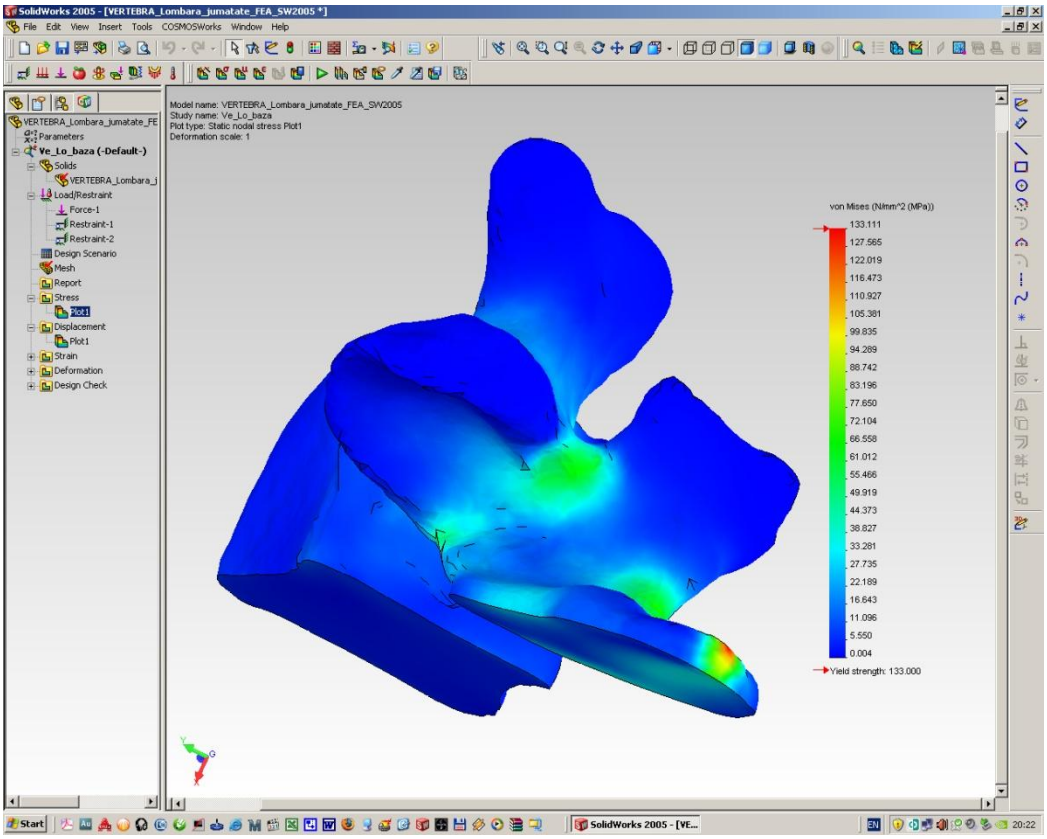

Fig.3a Lumbar vertebrae - horizontally back bump - deformations.

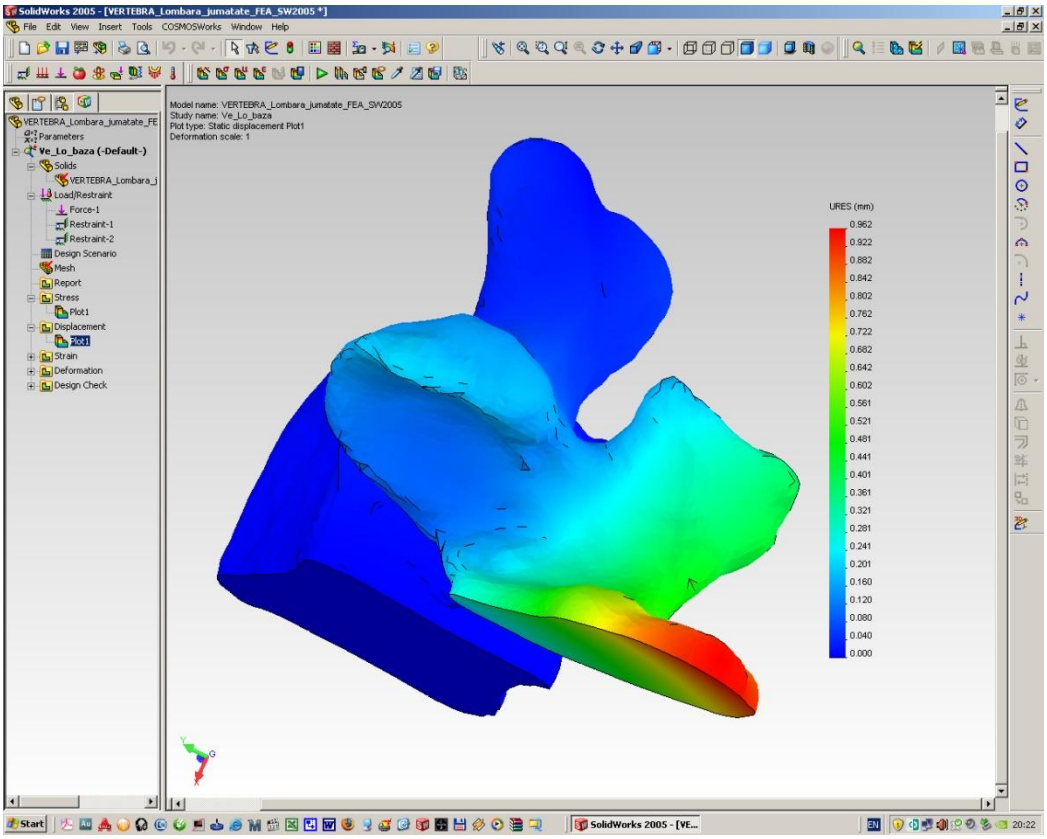

Fig.3b Lumbar vertebrae - horizontally back bump – deformations.

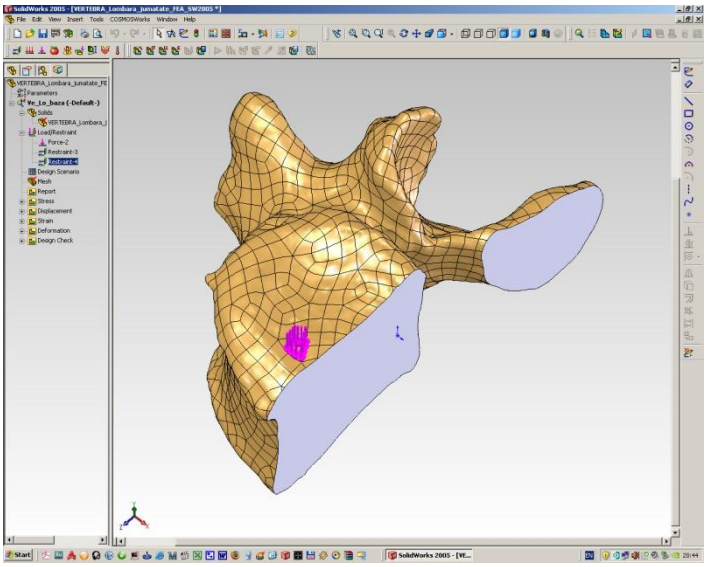

Fig.4 The lumbar vertebrae - vertically previous bump due to the compression - charges.

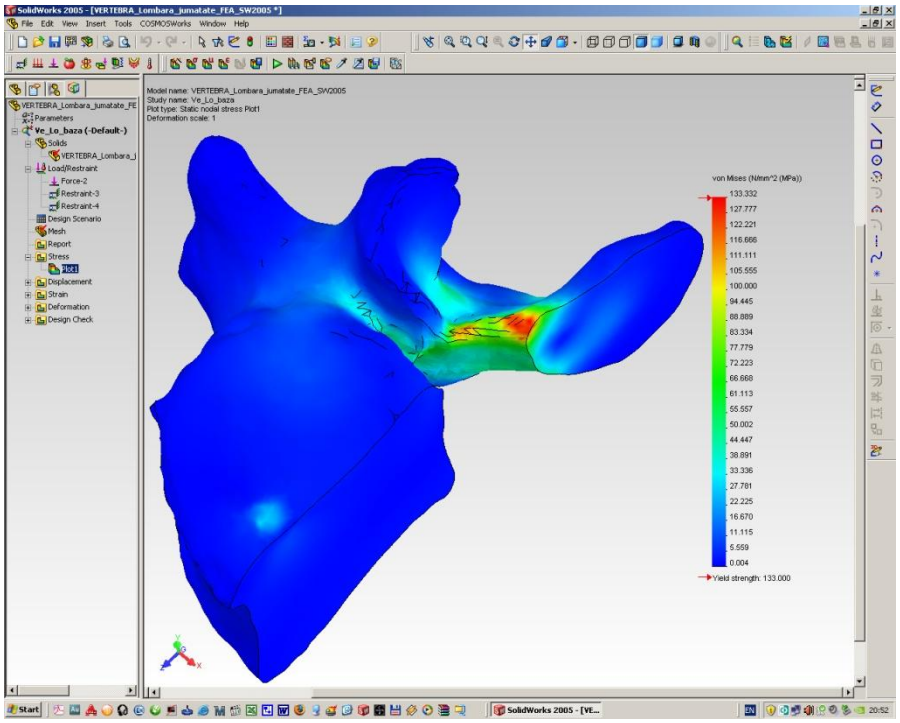

Fig.5 The lumbar vertebrae - vertically previous bump due to the compression – deformations.

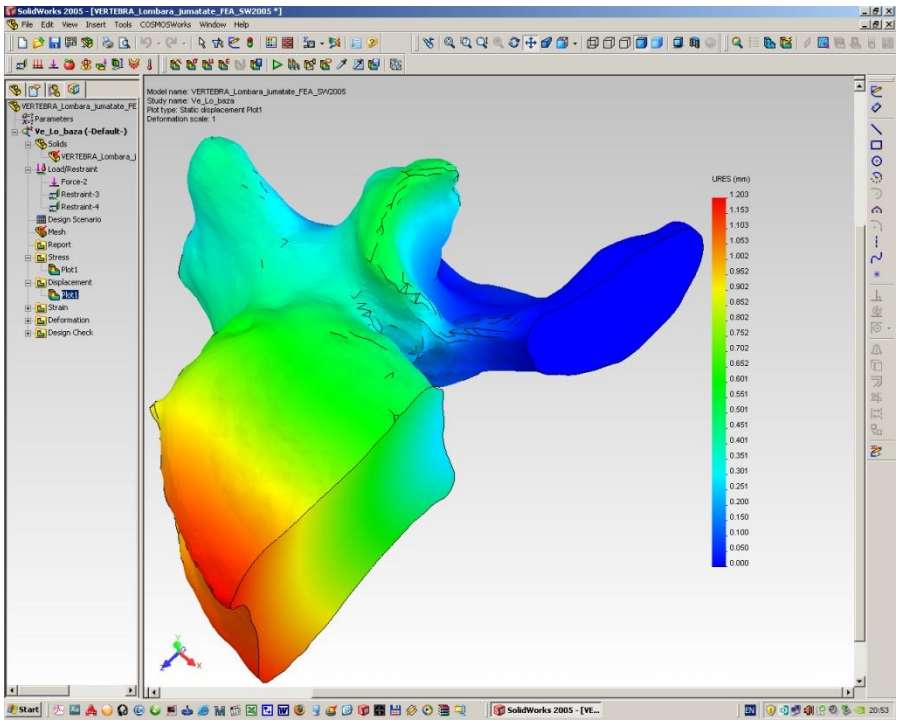

Fig.6 The lumbar vertebrae - vertically previous bump due to the compression – deformations.

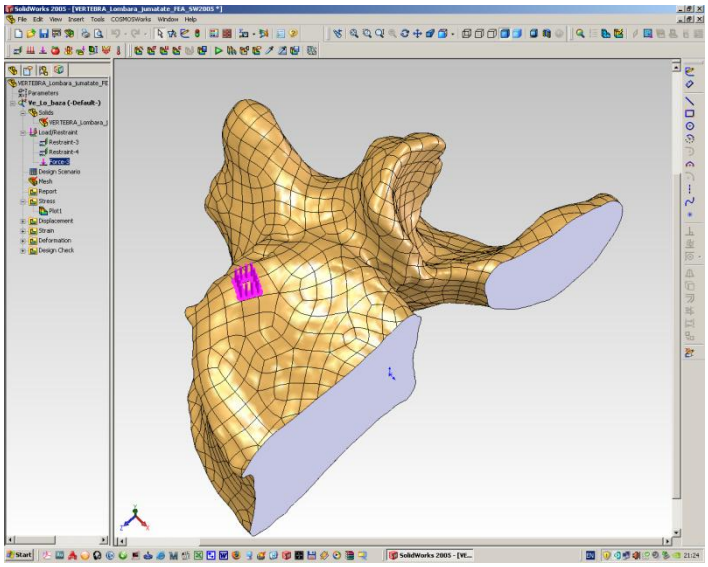

Fig.7 The lumbar vertebrae - vertically bump due to the lateral compression– charges.

