



**GRIGORE T. POPA UNIVERSITY
OF MEDICINE AND PHARMACY IASI**

HABILITATION THESIS

**CURRENT ERGONOMIC AND AESTHETIC INTERDISCIPLINARY
APPROACHES IN ORAL REHABILITATION. MODERN SCIENTIFIC
COORDINATES IN DENTAL, PERIODONTAL AND
MUSCULOSKELETAL TREATMENTS**

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TABLE OF CONTENTS

Abstract	5
Rezumat	7
OVERVIEW OF ACADEMIC, SCIENTIFIC AND PROFESSIONAL ACHIEVEMENTS	9
SECTION I. SCIENTIFIC ACHIEVEMENTS FROM THE POSTDOCTORAL PERIOD	
<i>DIRECTION 1 RESEARCH IN IMMUNE MEDIATED RHEUMATIC DISORDERS AND ORAL HEALTH – A COMPLEX INTERPLAY</i>	16
• <i>1.1.1. Chronic periodontal disease and inflammatory chronic rheumatic conditions</i>	
State of the art.....	17
Materials and methods.....	25
Results.....	29
Discussion.....	46
Conclusions	56
• <i>1.1.2. Oral health in autoimmune rheumatic disorders (Sjogren syndrome)</i>	
State of the art.....	57
Materials and methods.....	58
Results.....	59
Discussion.....	60
Conclusions	61
• <i>1.1.3. Temporomandibular joint in rheumatic conditions</i>	
State of the art.....	61
Materials and methods.....	64
Results.....	66
Discussion.....	76
Conclusions	79
<i>DIRECTION 2 ERGONOMICS AND MUSCULOSKELETAL DISORDERS IN DENTISTRY</i>	79
• <i>1.2.1. Cervical and lumbar spine pathology in dentists</i>	
State of the art.....	82
Materials and methods.....	85
Results.....	87
Discussion.....	93
Conclusions	97
• <i>1.2.2. Hand pathology</i>	
State of the art.....	98
Materials and methods.....	101
Results.....	101
Discussion.....	106
Conclusions	107
<i>DIRECTION 3 ERGONOMIC AND AESTHETIC APPROACHES IN DENTAL THERAPY AND DENTAL PROSTHETICS</i>	108
• <i>1.3.1. Ergonomic-aesthetic implications in prosthetic rehabilitation</i>	
State of the art.....	108
<i>1) Possibilities and limits in the rehabilitation of the parameters of the dento-somato-facial aesthetic balance through metal-ceramic</i>	112
Materials and methods.....	113
Results	113

Discussions.....	115
Conclusions	116
2) Improvement of acrylic resins structure in removable prosthesis base polymerizat	117
Materials and methods.....	118
Results.....	119
Discussions.....	120
Conclusions	122
3)Computer applications for the evaluation of the dento-somato-facial aesthetic balance.....	123
Materials and methods.....	123
Results.....	123
Discussions.....	128
Conclusions	129
• I.3.2. Ergonomic-aesthetic implications in restaurative dentistry.....	130
State of the art.....	130
1)Methods for the assessment of esthetic posterior restauration.....	130
Materials and methods.....	131
Results.....	131
Discussions	132
Conclusions	133
2) Composite resins – multifunctional restorative material and practical approaches in dental field	134
Materials and methods.....	136
Results.....	137
Discussions	138
Conclusions	139
3) Mechanical Properties of Bis-GMA/HEMA Resin Composite with Addition of Silicon Dioxide Nanoparticles.....	140
Materials and methods.....	140
Results.....	141
Discussions.....	144
Conclusions	145
<u>SECTION II. PERSPECTIVES AND STRATEGIES IN ACADEMIC, PROFESSIONAL AND SCIENTIFIC RESEARCH</u>	
II.1. Perspectives in research activity	145
II.2.Perspectives in academic career	148
<u>SECTION III. REFERENCES</u>	149