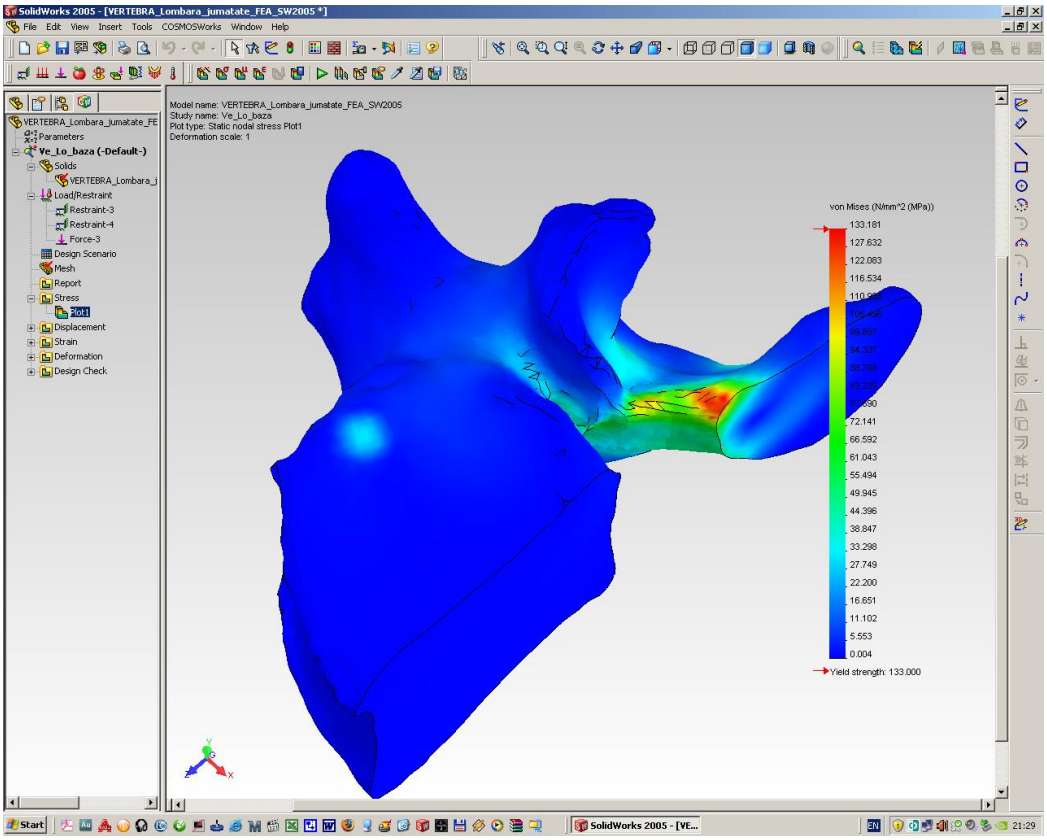

Fig.8 The lumbar vertebrae - vertically bump due to the lateral compression– deformations.

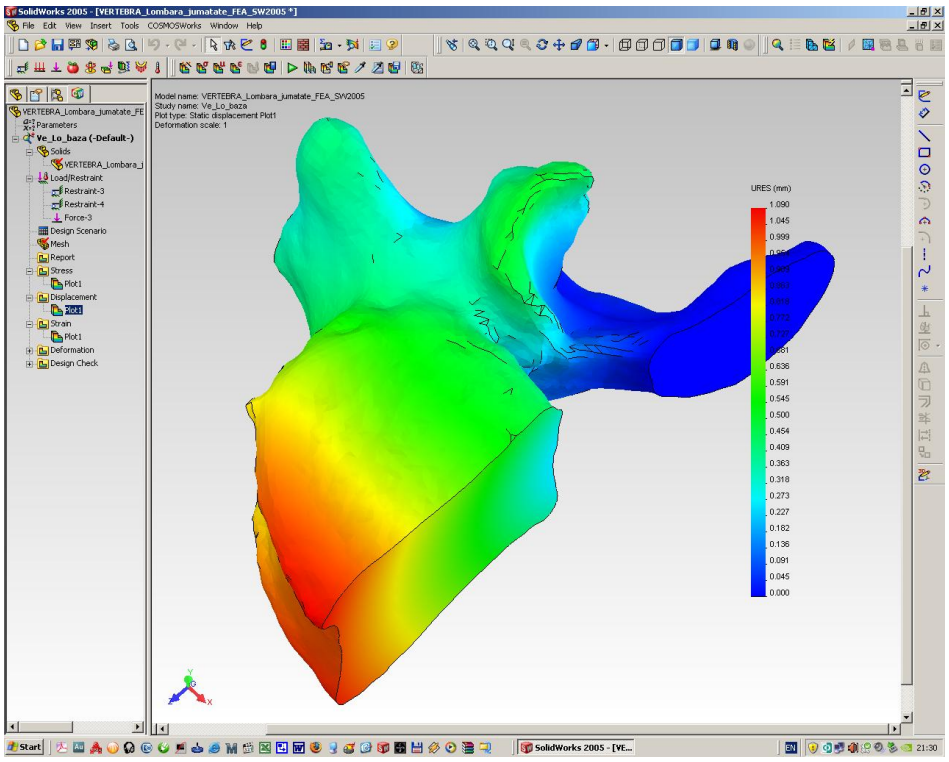

Fig.9 The lumbar vertebrae - vertically bump due to the lateral compression– deformations.

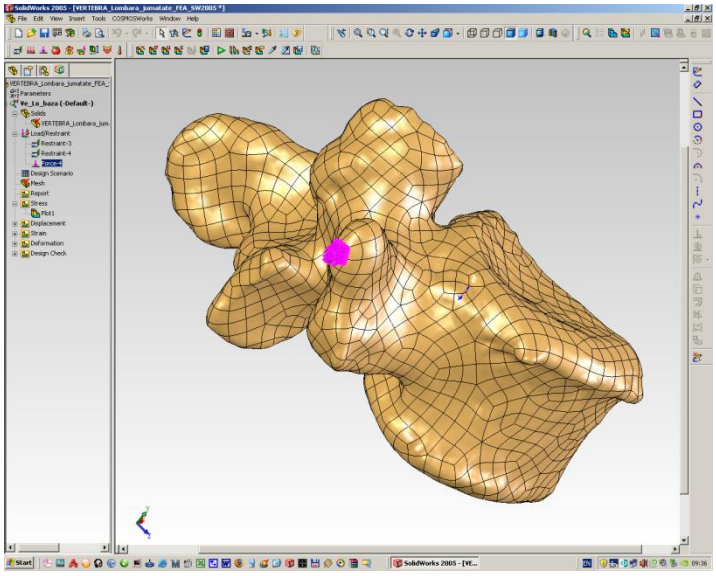

Fig.10 The lumbar vertebrae - horizontal lateral blow- charges.

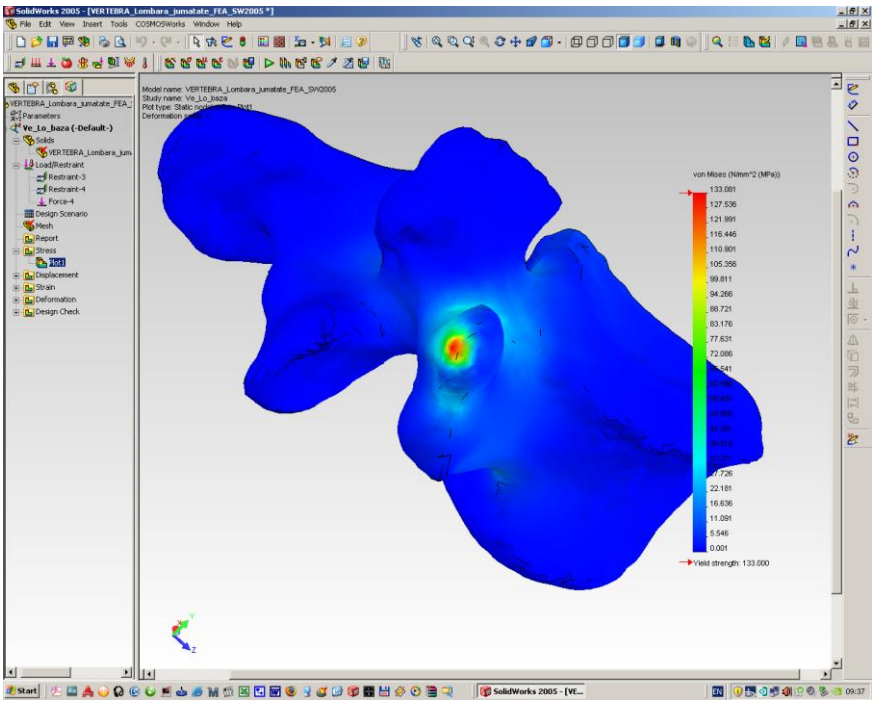

Fig.11 The lumbar vertebrae - horizontal lateral blow- deformations.

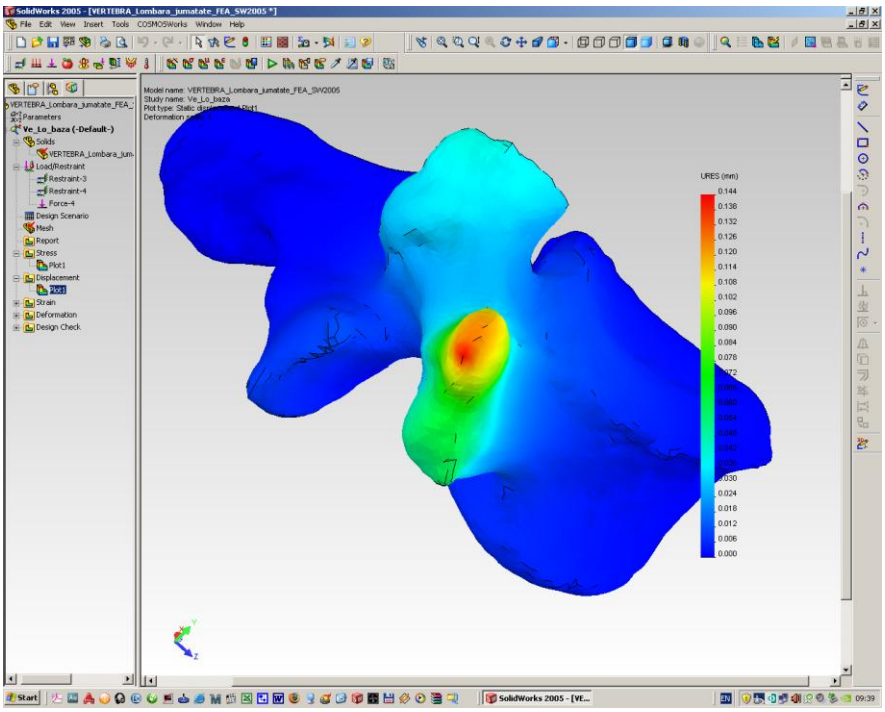

Fig.12 The lumbar vertebrae - horizontal lateral blow - deformations.

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HPV AND TEENAGERS

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ABSTRACT

Human papillomavirus (HPV), member of the papillomavirus family, is one of the most common causes of sexually transmitted infection in the world and it is found most commonly in young adults and sexually active teenagers. HPV infection is located only in the stratified epithelium of the skin or mucous membranes. There are over 100 types of human papillomavirus. Most are harmless, but about 30 types can cause cancer.

The major theme of HPV treatment is that while no effective antiviral drugs are yet available, a healthy immune response can clear or contain the infection. Abstinence is the only 100% way to avoid getting HPV. The HPV vaccine has been developed to immunize people against the high-risk types of HPV so that their body can fight the HPV if they contact HPV during sexual contact and so that the HPV infection can be prevented.

***Key words**: human papillomasvirus, teenagers, genital warts.*

INTRODUCTION

Papillomaviridae is an ancient and diverse taxonomic family of non-enveloped DNA viruses, collectively known as papillomaviruses.

Papillomaviruses affect a wide variety of animals. They cause tumors that erupt from DNA mutations in humans, monkeys, deer, horses, cattle, dogs, birds, and rabbits [(2)]. Papillomaviruses were first identified in the early 20th century, when it was shown that skin warts, or papillomas, could be transmitted between individuals by a filterable infectious agent. In 1935 Francis Peyton Rous, who had previously demonstrated the existence of a cancer-causing sarcoma virus in chickens, went on to show that a papillomavirus could cause skin cancer in infected rabbits. This was the first demonstration that a virus could cause cancer in mammals.

Human papillomaviruses (HPVs) produce epithelial tumors of the skin and mucous membranes. More than 100 HPV types have been detected, and the genomes of more than 80 have been completely sequenced. The current classification system, which is based on similarities in their genomic sequences, generally correlates with the 3 categories used to describe HPV clinically: anogenital and/or mucosal, nongenital cutaneous, and epidermodysplasia verruciformis (EV) [(9, 10, 11)].

Papillomaviruses are non-enveloped, meaning that the outer shell or capsid of the virus is not covered by a lipid membrane. A single viral protein, known as L1, is necessary and sufficient for formation of a 60 nanometer capsid composed of 72 star-shaped capsomers. Like most non-enveloped viruses, the capsid is geometrically regular and presents icosahedral symmetry. Self-assembled virus-like particles composed of L1 are the basis of a successful group of prophylactic HPV vaccines designed to

elicit virus-neutralizing antibodies that protect against initial HPV infection [2, 5].

The papillomavirus genome is a double-stranded circular DNA molecule ~8,000 base pairs in length. It is packaged within the L1 shell along with cellular histone proteins, which serve to wrap and condense DNA [5]. The papillomavirus capsid also contains a viral protein known as L2, which is less abundant. Although not clear how L2 is arranged within the virion, it is known to perform several important functions, including facilitating the packaging of the viral genome into nascent virions as well as the infectious entry of the virus into new host cells. L2 is of interest as a possible target for more broadly protective HPV vaccines. HPV infection is the most common sexually transmitted infection. The number of patients identified with HPV disease has increased markedly during the past 20 years because of heightened awareness of the various manifestations of HPV disease and because of increased use of HPV DNA testing [1]. Patients receiving immunosuppressive drugs and patients with defects in cell-mediated immunity, including those infected with the human immunodeficiency virus (HIV), are especially susceptible to developing HPV infections. The overall prevalence of HPV in women is 22-35%. In men, the prevalence is 2-35% depending on the sexual practices of the population being studied [3, 9]. Anogenital warts, or condylomata acuminata, are the most commonly diagnosed viral sexually transmitted disease (STD) in the United States and the United Kingdom. The annual incidence is estimated between 500,000 and 1 million cases [3]. The prevalence of anogenital mucosal HPV infections is highest among college-aged women and men. HPV types that tend to cause genital warts are not the same ones that cause cervical cancer [1].

The prevalence of HPV infection stratified by age in females is as follows (8):

- Age 14-19 years - 24.5%
- Age 20-24 years - 44.8%
- Age 25-29 years - 27.4%
- Age 30-39 years - 27.5%
- Age 40-49 years - 25.2%
- Age 50-59 years - 19.6%

Low-risk HPV types

Some types of genital HPVs can cause cauliflower-shaped warts on or around the genitals and anus of both men and women. In women, warts may also appear on the cervix and vagina. This type of "genital wart" is known as condyloma acuminatum and is most often caused by HPV-6 or HPV-11. Because these genital warts rarely grow into cancer, HPV-6 and HPV-11 are called "low-risk" viruses. These low-risk types can also cause low-grade changes in the cells of the cervix that do not develop into cancer [6].

High-risk HPV types

Other genital type HPVs have been linked with genital or anal cancers in both men and women. These types are called "high-risk" (6) because they can cause cancer. They also cause low-grade and high-grade changes in the cells of the cervix and pre-cancers. Doctors worry more about the high-grade changes and pre-cancers, because they are more likely to grow into cancers. Common high-risk HPV types include: HPV-16, HPV-18, HPV-31, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, and HPV-58. In 90% of cases, the body's immune system clears the HPV infection within 2 years. This is true of both high-risk and low-risk HPV types. The incidence of high-risk HPV infections drops after age 20-24 years, and the incidence of low-risk HPV types plateaus after age 30-39 years. Certain activities are associated with an increased risk of HPV malignant transformation, particularly in the anogenital/mucosal category.

Sexual activity

- A direct correlation exists between anogenital HPV infection and measures of sexual activity, such as the age of first intercourse and the lifetime number of sexual partners.

- Women with a history of cervical HGSIL or invasive SCC of the cervix are at increased risk for subsequent development of invasive cancer in other tissues of the anogenital/mucosal category, particularly vaginal and anal carcinoma, with relative risks of 5.6 and 4 respectively.
- Anal cancer has been strongly associated with male homosexuality and with specific male practices, such as engaging in receptive anal intercourse; relative risk is 33. However, the overall disease prevalence is higher in women than in men, with a female-to-male ratio of 1.5:1.

Tobacco smoking
- Women who smoke tobacco have an increased risk of developing cervical neoplasia.
- Measurable amounts of a potent carcinogen, as well as several compounds from cigarette smoke, have been identified in the cervical mucus of females who smoke. These agents are likely to play a role in the increased prevalence of HPV malignant transformation of patients who smoke tobacco.

Oral contraceptive use
- Women who use oral contraceptives for longer than 5 years have an increased relative risk of developing cervical carcinoma.
- This risk declines after stopping oral contraceptives, and no risk is demonstrated in users of less than 5 years duration.

Chewing Indian betel quid
- A high incidence of oral cancer associated with HPV infection has been demonstrated in India among patients who chew betel quid.
- This stimulant is made from the leaves of the betel plant and is used in a manner similar to chewing tobacco.

Ultraviolet and x-ray irradiation: EV is particularly susceptible to UV and x-ray irradiation; therefore, patients with EV should avoid activities that unnecessarily expose them to these forms of radiation.

Eradication or reduction of symptoms is the primary goal of treating warts, but elimination of dysplastic lesions is the goal in treating squamous intraepithelial lesions. Superiority of any single treatment modality has not been demonstrated, nor is one modality ideal for all types of warts. Factors that influence treatment of HPV disease include the size, morphology, number, and anatomic site of lesions, as well as cost, adverse effects, patient preference, and provider experience [10, 11]. Guidelines for cervical cancer screening and management of abnormal results in adolescents differ in important ways from those recommended for nonadolescent women [1]. These differences reflect the relatively low incidence of cervical cancer and the high incidence of human papillomavirus (HPV) infection in adolescents, compared with older females [12]. In 2006, the Food and Drug Administration (FDA) approved a vaccine that prevents the 2 types of HPV (HPV 16 and 18) that cause 70% of all cervical cancers. The vaccine also prevents 2 types of HPV (HPV 6 and 11) that cause 90% of all genital warts. This vaccine is named Gardasil®. There is another vaccine that is still being studied to see if it safely prevents HPV 16 and 18. It is called Cervarix®, and it is not yet approved by the FDA for use in the United States. Unlike Gardasil, it does not target the wart-causing HPV types. The vaccine will prevent HPV only if it is given before a girl has been exposed to HPV. The vaccine is recommended for girls' ages 11 to 12

because most girls at this age have not become sexually active [7].

Vaccination with the above HPV vaccines does not give 100% protection against cervical cancer: HPV types 16 and 18 covered by the vaccines account for around 70% of cervical cancers in women worldwide. To be most effective, the HPV vaccine should be given before a female has any type of sexual contact with another person. It is given in a series of 3 doses within 6 months. Here are the recommendations for each age group [12]:

- girls ages 11 to 12 - the vaccine should be given to girls ages 11 to 12 and as early as age 9.
- girls ages 13 to 18 - girls ages 13 to 18 who have not yet started the vaccine series or who have started but have not completed the series should be vaccinated.
- young women ages 19 to 26 - some authorities recommend vaccination of women ages 19 to 26, but the American Cancer Society experts believed that there was not enough evidence of the benefit to recommend vaccinating all women in this age group. It is now recommended that women ages 19 to 26 talk to their doctors or nurses about whether to get the vaccine based on their risk of previous HPV exposure and potential benefit from the vaccine.

There are some questions of general interest:

Are there some girls or women who should not get the HPV vaccine or who should wait?

- Anyone who has ever had a life-threatening allergic reaction to yeast or anything else in the HPV vaccine, or anyone who has had a reaction to an earlier dose of HPV vaccine should not get the vaccine. Tell the doctor if the girl getting the vaccine has any severe allergies.

Can boys get this vaccine?

- At this time boys cannot get the HPV vaccine. Boys were included in some of the studies - the vaccine was found to be safe and the boys' immune systems did respond to it. It is not known at this time if the vaccine will protect boys from genital warts or keep them from passing HPV to their partners. Studies are being done to find out if the vaccine will prevent HPV infection and genital warts in boys.

Modern medicine permits, through its new technical acquisitions, a depth exploration of human universe, for a better understanding of mechanisms involved in the etiopathogeny of diseases. Thereby therapeutic posibilities will be better.

It is important to recognize the infection with HPV as a major public health problem by all the factors involved in surveillance of the population health.

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A CLINICAL CASE OF KLINEFELTER'S SYNDROME WITH PARTICULAR PHENOTYPE

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ABSTRACT

Klinefelter's syndrome, also known as 47, XXY or XXY syndrome is a condition in which males have an extra X sex chromosome. It is the most common chromosomal disorder associated with male hypogonadism and infertility. In the same time, it is the second most common condition caused by the presence of extra chromosomes. The syndrome is characterized by hypogonadism (small testes, azoospermia/oligospermia), gynecomastia in late puberty, psychosocial problems, hyalinization and fibrosis of the seminiferous tubules, and elevated urinary gonadotropin levels.

The most common karyotype is 47,XXY, which accounts for 80-90% of all cases. Mosaicism (46,XY/47,XXY) is observed in about 10% of cases. Other variant karyotypes, including 48,XXYY; 48,XXXY; 49,XXXYY; and 49,XXXXY, are rare. The genetic variation is irreversible. Testosterone treatment is an option for some individuals who desire a more masculine appearance and identity.

***Key words**: Klinefelter syndrome, phenotype, child.*

INTRODUCTION

Klinefelter Syndrome (KS) is a sex chromosome abnormality affecting approximately 1 in 800 males. KS is most often identified during late puberty or early adulthood, when patients present for endocrinological testing, but the syndrome can remain undetected over a lifetime [1, 2].

The major consequences of the extra sex chromosome, usually acquired through an error of nondisjunction during parental gametogenesis, include hypogonadism, gynecomastia, and psychosocial problems. Klinefelter syndrome is a form of primary testicular failure, with elevated gonadotropin levels due to lack of feedback inhibition by the pituitary gland. Androgen deficiency causes eunuchoid body proportions; sparse or absent facial, axillary, pubic, or body hair; decreased muscle mass and strength; feminine distribution of adipose tissue; gynecomastia; small testes and penis; diminished libido; decreased physical endurance; and osteoporosis [3, 4, 5].

Klinefelter syndrome goes undiagnosed in most affected males; among males with known Klinefelter syndrome, many do not receive the diagnosis until they are adults. The most common indications for karyotyping are hypogonadism and infertility [5, 6].

Treatment should address 3 major facets of the disease: hypogonadism, gynecomastia, and psychosocial problems.

Androgen therapy is the most important aspect of treatment. Androgen therapy is used to correct androgen deficiency, to provide appropriate

virilization, and to improve psychosocial status [7]. A multidisciplinary team approach can assist in improving speech impairments, academic difficulties, and other psychosocial and behavioral problems. Surgical terapy (mastectomy) may be indicated for gynecomastia, which places considerable psychological strain on the patient and increases the risk of breast cancer.

Case report

A 1 year 2 month old boy presented at the pediatrician for a respiratory intercurrence. For the first moment, we noticed his particular clinical features: round face, hypertelorism, discreet epicanthal folds, a nasal bridge that looks pushed in, low-set ears, downward slant to the eye. The child derives from the 4-th pregnancy of a 29 years mother (the first and second pregnancy ended by spontaneous abortion in the first trimester, the third one was stopped in evolution). During pregnancy, mother was carefully followed by the obstetrician. She received treatment with Gravidin and made all tests necessary in order to avoid any complication.

The child was born premature, at 33 weeks, with 2820g weight, Apgar score 9, natural delivery in cranial presentation. He had a good postnatal adaptation without further incidents.

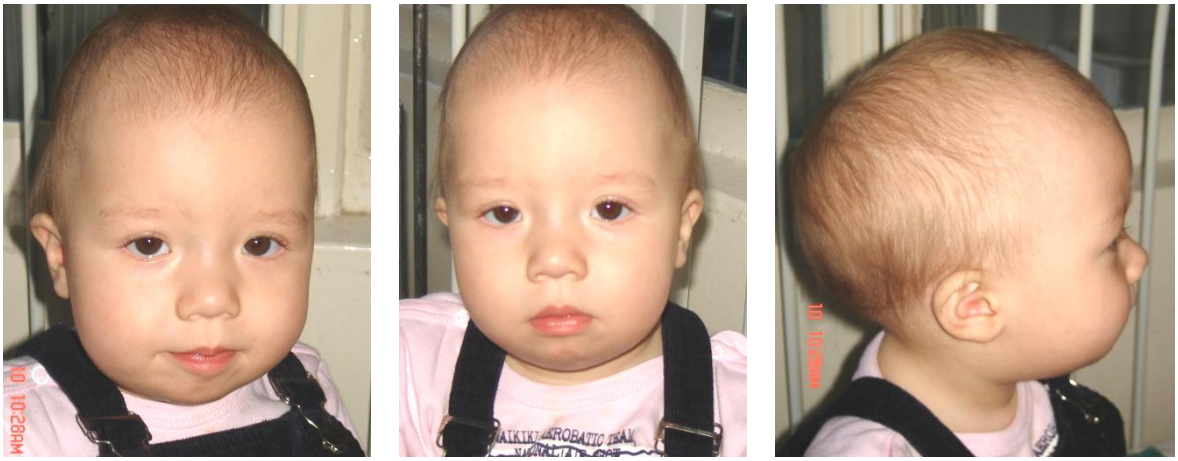

Fig.1 Photos of boy with Klinefelter's syndrome.

Due to his particular phenotype we decided to investigate him for a genetic syndrome. A karyotype was effectuated in order to determine the diagnosis.

There were evaluated 30 metaphases obtained through standard culture and GTG banding (resolution level of 450 strips).

There were noticed metaphases with 2 X chromosomes in proportion of 100%.

In conclusion, the karyotype of this child is 47XXY – Klinefelter syndrome.

The result was surprising, due to the fact that the patients with KS didn't present any phenotypic abnormalities, the most overwhelming of cases being diagnosed at puberty.

In this case, the early diagnose is useful for a carefully follow up (in order to improve speech impairments, academic difficulties, and other psychosocial and behavioral problems) as well as a precocious substitutive treatment with testosterone.