Abbreviations

IRD - Inflammatory rheumatic disorders
 RA – Rheumatoid arthritis
 JIA - Juvenile idiopathic arthritis
 SpA – Spondyloarthritis
 AS – Ankylosing spondylitis
 SLE- Systemic erythematosus lupus
 SSc – Systemic sclerosis
 SSj - Sjogren's syndrome
 TNF – Tumor necrosis fator
 IL – Interleukin
 PD – periodontal diseases
 RANKL – receptor activator of nuclear factor kappa – B ligand
 CRP – C-reactive protein
 HAQ – Health Assessment Questionnaire
 BASDAI – Bath Ankylosing Spondylitis Disease Activity Index
 BASFI - Bath Ankylosing Spondylitis Disease Functional Index
 DAS28 – Disease Activity Score on 28 joints
 TCZ – Tocilizumab
 EUSTAR – European Scleroderma Trails and Research Group
 EULAR – European League Against Rheumatism
 ACR – American College of Rheumatology
 RF – Reumathoid Factor
 PI – Plaque index
 GI – Gingival index
 BOP – Bleeding on probing
 PPD – probing pocket depth
 PDL – periodontal ligament
 CAL – clinical attachemant level
 CBCT – Cone Beam Tomography
 TMJ – Temporomandibular joint
 MSDs – musculoskeletal diseases
 EMG - Electromiography
 VAS – Visual analogue scale
 CAD-CAM – Computer aided design – Computer Aided Manufacturing
 DSD – Digital Smile Design

ABSTRACT

The present habilitation thesis entitled "*Current ergonomic and aesthetic interdisciplinary approaches in oral rehabilitation. Modern scientific coordinates in dental, periodontal and musculoskeletal treatments*" summarizes my activity on the three main coordinates - professional, educational (didactic) and scientific research after the completion of my doctoral research. Based on the recommendations of the National Council for Attestation of University Degrees, Diplomas and Certificates (CNATDCU), the thesis is structured in three major sections:

- **Section I** which presents the results of my scientific research in the postdoctoral period and their dissemination;
- **Section II** that reflects the major directions of my future teaching and research activities;
- **Section III** which includes a list of the main reference works consulted in order to support the data presented.

The three sections are preceded by a synthesis of the entire academic career that brings to attention the evolution from the time of my graduation (2000) to the current status, presenting the hierarchy of *professional training* (obtaining the title of senior physician in General Dentistry and in Dento-alveolar Surgery), *educational* (academic evolution, from the first stage in the university environment as a junior assistant to the level of associate professor), and, last but not least, *scientific research*.

The first section of the habilitation thesis, *Scientific achievements from the postdoctoral period*, is dedicated to the development and scientific acquisitions from the period immediately following the doctoral validation and summarizes the main personal contributions in the field of dentistry. My scientific research has materialized in several books published in both international and national publishers as author and/or co-author (three books, nine chapters, one in international publishing), numerous articles published in ISI Thompson journals and reviews (a total of 24 papers, 22 as main author) or journals indexed in international databases (56 papers, 45 as main author); I was also constantly involved in various national and international scientific events with original papers (oral communications and posters). Moreover, the national and international visibility of my activity is confirmed by a *Hirsch-index of 8 in the Thomson ISI Web of Science Core Collection with a total of 178 citations, and an h-index of 9 in the Google Scholar, with a total of 292 citations*.

We can distinguish three major research topics, as follows:

1. Periodontal disease and immune-mediated rheumatic conditions

Interdisciplinary research, focused on the dual approach of the *relation between periodontal disease and immune-mediated rheumatic disorders* (rheumatoid arthritis, spondyloarthropathies - SpA, lupus, SSc), in order to identify correlations between specific rheumatological parameters and oral pathology, as well as the impact of biological therapy on both articular as well as on dental manifestations.

Another important section of my interdisciplinary research was characterized by the analysis of the temporomandibular joint (TMJ) involvement in different rheumatic conditions based on multifactorial parameters that definitely prejudiced its morphology and functionality.

2. Ergonomics and Musculoskeletal Disorders in Dentistry

The second research topic entitled *Ergonomics and Musculoskeletal Disorders in Dentistry* provides data on the analysis of risk factors arising from the professional act in order to quantify them, priority elements in implementing prevention protocols that will play an important role in raising awareness among students of the Faculty of Dentistry in order to reduce the professional risk. Studies have shown that abnormal working postures, the use of tools adapted to long-term professional needs, accuracy and force engagement are the main elements that over-demand the musculoskeletal system leading to the early occurrence of different issues and generating mainly pain and limited mobility.

3. *Ergonomic and aesthetic approaches in dentistry*

The third direction of research, *Ergonomic and aesthetic approaches in dentistry*, brings together a series of studies focused on aesthetics in two broad registers of dentistry - dental prosthetics and dental therapy. The research focused on both the classic aspects of aesthetics combined with functionality and the avant-garde based on the evolution of biomaterials, contemporary digital systems that provide accuracy and precision and last but not least the individualization of the therapeutic decision in their choice.