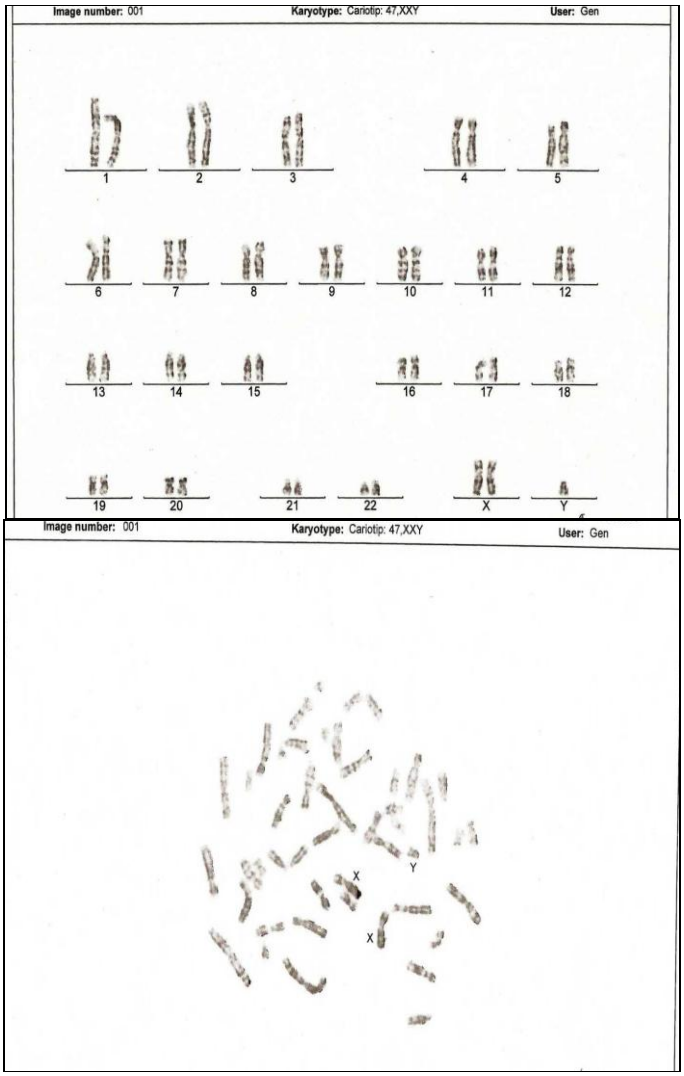

Fig.2, Fig.3 Klinefelter syndrome; the karyotype was 47XXY

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COBALT-CHROMIUM DENTAL ALLOYS DOPED WITH GOLD OR PLATINUM

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ABSTRACT

New generations of cobalt-chromium alloys doped with precious metals (Au, Pt, and Ru) are now coming on the market with the idea to improve the corrosion resistance. The goal of this study was to verify this hypothesis, by testing 4 different such alloys. Before electrochemical testing the alloys were analyzed micrographically, analysis of phases by energy-dispersive X-ray spectroscopy (EDX) was carried out and hardness properties were also tested. The microstructures of alloys #1 and #4 exhibited round "inclusions" with a diameter up to 0.1 mm. The chemical analysis of these zones showed of in (betweeen 42 and 51%), Pt (around 28%) and Au (between 18 and 27%). The Vickers tests of such zones for #4 gave a mean hardness value more than twice lower (147 HV) compared to the overall hardness value of the alloy (326 HV). The potentiodynamic curves reveal important differences in the behaviour of the studied alloys (#1-#4) as compared to the conventional Co-Cr alloy. The worst behaviour was given by the alloys containing only gold (#1 and #4). Alloys #1 and #4 showed a very complexe microstructure compared to the other studied alloys. The round "inclusions" with a diameter up to 0.1 mm are in part non miscible phases with a very low corrosion resistance. From the point of view of corrosion behaviour, the classical Co-Cr alloy is the best material followed by the alloys #2 and #3 (addition of respectively 4 % and 25 % precious metals). The worst alloys were #1 and #4 (with only addition of 2 % of Au).

***Key words**: Cobalt-Chromium dental alloys, corrosion, phase analysis, hardness properties, microstructure.*

INTRODUCTION

Cobalt-chromium alloys are known to have excellent corrosion resistance. Because of their outstanding mechanical properties (e.g. high stiffness) these alloys are mainly used for the fabrication of removable partial dentures, but also for metal ceramic prostheses, where fine frameworks constructions are needed. A new generation of cobalt-chromium alloys doped with precious metals (Au, Pt, Ru) are now coming on the market with the idea to improve the corrosion resistance.

MATERIALS AND METHODS

The compositions of the commercial tested alloys and of a "classical" Co-Cr alloy are listed in Table 1.

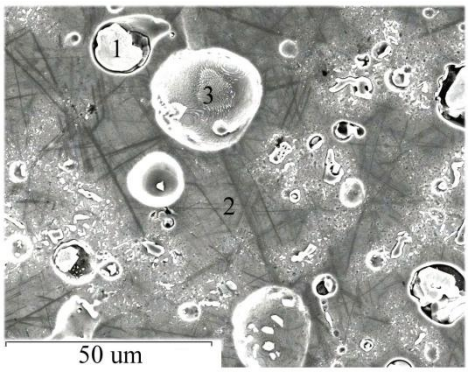
Before electrochemical testing the alloys were analyzed micrographically, analysis of phases by energy-dispersive X-ray spectroscopy (EDX) was carried out and hardness properties were also tested.

	Chemical composition (wt %)				
Element	**Co-Cr**	**#1**	**#2**	**#3**	**#4**
Co	63.7	63.5	52.0	50.6	59.3
Cr	28.9	21.0	25.0	18.5	25.0
Mo	5.3		4.5	3.0	5.0
Ga		4.5	6.0		2.5
In		trace	5.0		1.2
Au		2.0	2.0		2.0
Pt		trace	2.0	15.0	
Ru				10.0	
Sn			1.0		
Mn	0.8	6.5	0.5	1.0	
Si			2.0	0.75	
W	0.1			0.5	4.0
Nb				0.5	
Al		2.5			
Ti				trace	
Fe	0.4				

Table 1. Composition of the tested alloys (wt %).

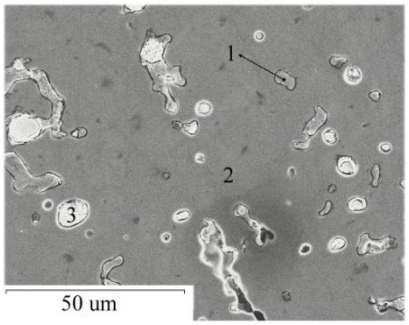
RESULTS

Metalographical structures



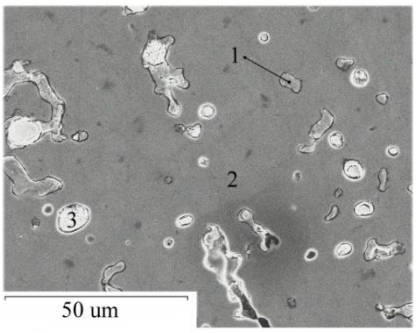
	Co	Cr	Mo	Si	Mn	Ga	In	Fe	Pt	Au
1	60.15	28.42	4.39	1.06	0.50	4.89		0.58		
2	1.30	0.62					42.77		28.31	27.01

Fig. 1. Microstructure of alloy #1 and phases composition (wt %).



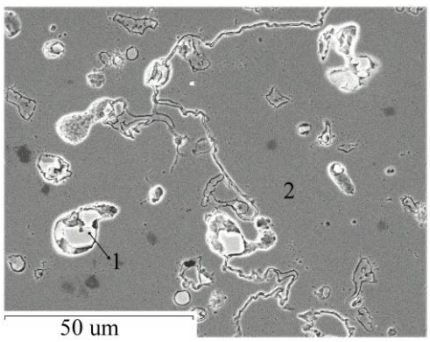
	Co	Cr	Mo	Si	Ti	W	Ga	In	Pt	Au
1	63.48	25.71	3.55			4.85	2.41			
2	28.46	32.83	22.98	1.74	0.95	11.31			1.73	
3	1.91	0.76						13.52		83.80

Fig. 2. Microstructure of alloy #2 and phases composition (wt %).



	Co	Cr	Mo	Si	Mn	W	Ti	Nb	Pt	Ru
1	48.96	17.48	3.44	1.02	0.70	1.25			16.44	10.72
2	42.75	19.51	11.76	4.36	0.88	1.56			8.25	10.93

Fig. 3. Microstructure of alloy #3 and phases composition (wt %).



	Co	Cr	Mo	Si	Ga	In	Pt	Au
1	59.61	28.04	5.37	0.63	6.35			
2	1.44	0.76				51.17	28.87	17.77

Fig. 4. Microstructure of alloy #4 and phases composition (wt %).

The microstructures of alloys #1 and #4 exhibited round "inclusions" with a diameter up to 0.1 mm. The chemical analysis of these zones showed of in (betweeen 42 and 51%), Pt (around 28%) and Au (between 18 and 27%).

Vickers –hardness values

alloys	#1 overall	#2 overall	#3 overall	#4 overall	#4 zone 2
$HV_{0.2}$	333	435	338	326	147

Table 2. Vickers-hardness of the tested alloys (n=5)

The Vickers tests of such zones for #4 gave a mean hardness value more than twice lower (147 HV) compared to the overall hardness value of the alloy (326 HV). Electrochemical measurements were conducted in artificial saliva of the Fusayama type (deaired with nitrogen, temperature 37°C, pH = 5) using the rotating electrode technique. The cathodic and anodic potentiodynamic polarisation curves were measured from - 1000 mV to + 1250 mV vs. saturated calomel electrod (SCE).

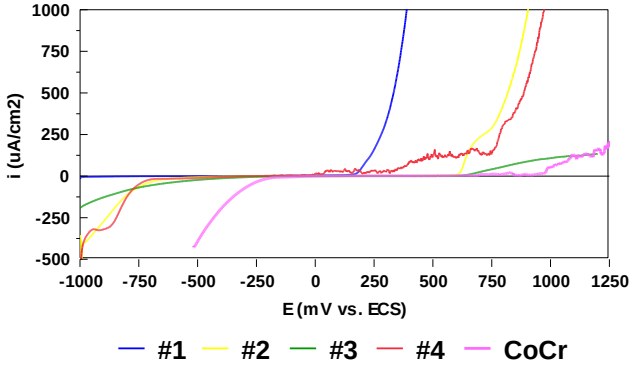


Fig. 5. Potentiodynamic polarization curves in linear system of alloys #1 to # 4 in comparison with a conventional Co-Cr alloy.

The potentiodynamic curves displayed in Fig. 5 reveal important differences in the behaviour of the studied alloys (#1 - #4) as compared to the conventional Co-Cr alloy. The worst behaviour was given by the alloys containing only gold (#1 and #4), confirming the results of Kappert and Schuster[1]. Au is not miscible to Co and Cr.

CONCLUSIONS

Alloys #1 and #4 showed a very complexe microstructure compared to the other studied alloys. The round "inclusions" with a diameter up to 0.1 mm are in part non miscible phases with a very low corrosion resistance. From the point of view of corrosion behaviour, the classical Co-Cr alloy is the best material followed by the alloys #2 and #3 (addition of respectively 4 % and 25 % precious metals). The worst alloys were #1 and #4 (with only addition of 2 % of Au). Scientifically speaking Co-Cr dental alloys enriched with precious metals is a non-sense.

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PROGNOSTIC FACTORS IN DIFUSE LARGE B CELL NON-HODGKIN'S LYMPHOMAS

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ABSTRACT

The prognosis of patients with non-Hodgkin's lymphoma (NHL) has improved with the introduction of cytotoxic chemotherapy, intensive chemotherapy-based treatment approaches also proving an improvement in the survival of patients with relapses of NHL, but present treatments using monoclonal antibodies are those which represent a revolution in the treatment strategy and have significantly improved the clinical evolution and the prognosis of these patients. Still, the therapeutic approach of NHL patients remains complicated due to the heterogeneity of lymphoma subtypes, patients apparently diagnosed with the same disease presenting extremely varied clinical signs, molecular profiles and clinical evolutions. It is necessary to define groups of patients with negative or positive prognostic factors in order to justify the therapeutic strategy and make it effective. Most prognostic indicators emerged following the results of clinical studies performed in order to define therapeutic strategies, such prognostic indicators being usually evaluated based on retrospective studies which do not entirely correspond to the new era of chemotherapy, needing at least one revalidation.

***Key words**: B cell, lymphoma, cancer, prognostic.*

INTRODUCTION

There are at least 30 different NHL subtypes according to the WHO classification and, additionally, there is a marked heterogeneity within this subtypes.[1]

Remarkable progress in the field of molecular biology will allow the improvement of this classification, with the emergence and recognition of new entities and homogenization of subtypes. At present, clinicians are confronted with the situation in which patients present similar diagnosis, with extremely different clinical manifestations, molecular profiles and clinical evolutions. The treatment of a patient with non-Hodgkin's lymphoma represents a complex task.

Efforts in establishing new prognostic factors followed two primary objectives. First, the formulation of a precise vital prognosis was aimed in order to facilitate physician-patient communication and to be able to realistically monitor the patient's evolution, in order to initiate the treatment, as well as to allow the stratification of clinical studies for a uniform report on evolution and comparisons in cross-sectional studies. The second purpose was to identify biologically unique subsets of patients who may be useful to identify some therapeutic targets which could support the development of some future specific therapies. Despite the fact that numerous prognostic factors have been

identified and many prognostic models have been proposed, certain conditions must be fulfilled in order for these factors to become clinically useful.

Logically, information needed for the prognosis must be obtained from accessible samples, and the technology used must be widely available with low costs (the technological limitations confronting our country must be noted). These conditions are usually successfully fulfilled for clinical factors, but biological markers raise multiple problems. Certain complex diagnostic procedures, requiring fresh or frozen tissues, limit the use of techniques such as genetic profiling, or PCR on RNA samples, while other techniques based upon immunohistochemical tests are more widely applicable.

In order for a test to be universally applicable, a standardized method is needed, with criteria able to establish reproductible cutoff values. The marker must offer information regarding the prognosis which must be independent of those obtained by other parameters. The clinical evolution period defined by the marker must be long enough to justify the change of treatment, or the marker must characterize a molecular profile which may benefit from a target specific therapy.

The relevance of the proposed marker or prognostic model must then be validated in an independent group of patients, treated by present therapeutic standards. Finally, alternative therapeutic strategies must be possible.

It is important to understand that risk assessment represents a variable target. The introduction of a new treatment may significantly alter the relevance of the prognosis factors in use up to that moment, by underlining their mechanisms of action. For these reasons, clinical progress requires the reassessment of present prognostic models and markers, in order to ensure they remain applicable.

The present paper addresses one of the NHL subtypes most frequently encountered in the Clinic of Hematology Timişoara, namely the difuse large B cell lymphoma (DLBCL), as well as the utility of certain prognosis factors acknowledged in present therapeutic strategies

DIFUSE LARGE B CELL NON-HODGKIN'S LYMPHOMA

DLBCL is the most frequent NHL subtype, being encountered in 35% of new cases and in over 80% of aggressive lymphomas. DLBCL is a heterogeneous entity. The WHO classification includes a number of morphological variants, with a large number of molecular and genetic abnormalities, patients presenting varied clinical characteristics and different clinical evolutions. CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) represents the main therapeutic strategy used for the past several decades, and attempts to apply a more aggressive chemotherapy have not proven more effective for the clinical evolution.

The age of monoclonal antibodies has transformed the treatment of aggressive lymphoma. The GELA (Le Groupe d'Etude de Lymphome d'Adultes) researchers reported the first results of a randomized controlled study, demonstrating the benefits obtained by adding rituximab, a chimeric IgG-type monoclonal antibody which targets CD20, to the CHOP-type therapy, this treatment being given to elderly patients (aged over 60 years) recently diagnosed with DLBCL. Bringing this study up to date after 5 years demonstrates that the benefits are kept by adding rituximab with an improvement of the healing rate in this group of patients (58% vs 45% general 5 years survival rate, $P = 0.0073$).[2]

These benefits have been confirmed by three additional randomized studies performed on selected groups of DLBCL patients. The US Intergroup3 and RICOVER-604 studies assessed the use of rituximab and chemotherapy among elderly patients, while the MInT5 study investigated their use in younger patients (aged under 60) with a good prognostic profile. The results of a populational study additionally proved the value of adding

rituximab to chemotherapy in a group of unselected patients diagnosed with DLBCL in British Columbia.[6, 9]

Even though adopting R-CHOP as the new therapeutic standard lead to an improvement in the evolution of this curable lymphoma, patients who did not benefit from the first line of treatment are still confronted with difficulties. Despite the progress made in the understanding DLBCL diversity and the increase in the number of therapeutic options, most clinicians continue to treat this entity using a single therapeutic strategy. It would be advisable to try to establish if there is an effective prognostic marker which could be used as a therapeutic guide.

Clinical prognostic factors

The International Prognostic Index (IPI) represents the first clinical marker used for assessing the evolution of patients with aggressive NHL.7 Based upon the number of negative prognosis characters present at the time of diagnosis (age over 60, stage III/IV of the disease, high lacticodehydrogenase (LDH) concentration, Eastern Cooperative Oncology Group (ECOG) score > 2, more than one extralymphatic location) four evolution groups with a 5 year survival rate between 26% and 73% have been identified.

Clinical studies testing for R-CHOP revealed limited information on the utility of clinical prognostic factors in patients diagnosed with DLBCL and treated with immunochemotherapy. Predictions on the evolution after R-CHOP therapy are complicated by the fact that the benefit of rituximab is not evenly translated in all subgroups of patients. In the GELA study, in which patients were classified according to age-adjusted IPI (aaIPI), low risk patients seem to benefit more by adding rituximab as compared to high risk patients.[2]

Clinical information obtained in randomized controlled studies does not reveal any group with an evolution unfavourable enough to impose treatment stratification. Because these studies were limited to selected populations (either young or elderly patients with favourable prognosis), the utility of IPI cannot be determined in the age of immunochemotherapy. In order to assess the applicability of IPI, a retrospective analysis was conducted in a group of unselected patients, recently diagnosed with DLBCL and treated with R-CHOP.8 The observation was made that the redistribution of IPI factors into a Revised-IPI (R-IPI) offers a more acurate prediction on the evolution and differentiates three evolutive groups with a whole 4 year survival between 55% and 94%. Even though R-IPI allows the identification of a group with unfavourable evolution, IPI factors can no longer be used to identify groups of patients with a survival chance under 50%. These results should be validated by a prospective study in an independent group of patients.

Molecular prognostic markers in DLBCL

The clinical-biological variability of DLBCL is revealed by the variable expression of a variety of molecular abnormalities, some of which proving to be predictive for the evolution of the disease. Even though the study of individual markers facilitated the understanding of DLBCL pathogenesis, many studies showed contradictory results. Reasons for these discrepancies are the retrospective nature of most studies, the reduced dimensions of the groups of patients, the lack of uniformity of certain techniques and the lack of control on other simultaneous biological processes which might influence the evolution. It is important for these markers to be revalidated for patients treated by immunochemotherapy.

Bcl-2 is an anti-apoptosis protein important for the development and differentiation of B cells. The Bcl-2 overexpression has been detected in 40-60% of patients diagnosed with DLBCL and it has been associated with a lower survival rate. In vitro studies proved that rituximab causes the down-regulation of

Bcl-2 protein expression and can thus eliminate the resistence to chemotherapy by this mechanism. The significance of Bcl-2 overexpression has been reevaluated in patients treated with R-CHOP, in the GELA study.[9] Unlike patients treated with CHOP only, no correlation between Bcl-2 overexpression and survival has been detected in patients treated with R-CHOP, suggesting that the addition of rituximab exceeds its negative influence. Other investigations also demonstrated that adding rituximab to chemotherapy lead to the elimination of the prognostic significance of Bcl-2 overexpression in DLBCL.[10] The expression of the Bcl-6 protein, a marker of the germinal centre, predicts a favourable evolution of DLBCL. A correlated prospective study, preformed in cooperation with the US Intergroup Trial examined the prognostic value of Bcl-2 expression in patients treated with R-CHOP.11 CHOP treated patients showed a better evolution if Bcl-6-positive, as compared to those who were Bcl-6-negative. At the same time, the evolution of R-CHOP treated patients was not influenced by the Bcl-6 status. Adding rituximab to CHOP therapy seems to eliminate the prognostic significance of Bcl-6 expression in DLBCL patients.

The profile of DLBCL gene expression

Studies on the profile of DLBCL gene expression tried to characterize tumor cell specific abnormalities by measuring the differences in mRNA expression on a wide genomic scale. These studies confirmed the exisstence of distinctive molecular subgroups among DLBCL, as well as a different evolution of these cases after antracyclin-based chemotherapy.12 At least two major subtypes have been identified, one having a similar gene expression with B cells in the normal germinative centre (CGB) and the other mimicking activated peripheral B cells (CBA).13 Patients with a CGB profile present a better overall survival, regardless of the IPI score, after CHOP type treatment (60% vs 35% overall 5 year survival rate, P<0.001).

Due to the absence of a standardized and available comercial test, as well as due to the need of fresh or frozen tissue specimens, the gene expression profile does not represent a practical method for the routine risk assessment of these patients. Many researchers used the information provided by genetic studies in order to create prediction models based upon more accessible techniques, such as immunohistochemical methods or the PCR technique.14 Hans et al used three markers (CD 10, BCL6 and MUM1) to classify patients as CGB or non-CGB and proved a better correlation with the evolution, as compared to that demonstrated by genetic tests. Still, a similar study performed by Colomo et al did not reveal any association with the evolution. Lossos et al used the PCR techniqque and evaluated 36 genes with evolution predictive proprieties in genetc tests and created a predictive model composed of the six most influencial genes (LM02, BCL6, FN1, CCND2, SCYA3 and BCL2), thus resulting three independent risk groups.[15] The predictive value of the gene expression profile, as well as the above mentioned models must be reassessed in patients treated with R-CHOP. Rituximab proved to selectively improve the evolution of Bcl-6 negative patients, 15 and for this reason it should be beneficial for the CBA subgroup. In a recent and extremely interesting report, the expression of the Bcl-2 protein proved to be a negative predictive factor in the evolution of the CBA subgroup of patients, but not in the case of the CGB subgroup.[14] As rituximab proved to improve the impact of the negative prognosis of Bcl-2 overexpression, this could be beneficial for the CBA subgroup and might eliminate the previously observed differences in the evolution of the two subtipes, CGB and BCA.

PET scan as prognostic index in DLBCL

Positron emission tomography (PET) using fluorine, 18-fluorodeoxiglucose

(18FDG), represents a more sensitive imagistic method than computerized tomography in aggressive NHL. When performed early, after one to four treatment cycles, it proved to be predictive for the further evolution. Spaepen et al conducted a prospective study by which they revealed the utility of an early performed PET after 3-4 doxorubicin chemotherapy cycles, on a group of 70 pateints with aggressive NHL. None of the 33 PET positive patients recorded a durable remission, while 84% of the negative early PET remained in remission.

Haouin et al revealed the utility of early PET after 2 antracyclin chemotherapy cycles (associated with rituximab in 41% of cases) in a group of 90 patients with aggressive NHL.13 Two year EFS (82% vs 43%, P<0.001) and overall 2 year survival rate (90% vs 61%, P= 0.006) were significantly better in PET negative patients, as compared to PET positive ones, and PET was considered to be a stronger predictive factor than IPI. The same researchers compared the prognostic value of early PET with the phenotypic profile (CGB versus non-CGB) obtained by immunohistochemistry.[12] The value of early PET was confirmed but no prognostic value was revealed for phenotyping.

More studies are needed in order to explore the optimal use of early PET in DLBCL. The ideal moment for the procedure must be set, because a PET scan performed too early could lead to prematurely abandoning the curative treatment. We must also decide on the moment of performing the procedure reported to chemotherapy, because the side effects of therapy could cause false positive results. Given its strong predictive potential, as well as the apparent independence from the selected treatment, early PET could become one of the dominant prognostic models used as a therapeutic guide for DLBCL during the following years.

Are there prognostic markers of veritable importance in DLBCL?

The association of rituximab to CHOP chemotherapy determined a marked improvement in the evolution of patients and changed the parameters for the risk assessment in DLBCL up to this moment. IPI (or R-IPI) remains a useful parameter for predicting the evolution, but can no longer distinguish between subgroups of patients who have a survival chance under 50%. Considering the excellent evolution recorded, we must be careful not to deviate from the decided therapy and not to add useless toxicity. During the present age of R-CHOP there are no validated molecular markers to predict the evolution of DLBCL. The molecular markers used up to present must be reevaluated as its has been demonstrated that a part of them do not represent prognostic markers. It is highly probable that early PET is a useful parameter which allows the initial treatment of patients with standard therapy which can be changed with alternative treatments if an unfavourable evolution is revealed, but this parameter should be further evaluated.

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LISTERINE® IN ROMANIA – A NEW BEGINNING

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ABSTRACT

Periodontal disease continues to be a major challenge for dentists and a concern for patients. Periodontitis can be prevented, but once it is present it can be controlled but not eliminated. In present, it is demonstrated that accumulation of bacterian plaque and inflammation of periodontal tissue are strongly linked (1). Patients play an important role in controlling the oral microbial biofilm that is essential to the initiation and progression of periodontal disease. Studies show us that periodontal disease can be controlled by having a personal correct daily oral hygiene routine. Brushing alone is not sufficient to control plaque. This must be supplemented by interdental cleaning (flossing, interdental brush) and, also, by using of antiseptic mouthwashes (2).

Common antiseptics in mouthwashes include: essential oils, chlorhexidine, triclosan, iodine. Among these, Listerine® (essential oil-containing mouthrinse) has become a brand after over 114 years of using.

***Key words**: oral health, essential oil-containing mouthrinse, plaque control.*

INTRODUCTION

Listerine® was used for the first time in 1879 by Dr. Nicole Dyer Lawrence and Christian Bach from U.S.A. as a surgical antiseptic. It was used to disinfect surgical wounds but also, as floor cleaner. In 1890, W. D. Miller wrote in his book Microorganisms of the human mouth that "Listerine has proved to be an active and very useful antiseptic". The name - Listerine® - it was chosen in honor of Joseph Lister, who has argued the idea of using disinfectants in hospitals and during surgery. Lister's work paved the way to the modern antiseptic operating room and has determined an important downturn in patient mortality. During the First World War, Listerine® was used to clean wounds on the field in battle.

The producer claimed that Listerine® it could be also used to treat colds could prevent dandruff and in cure for gonorrhea.By 1895, Listerine® was used in dental care but it wasn't runaway success until the 1920s, when it was sold as solution for "chronic halitosis". Until that time, bad breath was not considered social catastrophe, but Listerine®'s campaign changed that. James B. Twitchell wrote: "Listerine did not make mouthwash as much as it made halitosis."In the present, Listerine® is manufactured and distributed by Johnson and Johnson Company after acquisition of Pfizer's Consumer Healthcare division in December of 2006. Currently, eight different kinds of Listerine mouthwash are on the market in the U.S.A.

In Romania, Listerine® is commercialized since 2008.

HOW DOES LISTERINE® WORK?

The efficiency of Listerine® as an oral antiseptic is based on a formula of four essential oils: thymol 0.064%, eucalyptol 0.092%, methyl salicylate 0.06% and

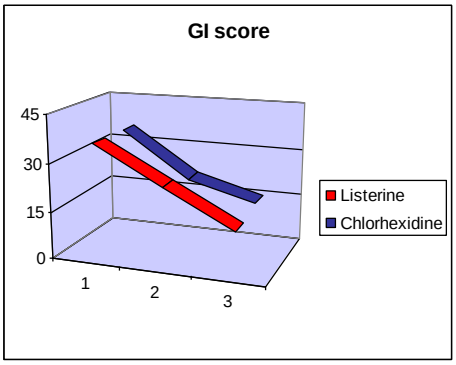
menthol 0.042%. This essential oil penetrate oral microbial biofilm and kill microorganisms by disrupting their cell wall and by inhibiting their enzyme activity [3,4,5].This reduce bacterial load, slow plaque maturation and decrease plaque mass and pathogenicity [6].

Have been shown that essential oil mouthwashes kill numerous microorganisms involved in oral plaque biofilm and inflammation: Aggregatibacter actinomycetemcomitans, Actinomyces viscosus, Streptococcus mutans and S. sanguis are killed within 30 seconds, as are Bacteroides species and Candida albicans [7]. Okuda et al. [8] has found that Listerine® completely kill microorganisms as Staphylococcus aureus, Streptococcus pyogenes, Helicobacter pylori, Candida albicans, Streptococcus mutans, Actinomyces viscosus, Porphyromonas gingivalis, Prevotella intermedia and Agregatibacter actinomycetemcomitans. Additional evidence is provided, also, by Whitaker's study [9]. After Listerine long time using, the oral microflora do not presents antimicrobial resistance and also, there is no evidence of increased opportunistic oral pathogens [10].

WHEN MAY WE USE LISTERINE®?