The second section of my habilitation thesis, *Perspectives and strategies in academic, professional and scientific research*, outlines the main lines and development projects that I propose in the next few years as well as in long-term stage, focusing on the complex interrelation between professional, academic and scientific research domains. Promoting a growing and sustained attention in a intricate multidisciplinary research, intended to gain both national and international visibility, I anticipate to advance some clinical and translational research topics addressing.

➤ *Prevention of musculoskeletal disorders in dentistry (MSD)*

MSD issues related to dental profession are related to exposure and stress to many mechanical factors including prolonged vicious positions, force activities, repetitive movements and vibrations. In future studies I intend to increase the number of enrolled subjects as this is an important element that gives relevance to the results obtained; I also intend to diversify the evaluated parameters, in order to be able to reach valid conclusion and be able to generalize results. Although the closer bidirectional relationship between cranio-mandibular disorders and posture imbalances is intensely debated, there are still unmet needs. Thus, I intend to develop new directions of collaboration with high-performance simulation and research laboratories in order to design a 3D analysis model, which brings together TMJ, different types of occlusion, posture, and musculoskeletal impairment; moreover, I want to perform a complex analysis of general, locoregional and local specific markers. Remaining in the same register of the dentist's exposure to occupational diseases, I propose to add different studies that will take into account the analysis of other organs and systems exposed in its professional activity.

➤ *Evaluation of the link between chronic inflammatory rheumatic disorders (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), systemic sclerosis and other conditions and periodontal disease*

Another future direction of research I want to develop is the dynamic analysis of rheumatic pathology in the context of periodontal pathology; I intend to realize a complex immunological approach and to assess the bidirectional relation between chronic periodontitis and rheumatic conditions in various therapeutical settings.

In my future approaches related to periodontal disease I also intend to initiate new studies based on the interrelationship with *metabolic diseases - diabetes and cardiovascular diseases*.

➤ *Evaluation of the link between chronic inflammatory rheumatic disorders and temporomandibular joint (TMJ)*

Another future research direction is based on the continuation of the research carried out within my doctoral thesis "TMJ changes in rheumatic diseases". I want to retake the research and to perform a detailed analysis of TMJ morphology in various rheumatic conditions, through modern paraclinical examinations such as CBCT and scintigraphy. I would like to be able to develop this research on other coordinates with other pathologies, thus extending the area of corroboration of data in the interdisciplinary sphere.

Finally, the **third section** of the current thesis proposes a list of bibliographic references accessed during the habilitation thesis, providing the international context of knowledge for the research topics addressed.

REZUMAT

Prezenta teză de habilitat intitulată ”*Current ergonomic and aesthetic interdisciplinary approaches in oral rehabilitation. Modern scientific coordinates in dental, periodontal and musculoskeletal treatments*” rezumă activitatea mea pe cele trei coordonate principale - profesională, didactică și de cercetare științifică de după finalizarea cercetării doctorale.

Respectând recomandările Consiliul Național de Atestare a Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU), teza este structurată în trei secțiuni majore, și anume:

- **Secțiunea I** care prezintă rezultatele cercetării științifice din perioada postdoctorală și diseminarea lor;
- **Secțiunea II** care reflectă direcțiile majore ale viitoarelor activități didactice și de cercetare;
- **Secțiunea III** care include o listă a principalelor lucrări de referință consultate în vederea susținerii datelor prezentate.

Cele trei secțiuni sunt precedate de o sinteză a întregii cariere academice ce aduce în atenție evoluția de la momentul finalizării studiilor universitare (anul 2000) până la statusul actual, prezentând ierarhizarea pregătirii pe plan *profesional* (dobândirea titlaturii de medic primar în Stomatologie Generală și medic specialist Chirurgie dento-alveolară), *didactic* (parcursul academic, de la prima etapă în mediu universitar ca preparator titular prin concurs până la treapta de conferențiar universitar), și, nu în ultimul rând, de *cercetare științifică*.

Prima secțiune a tezei, **Scientific achievements from the postdoctoral period**, este consacrată dezvoltării și achizițiilor științifice din perioada imediat următoare validării doctorale și rezumă principalele contribuții personale în domeniul stomatologiei.

Cercetarea științifică pe care am avut-o până acum s-a materializat în publicații de carte atât în edituri internaționale cât și naționale (autor, coautor) (3 cărți, 10 capitole în editură națională, 1 capitol în editură internațională), articole publicate în reviste din fluxul internațional cotate ISI Thompson (24, 22 autor principal) sau indexate în baze de date internaționale (56, 45 în calitate de autor principal), prezența constantă la manifestări științifice naționale și internaționale cu lucrări originale (comunicări orale, postere). Mai mult, vizibilitatea națională și internațională a activității este demonstrată de un *Hirsch-index de 8 în Thomson ISI Web of Science Core Collection (178 citări)*, și un *indice h-index de 9 în Google Scholar (292 citări)*.