Sharma N and co. [11] confirm that for patients with gingivitis and periodontitis who have a correct oral hygiene (brushing and flossing), the use of an essential oils containing mouthrinse provides a clinically significant benefit in reducing plaque and inflammation. Studies have also shown that Listerine® has important benefits in supporting gingival health around implants [12]. Listerine® is useful in periodontal surgery in the early postoperative phase. This has been assessed in two studies. The first [13] has examined plaque formation, gingival bleeding and patient comfort and the second [14], has investigated the effects of Listerine® on periodontal healing. The authors of both studies concluded that Listerine®, despite its relatively low pH, it is safe and does not interfere with the healing process. Another demonstrated benefit of using Listerine® is to significantly reduce the level of viable bacteria in an aerosol produced during ultrasonic scaling, even after 40 minutes after rinsing. Also, it is observed the reduction of bacteraemia [15]. Thus confirme the value of preprocedural mouthwash rinsing as a part of dental office infection control policy.

We find very interesting to mention a few comparative studies between Listerine® and another frecvently used antiseptic: chlorhexidine digluconate. These studies [16, 17, 18] have demonstrated that the essential oil mouthrinse and the chlorhexidine mouthrinse have the same clinical effectiveness, both producing a significant reduction in supra and subgingival plaque and, so, in inflammation (graphic 1).



Graphic1. GI score at baseline, at 3 months and 6 months during rinsing with Listerine®, respective with chlorhexidine (17)

Levels of calculus depositions and extrinsic tooth stain were significantly higher after chlorhexidine using than after the essential oil mouthrinse.This finding suggests that each of these products may have a distinct and useful place in the management of periodontal disease. It is likely that the chlorhexidine mouthrinse is more indicated in situations when short-term plaque control is critical but usual mechanical oral hygiene procedures are difficult, e.g., in the immediate post-operative period, in the convalescence period. The essential oil mouthrinse could be more indicated in the longer-term control of plaque and inflammation so, during the maintenance phase of therapy. It is important to underline here the demonstrated in vivo [19] interaction between chlorhexidine digluconate and sodium lauryl sulfate, a commonly used dentifrices ingredient, interaction which diminishes antiseptic's activity.

SAFETY :

It is known: the excessive alcoholic consumes represents a risk factor in developing oral cancer. So, a series of epidemiological studies have sought to investigate a possible association of the use of Listerine® (alcohol-containing mouthrinse) and oral cancer. Listerine® contains ethanol in concentrations of 21.6% and 26.9%, as a solvent for the active ingredients. Recent studies [20-24] have concluded that was no evidence to support a causal association between alcohol-containing mouthwashes and oral cancer.

Most European, American and Asian dental professional organizations affirm that there is no reason for patients to refrain from using this type of mouthwashes. We must caution people who are recovering from alcohol abuse that using an alcohol-containing mouthrinse may put them at risk of relapse. Another concern it could be that Listerine® having a pH below 5.5, it may cause tooth erosion. Studies have shown that during rinsing, salivary flow significantly raises and so, although a little acid pH of Listerine®, salivary pH remains above 5.5 following rinsing and for 15 minutes postrinse [25].

Also, Listerine® does not appear to exert any significant influence on plaque calcium and phosphate contents, thereby suggesting that no enamel demineralization occurs [26]. During our work, we have found in literature another speculation: regular use of alcohol-containing mouthrinses can cause desiccation of the oral mucosal membranes, provoking xerostomia. A recent study comparing the effect of Listerine® with that of non alcohol-containing mouthrinse on salivary flow and symptoms of dry mouth found no clinically meaningful differences [27]. Some patients have reported "oral burning" syndrome after using Listerine® [28]. In this case, diluting the product for the first few days of use could be a good solution. Also, reducing the alcohol content or adding a less intense flavor, such as citrus, is taken into consideration.

CONCLUSIONS:

Dentists have the responsibility to instruct their patients to play an active role in controlling the accumulation of bacterial plaque using brushing, flossing and antiseptic mouthrinsing. Its long history certifies that Listerine®, as mouthrinse, it is safe and effective as part of a daily oral care. Understanding that, we, as practitioners, can offer additional benefits to romanian patients.

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CONTROVERSES AND DILLEMAS ON THE USE OF B-BLOCKERS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE ASSOCIATED WITH CARDIOVASCULAR DISEASE

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ABSTRACT

In the last decade, chronic obstructive pulmonary disease (COPD) has been considered a syndrome with multiple phenotypical facets and systemic components. Chronic diseases are associated, in time, with several comorbidities. Cardiovascular pathology represents the most common comorbidity in COPD, increases its handicap and mortality indices. Most entities associated with cardiovascular pathology require treatment with β-blockers. However, β-blockers are a "two-edged sword" when administered in obstructive pulmonary disorder. The use of β-blockers should be assessed by their action on three areas: their effect on FEV1, their effect on bronchial hyperreactivity, the result obtained when additionally administering β-agonists. The result of β-blocker administration is influenced by the involvement of several other factors: the cardioselectivity of the β-blocker, the dosage, the concomitant administration of β-agonists, the stage of the disease (stable or exacerbation of COPD), smoker status, etc. Their administration under strict monitoring results in a decreased morbidity and mortality, including in patients who had undergone cardiovascular surgery. The overall conclusion is that β-blockers may be administered in COPD associated with cardiac comorbidity, but this administration requires utmost care.

***Key words**: beta blockers, COPD, cardiovascular comorbidities.*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is considered a complex disorder because it does not affect only the lungs but, as it develops, it acquires multiple systemic components. An intriguing fact is that guidelines ignore the fact that most patients with a chronic disease also have one or more comorbidities associated (heart failure, peripheral arteriopathy, diabetes mellitus, cancer, etc.), which may have a major impact on COPD.[1]

As far as death causes are concerned, all statistics place cardiac comorbidity on the second place after respiratory failure. As most cardiac disorders require the administration of β-blockers, their use in an obstructive bronchial syndrome such as COPD may have a deleter impact. Therefore, the beneficial cardiovascular effects of a β-blocker should be balanced by estimating its effect on FEV1, bronchial hyperreactivity and the additional response to short-acting β2-agonists (which estimate the b2 receptor reserve).[2] Still, mainly in the cases where β-agonists are given, the tolerance to β-blockers seems to change. The pneumologist in cooperation with the cardiologist should balance the

dose, the type of blocker and the moment this "two-edged sword", i.e. the use of β-blockers, is to be introduced.

The impact of cardiovascular comorbidity on COPD

J. J. Reilly shows that we cannot speak solely of COPD but of a "sum" of COPD, a "syndrome" deriving from the interference of multiple fenotypes.3 Ever since 2006, B. Celli has divided COPD in fenotypes according to the degree of hyperinflation (early or late hyperinflators), the incidence of exacerbations, the association with comorbidities, the polymorphism of β2-receptor encoding genes, etc. In 2008, the Ning study translated the COPD transcriptome.[4] There is a broad interference between COPD and CV, induced by:

- Common risk factors: smoking, sedentary life style
- Common pathogenic mechanisms:
  - Systemic inflammation
  - Oxidating stress
  - Hypoxia
  - Non-neutralized proteolysis
  - Autoimmunity
- Certain common therapeutic schemes.

The onset and development of COPD is based on a certain inflammation pattern (neutrophilic) which initially generates multiple pulmonary alterations (bronchitis, ciliary dysfunction, emphysema, structural parietal alterations), which lead to bronchial obstruction. In time, the inflammation is no longer limited to the pulmonary area, inducing systemic alterations (muscular, cardiovascular, endocrino-metabolic, etc).Obstructive alterations set in long before the appearance of any clinical symptoms, so that when the patient goes to the doctor, the pulmonary function (assessed by FEV1) has already been compromised with about 30 – 40%, and some of the comorbidities are already present. The extent of cardiovascular damage in COPD has been documented in several epidemiological studies. Thus, the incidence of coronary disease in a group of ~ 400,000 COPD veterans, hospitalized between 1991 – 1999, was 33.6%, significantly greater than the incidence of the same disease in non-COPD patients – 27.1%.5 An autoptic study revealed the existence of an associated cardiac disorder in 106 of 144 (74%) COPD patients.6 The TORCH7 study analyzed the death causes of 6,225 patients, 875 of them suffering from a moderately-severe form of COPD for more than three years; in the latter, death was caused by: respiratory causes (35%), cardiovascular causes (27%), lung cancer (21%), other (10%), unknown (7%). The cardiovascular component mainly refers to the dysfunction of the right ventricle (RV), pulmonary hypertension (PHT), coronary disease (CD), arrhythmias. The development of any of these disorders will increase morbidity and reduce survival. A three-year trial conducted on more than 10,000 patients showed that COPD patients have a twice to four times greater risk of dying of CV disorders than non-COPD patients of the same age and gender.[8]

β-blockers vs. β-agonists in the treatment of COPD associated with cardiovascular disease

When assessing the effects of a drug on a certain disease, such as COPD, the following aspects should be considered:

- The phenotype of the disease.
- The stage of the disease: exacerbation or stable stage. For example, β-agonists cause tachyphylaxis during the inflammation stage of the exacerbation.
- Drug associations/interferences: ICS, β-blockers, β-agonists, etc; for example, certain studies maintain that β-blockers might have an additive effect with ICS.
- The drug's pharmacological properties: selectivity, dose, lipophilia, hydrophilia, etc.
- Others: old age, smoking, etc.

The classical approach classifies ligand receptors either as agonists (partial or total) or as antagonists, according to their efficiency in binding with the G protein. Later on, this approach has become more complex, including the notions of "reverse agonist", noting that several classical neutral antagonists actually act either as partial agonists, or as reverse agonists.9 Acebutolol, alprenolol, atenolol, labetalol, oxprenolol, pindolol and practolol are Gs protein adenyl cyclase (AC)-activation dependent weak partial agonists. Ligands that do not activate AC (therefore do not increase cAMP generation), such as betaxolol, bisoprolol, carvedilol, metoprolol, narvedilol, propranolol, sotalol and timolol, represent reverse agonists.[10] The classical dogma of ligand receptor stimulation assumed that a certain ligand would be effective in initiating cellular responses only if connected to/by the activation of the respective ligand. Still, comprehensive research in the last 15 years has shown that a single ligand may also have intrinsic effects on the various intracellular systems subjacent to the respective receptor. Consequently, the pharmacological effectiveness of a certain ligand, or its capacity to produce an envisaged therapeutic effect, can no longer be fully accounted for by its ability to stimulate only the initial receptor of a complex signal translation/transmission pathway. There are several receptors, including β2 that can exist in multiple "active" configurations after their binding to a ligand. These variable configurations may engage extremely diverse intracellular pathways/effectors, thus accounting for the various cellular response profiles that emerge after administering different β-blockers. The analysis of sixteen different β-blockers showed their broad range of effectiveness, both for the dependent Gs pathway and for the ERK1/2 β-arrestin-dependent subjacent activation (Fig. 1).[11]

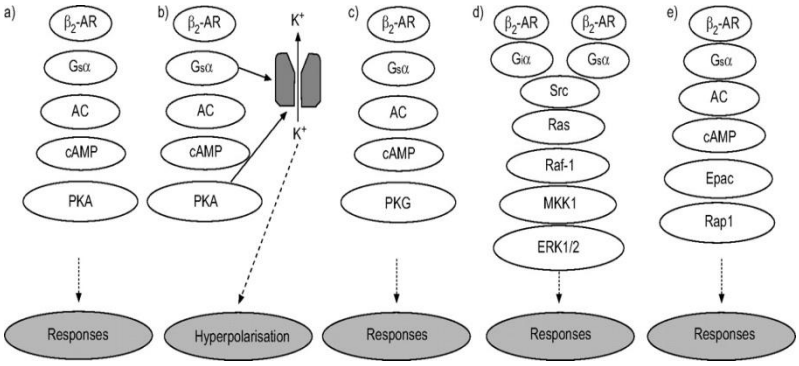

Fig. 1. The translation of β2 adrenergic receptor stimulation is mediated by a complex cascade of events which involves the participation of multiple G, AC, PK and PDE protein isoforms/subunits, as well as of their scaffolds. Thus, (a) the interaction of the agonist with the β2 receptor (β2-AR) in the bronchial muscle cell membrane triggers the release of the α-subunit-stimulating G protein (Gs) from an αβγ heterotrimetric complex. Subsequently, the released Gsα will boost the activity of one or more AC isoforms, resulting in the intensification of cAMP formation from ATP. cAMP will be associated with the PK (A) regulating subunit which, by target protein phosphorilation, will induce cell bronchodilatation response. (b) K+ channels may also be targets for the PKA, opening after phosphorilation and producing a flow of K+, which will induce a diminishing of the excitability and the subsequent bronchial relaxation. The opening of the K+ channels may also take place through the direct interaction of Gs with the respective channels, independent from cAMP and PKA. (c) The β2-AR agonist couple may induce an increase in the cAMP concentration triggering bronchial relaxation and PKG activation. (d, e) Still, the cascade initiated by β2-AR linking may follow the pathway of tyrosine kinase activation (Src), either through the Giα or the Gsα subunit, leading to the formation of Ras, Raf-1 or MKK-1 (mitogen-activated protein kinase linase) and ERK (extracellular signal-regulated kinase) activation; or, independent from PKA, cAMP activation can, through Epac (exchange proteins directly activated) lead to the same result (bronchodilatation) via Rap-1.

From this spectrum we should remark carvedilol, which has the unique profile to block AC activation in the Gs, but can subjacently activate ERK1/2 (practically doing a by-pass or short circuit).[12] Consequently, the definition of pharmaceutical effectiveness has been radically changed by admitting that intrinsic effectiveness is no longer correlated with linking to/with the Gs protein and that it may greatly vary according to which effector system is involved. In the above mentioned cardiovascular comorbidities, β-blockers are recommended in all of them, except for PHT. The rationale of their administration lies in their capacity to prevent vascular remodelling, arrhythmias, their antioxidating, antiinflammatory, antiproliferative and α1-antagonist-adrenergic capacity.[13, 14, 15]

The reserves in using β-blockers are based on:

Selective or not, β-blockers increase bronchial hypersensitivity that is present in asthma and, to a lesser extent, in COPD.16 The length of the treatment seems to influence β-receptor-ligand connection response. Thus, acute treatment with β-blockers increases bronchial hyper-reactivity, while chronic treatment significantly decreases it. The underlying mechanism is still unknown, but it has been suggested that it would be connected to an increased density of β-receptors (up-regulation). Practice has shown that the danger in administering β-blockers is manifest at the first doses; if FEV1 does not decrease during the first weeks, then administration can be continued. If, however, FEV1 does decrease but the patients' cardiac condition requires the administration of β-blockers, then their effect might be „alleviated" by administering anticholinergic drugs (e.g. tiotropium). The rationale in their administration lies in the fact that, in virus-induced exacerbations, the M2 and M3 muscarinic receptors are stimulated, thus ensuring acetylcholine secretion and re-capture, receptors which otherwise are blocked exactly by tiotropium.[17, 18, 19]

The antagonist effect of β-blockers may neutralize the adverse effects of β-agonists, and in this case we may speak of a complementary reaction. Thus, the risk of adverse cardiac events associated with β-agonists may differ in individuals who already use β-blockers from those who do not use β-blockers. On the other hand, if it is true that β-blockers might induce an increase in the density of β receptors, then this might mean an increase of the risk associated with the concomitant use of β-agonists and of β-blockers in COPD. Apparently, cardioselective β-blockers not only do not worsen respiratory symptoms in COPD patients, but they would seemingly associate with a higher bronchodilator response to consecutive β-agonist administration.[20] Selectivity is not an irrefutable fact. Many cardioselective β-blockers also block β2 bronchial receptors concomitantly with blocking β1 cardiac receptors. This would explain why the effects of metoprolol (cardioselective β-blocker) on bronchial hyper-reactivity are as strong as those of propranolol (unselective β-blocker) in COPD patients. That is why, when using β-blockers, it is advisable to use celiprolol or nebivolol, i.e. β-blockers that combine a high cardioselectivity with ISA activity.[21]

The reasons in favour of β-blockers would be as follows:

Various COPD studies show that mortality generated by cardiac comorbidity varies between 25 – 50%, and in most cardiac assessments β-blockers represent a major indication.[7]The use of β-blockers induces an increase of β2-receptor density for agonists.[22] There is a great tolerance for β-blockers. Exposure to β-agonists may damage the receptor in such a way that ligand affinity may decrease ten times. Consequently, previous exposure to β-agonists might decrease affinity for β2-blockers, and on the other hand, inflammation accelerates β-blocker metabolism. That is why long-term β-

agonist users have a greater tolerance to β-blockers. The maximum therapeutic dose recommended and used for various β – blockers was: metoprolol - 400 mg/day, bisoprolol - 10 mg/day, and atenolol - 100 mg/day.[23,] [24]Cardioselective β-blockers reduced mortality in COPD patients undergoing cardiovascular surgery.[21]A study conducted on 825 patients with respiratory failure showed that the use of β-blockers in patients with COPD exacerbations is well-tolerated and is associated with lower mortality. (OR = 0.39; 95% CI 0.14 to 0.99).[25]

The selection of a β-blocker should take into consideration its effect on FEV1, on bronchial hyper-reactivity, and the additional response to short-acting β2-agonists, which estimates, in fact, the β2-receptor reserve (when the bronchial tonus increases, as it happens after administration of metacholine, bronchial dilatation will require an intensified β2-receptor activity, and their functional impairment is thus easier to detect. As β-blockers and β2-agonists compete for β2-receptors, treatment with β-blockers may alter the dilatation induced by a short-acting β2-agonist in order to eliminate metacholine-induced bronchospasm). For example, propranolol reduces FEV1 and bronchodilator effect to formoterol. Metoprolol and propranolol increase bronchial hyper-reactivity. However, none of these unwanted effects occur after using celiprolol. Thus, different classes of β-blockers have different pulmonary effects.[26]

Consequently, β-blockers are safe for COPD patients but only used with caution, as they act like a "two-edged sword".

Conclusions

COPD is a multi-faceted disease due to its various component phenotypes.

Guidelines ignore the fact that most individuals suffering from a chronic disease also have one or more comorbidities (heart failure, peripheral arteriopathy, diabetes mellitus, cancer, etc.) which may have a major impact on COPD. A careful examination of the cardiovascular, metabolic and endocrinological components should become a routine procedure in assessing all COPD patients and, at the same time, pulmonary function should be assessed in all patients with cardiovascular, metabolic and endocrinological comorbidity.

The treatment of comorbidities may reduce the morbidity and mortality of COPD patients.

Therefore, β-blockers are safe for COPD patients, but only if used with caution, as they are a "two-edged sword".

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LASER SINTERING OF CO-CR ALLOYS

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ABSTRACT

The use of Co-Cr alloys is traditionally carried out by casting, but it can also be done by using the CAD/CAM system. An alternative is the use of the laser sintering technique. By means of a laser, using a well-established energy/local surface unit, the fine alloy powder used is locally sintered in order to form the prosthetic element. The ST2724G alloy used consists of 64-67% Co, 28-30% Cr and 5-6% Mo, and has the balance of a γ monophasic structure. Mechanically, the breaking limits of the metalo-ceramic elements resulting from this technique are comparable to metalo-ceramic elements obtained by classical casting. The metallographic observations show a slight porosity in the horizontal sample (compared to the sintering plane), while in vertical sample, the pore lines are uninterrupted. The chemical attack shows, just like on the surface, a very fine layered structure roughly corresponding to the original granular structure of the base powder. Punctual analysis shows a high regularity of the local chemical composition. The laser sintering technique makes possible the manufacture of extremely accurate prosthetic elements with mechanical properties that correspond to any clinical requirement.

***Key words**: laser sintering, ST2724G alloy*

INTRODUCTION

The use of Co-Cr alloys is traditionally carried out by casting, but it can also be done by using the CAD/CAM system. The use of a ring-shaped material has a disadvantage: most of the alloy is lost, i.e., only a small part of the material is actually used in the prosthetic element. An alternative which prevents this material loss is the use of the laser sintering technique.

MATERIAL AND METHODS

THE LASER SINTERING TECHNIQUE

By means of a laser, using a well-established energy/local surface unit, the fine alloy powder used is locally sintered in order to form the prosthetic element. The topography of the respective restorations is designed by numerical monitoring after having scanned the devised objects (Fig. 1). Several objects are numerically programmed on the tray. (Fig. 2). Subsequently, a computer-based programme is run in order to monitor the laser beam. The laser is thus programmed in such a way that it only becomes active at the site where the elements should be achieved. The alloy particles will consequently be sintered by the laser energy.The programmed objects, virtually presented (Fig. 2), are obtained by superposing several layers, a process during which, after each period of laser exposure, the tray is raised by 60-80 μm and is subjected to another laser exposure

after the application of each additional layer of powder. Thus, the whole reconstruction process is achieved layer by layer. This results in a fast prototype making process (Fig.3). As the sintered layers are spaced at intervals of 20-30 µm, the powder has to be as spherical as possible (Fig. 4) and its granulometry has to be below those values (Fig. 5). The ST2724G alloy consists of 64-67% Co, 28-30% Cr and 5-6% Mo1, and has the balance of a γ monophasic structure (Fig. 6). After sinterisation, the elements are removed from the tray using an abrasive disc.

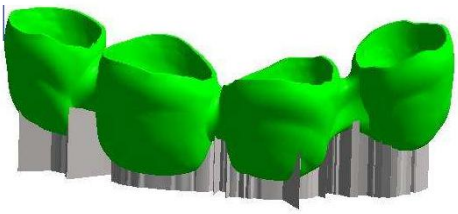

Fig. 1. Virtual image of an programmed element, on it's holder.

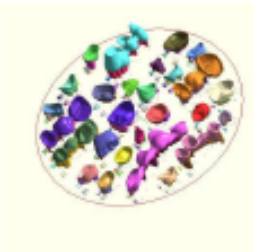

Fig. 2. Virtual image of the computer-based programme for a fabrication tray.

Fig. 3. Some prosthetic elements on the tray, after sintering.

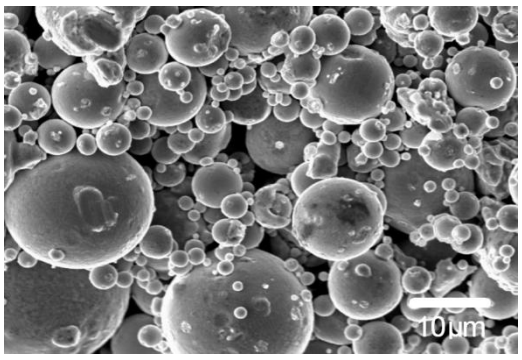

Fig. 4. MEB image of the metallic powder ST2724G1 for the sintering technique

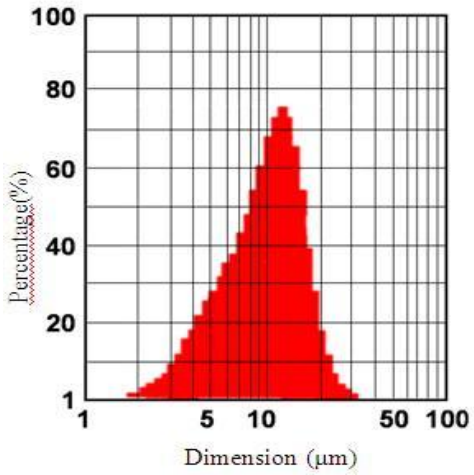

Fig. 5. The characteristics of powder granulometry by using optic analysis.

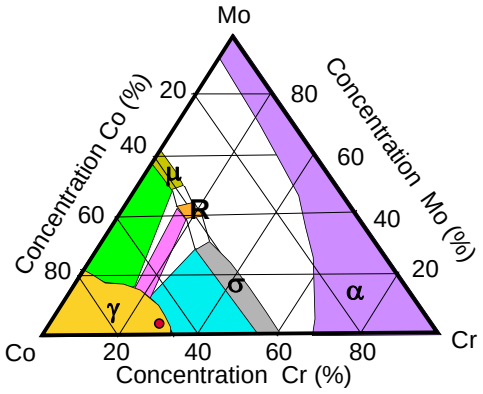

Fig. 6. Ternary isothermal phase diagram of Co-Cr-Mo at 1300°C2. The composition of the ST2724G alloy is represented by the red dot.

Fig. 7. A bridge, immediately after separation from the tray, on the model.

RESULTS

Dimensional observations show that adjustment leads to satisfactory clinical results with a precision of 25 μm (Fig. 7). The surface presents stratified structure with its granulometry matching the granulometry of the basic powder (Fig. 8). Mechanically, the breaking limits of the metalo-ceramic elements resulting from this technique are comparable to metalo-ceramic elements obtained by classical casting.[3] The average hardness is 395 HV. The metallographic observations show a slight porosity in the horizontal sample (compared to the sintering plane) (Fig. 10), while in vertical sample, the pore lines are uninterrupted (Fig. 9). The chemical attack shows, just like on the surface, a very fine layered structure roughly corresponding to the original granular structure of the base powder (Fig. 11). By comparison, the structure obtained for the same alloy by traditional casting, shows a classical dendritic structure. (Fig. 12).

Punctual analysis shows a high regularity of the local chemical composition: Co between 62.6 and 64.1%, Cr between 29.3 and 30.5%, and Mo between 4.9 and 6.4%. Mn and Si have values less than 1%.

Fig. 8. The internal surface of two crowns, immediately after sintering.

Fig. 9. Metallographic observation of a vertical sample.

CONCLUSIONS

The laser sintering technique makes possible the manufacture of extremely accurate prosthetic elements with mechanical properties that correspond to any clinical requirement. However, there seems to be a rather significant risk of internal porosity which might lead to fracture, cracking or corrosion.

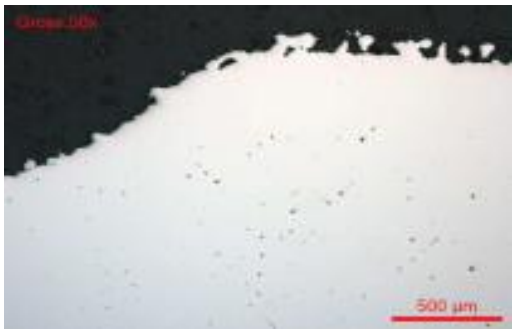

Fig. 10. Metallographic observation of a horizontal sample, without chemical attack.

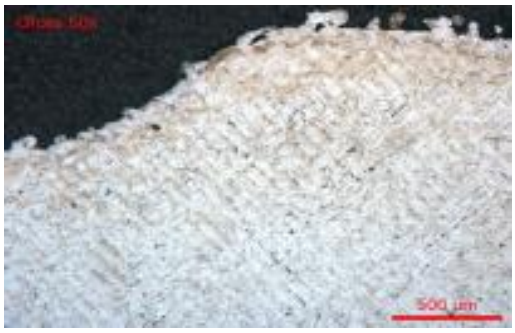

Fig. 11. Metallographic observation of a horizontal sample, after chemical attack.

Fig. 12. Metallographic observation of a cast structure.

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GENETIC AND MOLECULAR EVALUATION IN NON-HODGKIN'S LYMPHOMA

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ABSTRACT

Given the diversity of clinical and pathological aspects of non-Hodgkin's lymphomas, as many data as possible are needed for a positive diagnosis. The quality of bioptic material is one of the most important factors involved in specific investigations and for obtaining pathological, immunohistochemical, molecular biology and cytogenetic data. The correlation of these data obtained from bioptic material helps the positive diagnosis of the patient in order to design an individualized treatment.

***Key words**: non-hodgkin s lymphoma, cancer, genetics.*

INTRODUCTION

Malignant lymphomas are cytogenetically well characterized neoplasms. Together with the proof of the neoplastic nature of lymph cell proliferation, the description of cytogenetical abnormalities which characterize various types of malignant lymphomas alowed the much more detailed understanding of the biology of lymphoid neoplasms, facilitating the description of distinctive entities within this group of diseases. In the XXIst century, the diagnosis of hemato-lymphoid tissue tumors requires an exhaustive combination of clinical, pathological, immuno-phenotypical and molecular genetics data. It is common knowledge that a successful pathological analysis is most easily obtained by examining the lymph nodes entirely excised and with an intact capsula. Fine needle aspiration (FNA) cytology plays an important role in the diagnosis of lymphoid pathology, but it is best achieved in clinics where high quality flow-cytometry is available, alowing immune-phenotyping of lymphoid cells.[1] FNA is extremely useful for tissues collected in the cephalo-cervical area, in order to exclude metastatic tumors. It is extremely important to know how to choose the lymph node to be examined, the choice being mandatorily made in tandem, together with the the surgeon and the pathologist. When the region may be chosen, the best is to avoid the inguinal region, because nodes in this area often present architectural abnormalities due to fibrosis. Cervical lymph nodes are the easiest to analyze. The lymph node bioptic sample must show pathological changes with the highest fidelity, and in case reactive transformation must be rulled out, a rapidly growing lymph node must be chosen. The best would be to rapidly transport the tissue to the pathology department, while still in fresh state. This allows the preparation of sections which will be used for cytological examination and for fluorescent marker in-

situ hybridization studies (FISH), the collection of fresh material for conventional genetic studies and for microbiological studies (if needed), as well as the preparation of frozen material for DNA or RNA analysis, if needed. The lymph node must be finely cut and left to be fixed in an adequate quantity of reagent for an appropriate period of time. In our country, fixation is usually made with buffered formaline solution for 12-24 hours. A longer fixation period may inhibit antigen reactivation (even though this could be compensated by the antigenic reactivation process), while under-fixation may ireversibly interfere with morphological preservation. [2] Ideally, histological sections must be cut at 3-5 μm and stained with hematoxylin-eosin. Giemsa, Schiff periodic acid and reticulin staining may offer valuable additional information. Phenotyping the lymphoid infiltrate is an essential part of diagnosing a lymphoma. There is a wide range of immunological markers which are reactive in paraffin-fixed material, decreasing the need for immune-phenotyping of frozen sections, even though some antigens remain undetected in fixed tissue. Solid tissue flow cytometry may be used for antigens non-reactive in fixed material and it may be useful for detecting the expression of light chains and membrane immunoglobulins.[3] Flow cytometry may also demonstrate the co-expression of various antigens in certain cells, which may be difficult even in serial sections of incorporated material. In most laboratories, immunocytochemical marking is frequently routinely performed, using devices for automatic marking which offer a superior quality analysis and maintain a constant and controlled environment. The reactivation of fixation-masked antigens is obtained with a combination of heat (boiling under pressure, microwave or both) and enzyme pre-treatment in a suitable buffer solution. The necessary pre-treatment varies with the type of antigen, but also with the laboratory or the equipment used for marking. In all laboratories, marking must be performed including positive and negative control sections. All laboratories involved in the diagnosis of hemato-lymphoid tumors should participate in external quality assessment programmes.

The investigation and immunocytological analysis should only be performed by persons who are familiarized with the model of antigenic reactivity (cytoplasmatic vs. membrane vs. nuclear), as well as with the characteristic prophiles of various types of lymphoma. Normally, the analysis should be performed by immunologists. The traps associated with various abnormalities of antigenic expression, as well as the antigenic loss often associated to neoplastic lymphoid infiltrates, must be cautiously avoided, and immunohistochemical marking must be interpreted in the context of histological characteristics of the infiltrate.

Molecular and cytogenetic technologies

The major element in the diagnosis of malignant lymphomas is represented by genotyping studies. The identification of cloned lymphoid cells is possible, because, during the maturation process, lymphoid cells rearrange the genes for the heavy chains of immunoglobulins (IgH) as well as those for the light chains (IgL), or the genes for T cell receptors. Other gene rearrangements may also be detected, such as chromosomial translocations, with the help of DNA rearrangement studies. It is estimated that, by the sensitivity of Southern blotting, 1-5% of cloned cells in a cell population may be detected.4 As B and T cells rearrange the genes of their specific receptors, these analysis may discriminate between B and T cell neoplasms.[6] It is a known fact that the sensitivity of Southern blotting may be additionally increased by using polymerase chain reaction (PCR). PCR represents a technique by which a small amount of DNA may be amplified in vitro, by using primers of certain regions in a DNA section. As it requires only minimal amounts of short DNA sequences, PCR may be used for detecting clone cell populations or for the detection of DNA rearrangements even in formaline-fixed and paraffin-incorporated material (in

which DNA is usually degraded). Due to its increased sensitivity, PCR may be also used in monitoring minimal residual disease (MRD), especially if clone-specific primers are used, PCR being an extremely useful technique for the reassessment of hematologic patients. [5] Normally, by DNA sequence analysis of Ig receptor genes, non-mutant (naive) prefolicular and mutant (memory) postfolicular B cells may be differentiated. In the population of folicular cells, the so-called „continuous" somatic mutations reflect the process associated to the germinal centre, known as afinity maturation. Thus, the detailed analysis of the genes of Ig receptors allows us to formulate conclusions on the status of antigen-dependent selection and mutation, as well as on the genetic repertoire of immunoglobulin heavy chain variability (IgVH).[6]

TABLE I Genetic Abnormalities in Lymphoid Neoplasms

Proto-oncogenes Gene*	Chromosomal Translocation		Biologic Function	Lymphoma
alk			Anaplastic lymphoma kinase = tyrosine kinase	
	t(2;5)p23;q35)†	NPM/ALK†	Nucleophosmin-ALK fusion	Anaplastic large-cell lymphoma (75%) ‡ Diffuse large B-cell lymphoma, ALK+ (rare)
	t(l;2)(q21;p23)†	TPM 3/ALK†	Tropomyosin 3-ALK fusion	Anaplastic large-cell lymphoma (15%)‡
	t(2;17)(p23;q23)†	CLTC/ALK†	Clathrin heavy chain-ALK fusion	Anaplastic large-cell lymphoma (2%)‡ Diffuse large B-cell lymphoma, ALK+
	t(2;3)p23;q21)†	TFG/ALK†	TRK-fused gene-ALK fusion	Anaplastic large-cell lymphoma (2%)‡
	inv(2) (p23;q35)†	ATIC/ALK†	ATIC enzyme-ALK fusion	Anaplastic large-cell lymphoma (2%)‡
bcl-1	t(ll;14)(ql3;q32)	Bcl-l/IgH	Cell cycle regulator	Mantle cell lymphoma (all) Hairy cell leukemia (some) Multiple myeloma (15%)
bcl-2	t(l4;18)q32;q21)	Bcl-2/IgH	Negative regulator of apoptosis	Follicular lymphoma (90%)
	t(2;18)(qll;q21)	Bcl-2/Igκ		Diffuse large B-cell lymphoma (20%)
	t(18;22)(q21;qll)	BcI-2/Igλ		
bcl-3	t(l4;19)(q32;ql3)	Bcl-3/IgH	NF-kB subunit	B-CLL/SLL (rare)
*bcl-6**	t(3;14)(q27;q32) der(3)(q27)	Bcl-6/IgH Bcl-6/var	Transcriptional repressor necessary for germinal center formation	Diffuse large B-cell lymphoma (30%)
bcl-10	t(l;14)(p22;q32)		Activator of the NF-kB pathway	MALT lymphoma (<5%)
FGFR3	t(4;14)(pl6;q32)	FGFR-3/IgH	Receptor to fibroblast growth factor	Multiple myeloma (15%)
c-maf	t(l4;l6)(pl6,q32)	c-Maf/IgH	Transcription factor	Multiple myeloma (5%)
MALT 1	t(14;18)(q32;q21)	MALT-l/IgH	Paracaspase, binds to Bcl-10	MALT lymphoma (18%) (other than gastrointestinal & pulmonary)
	t(ll;18)(q21;q21)†	API-2/MALT-l†	Fusion protein, increases NF-kB activity	MALT lymphoma (50%)
*c-myc**	t(8;l4)(q24;q32)	c-Myc/IgH	Transcription factor regulating cell proliferation	Burkitt's lymphoma (30-100%)
	t(2;8)(pll;q24)	c-Myc/lgK		Diffuse large B-cell lymphoma (10%)
	t(8;22)(q24;qll)	c-Myc/Igλ		
	t(8;l4)q(24;qll)	c-Myc/TCR-ß		Precursor T-lymphoblastic lymphoma
MUM 1(IRF4)	t(6;l4)(p25;q32)	MUM-l/IgH	Transcription factor Involved in plasma cell differentiation	Multiple myeloma (rare)
pax-5	t(9;l4)(pl3;q32)	PAX-5/IgH	Transcription factor regulating B cell proliferation and differentiation	Lymphopiasrnacytic lymphoma (rare)

Table II. Typical immunophenotype of B-cell non Hodgkin's lymphomas

	CD20	CD79a	CD10	bcl-6	CD5	CD23	Cyclin Dl	bcl-2	Others
Follicular lymphoma	+	+	+/-	+	-	-/+		+/-	MUM1-
Small lymphocytic lymphoma/chronic lymphocytic lymphoma	+	+	-	-	+	+	-	+	
Lymphoplasmacytic lymphoma	+	+	-	-	-	-	-	+	CD25-/+,CDllc-
B-cell prolymphocytic leukemia	+	+	-/+	-/+	-/+	-	-	+	
Hairy cell leukemia	+	+	–	–	–	–	-/+	+/-	DBA44 + ,TRAP + , CD25 + ,CDllc +
Nodal marginal zone lymphoma	+	+	-	-	-	-	-	+	CD11C-/+
Extranodal marginal zone lymphoma	+	+	-	-	-	-	-	+	CD11C-/+
Splenic marginal zone lymphoma	+	+	-	-	-	-	-	+	DBA44-/+, CD25-/+
Mantle cell lymphoma	+	+	-	-	+	-	+	+	MUM1-, CDllc-
Myeloma/ plasmacytoma	-/+	+/-	–	–	–		-/+		MUM1+,CD138-)-, CD38 +
Diffuse large B-cell lymphoma, germinal center type	+	+	+	+	-/+	-/+	-	+/-	MUM1-
Diffuse large B-cell lymphoma, non-germinal center type	+	+	-	-/+	-/+	-/+	-	+/-	MUM1+
Mediastinal large B-cell lymphoma	+	+	-/+	+	-	+/-	-	+	
Burkitt's lymphoma	+	+	+	+	-	-	-	-	MUM1-

Cytogenetic analysis

As in most human neoplastic diseases, the genetic lesions involved in the physiopathology of non-Hodgkin's lymphoma include proto-oncogene activation and the disaggregation of tumor suppressor genes. The type and nature of these genetic disfunctions associated to hematologic malignant tumors or to other tumors are essentially different. Unlike many carcinomas which sometimes present a genomic instability, the genome of lymph cells is relatively stable, and lymphomas do not present irregularities in the correction of deteriorated DNA molecules which usually causes microsatelite instability.[7] The karyotype of a lymphoma is characterized by rare irregular cyclic chromosomial abnormalities. Over time, analyzing the karyotype of non-Hodgkin's lymphoma metaphase has been the main indicator for identifying and cloning most abnormalities in NHL lymphogenesis; several cellular oncogenes and tumor suppressor genes have been identified in association with chromosomial translocations which characterize lymphoid malignant tumors. [8, 9] In the pathogenesis of non-Hodgkin's lymphomas, chromosomial mutations represent the main mechanism of proto-oncogene activation. Each of these mutations is associated with a specific lymphoma subtype. The most common mutations encountered in lymphoid neoplasms are those involving a gene which is usually silent in the cell under the influence of a promoter associated either with an immunoglobulin (Ig) or with a T-type receptor gene, causing gene deregulation and offering the cell either a growth or a survival advantage.[10] This principle is illustrated by the close association between mantle cell lymphoma

and t (11;14) (q13;q32) translocation, due to which mantle cell lymphoma has been accepted as an independent entity. [12] Table I present some of the most important and characteristic chromozomial abnormalities of this lymphoma and of the other types of lymphoma, and table II presents the characteristic immunophenotype for the B lymphocyte in non-Hodgkin's lymphomas.

Despite their importance in defining various types of lymphoma, primary genetic abnormalities cannot be used as unique classification criteria for these tumors because some do not present well defined abnormalities and because the same chromosomial translocation may be associated with more lymphoma types. For example, t (14; 18) (q32; q21) is present in 85-90% of folicular lymphomas, but also in 20% of large B cell lymphomas. Moreover, certain cytogenetic abnormalities are only sometimes present in certain classes of lymphomas: for example, 10-15% of folicular lymphomas are t (14; 18) negative.[11, 13]

During the latest years, the use of DNA in-situ hybridization with fluorescent markers managed to overcome the limitations of conventional analysis, i.e. the need for viable dividing cells. The FISH technique may be performed on cells in interphase even on incorporated material, allowing the recognition of numeric or structural chromosomial disorders without the need of cell culture. This technique is sometimes called „molecular cytogenetics".

The comparative genomic hybridization technique (CGH) offers a wider picture of genetic disorders (over-exposures and deletions) in paraffin included materials from malignant tumors and may be used to assess the whole genomic instability which seems to be a new and important prognostic factor.[14]

During the last decade, the development of high precision techniques, especially DNA microarrays, allowed the characterization of the whole transcriptional profile of human tumors. In the case of lymphomas, the genetic expression characterized by these techniques, allowed a more accurate molecular classification of various lymphoma subtypes, and within some lymphoma sub-groups important predictive factors have been created based upon gene expressions, with the possibility of using them for future treatment guidelines.

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