Se pot distinge **3 mari teme** de cercetare ce au constituit domeniul de interes, și anume:

1. Interrelația boală paradontală – patologie reumatismală imun mediată

Cercetarea interdisciplinară, focalizată pe abordarea duală a *interrelației boală paradontală – patologie reumatismală imun mediată* (artrita reumatoidă - AR, Spondilartrite - SpA, sclerodermie sistemică - SSc), cu scopul identificării de corelații între parametri specifici reumatologici și de patologie orală, ca și impactul terapiei biologice atât asupra componentei articulare cât și asupra celei stomatologice.

O altă componentă importantă a cercetării în teritoriul interdisciplinar a fost reprezentată de analiza *binomului articulație temporo-mandibulară (ATM) - boală reumatismală* în contextul analizei cumulului factorial ce a influențat în mod definitoriu morfologia și funcționalitatea acesteia.

2. Ergonomia și patologia musculoschetală la medicul dentist

Cea de-a doua temă de cercetare intitulată **Ergonomics and Musculoskeletal Disorders in Dentistry** oferă date despre analiza factorilor de risc ce derivă din actul profesional în vederea cuantificării acestora, elemente prioritare în implementarea protocoalelor de prevenție ce vor avea un rol important în conștientizarea studenților de la Facultatea de Medicină Dentară în vederea diminuării riscului profesional. Studiile derulate au evidențiat faptul că poziția de lucru, utilizarea instrumentarului adaptat necesităților profesionale timp prelungit, precizia și angajarea forței sunt

principalele elemente care solicită în exces sistemul musculoscheletal conducând precoce la apariția fenomenelor patologice generatoare în principal de durere și de limitare a mobilității.

3. Abordări ergonomice și estetice în protetica dentară și odontoterapie

Cea de-a treia direcție de cercetare, *Ergonomic and aesthetic approaches in dentistry*, reunește o serie de studii focusate pe estetică în două registre ample ale medicinei dentare - protetica dentară respectiv odontoterapia. Cercetările abordate au vizat atât aspectele clasice ale esteticii coroborate cu funcționalitatea cât și cele de avangardă bazate pe evoluția biomaterialelor, pe sistemele digitale contemporane ce conferă acuratețe și precizie și nu în ultimul rând individualizarea deciziei terapeutice în alegerea acestora.

Cea de-a doua secțiune a tezei, *Perspectives and strategies in academic, professional and scientific research*, creionează principalele linii și proiecte de dezvoltare pe care mi le propun în etapa imediat următoare și pe termen lung, axându-se pe interrelația complexă între domeniile profesional, didactic-universitar, cercetare științifică.

➤ *Prevention of musculoskeletal disorders in dentistry (MSD)*

Un procent important de afectare revine sistemului musculo-scheletal, prin expunerea și solicitarea la numeroși factori mecanici care provin din promovarea pozițiilor vicioase, din promovarea unor activități de forță, mișcări repetitive, vibrații. În studiile viitoare doresc a lărgire a numărului de subiecți luați în studiu element important ce conferă relevanță rezultatelor obținute și să diversific în același timp parametrii evaluați. Interdependența între tulburările cranio mandibulare și dezechilibrele de postură este intens dezbătută în cercurile de specialitate internaționale, rămânând încă suficient de multe necunoscute în acest teritoriu. Pornind de la această realitate, doresc să pot realiza în viitor dezvoltarea unor noi direcții de colaborare cu laboratoare de simulare și cercetare performante în vederea proiectării unui model de analiza 3D, care să reunească articulația temporo-mandibulară (ATM), diferitele tipuri de ocluzie, postură, și stadiul de afectare musculoscheletală, în dinamica evolutivă pe fondul analizei markerilor specifici generali, locoregionali și locali. Rămânând în aceleași registru al expunerii medicului dentist la bolile profesionale îmi propun ca pe lângă analiza sistemului musculo-scheletal să pot adauga studii ce vor avea în vedere analiza și a altor organe și sisteme expuse în activitatea profesională a acestuia.

➤ *Evaluation of the link between chronic inflammatory rheumatic disorders (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), systemic sclerosis and other conditions and Periodontal Disease*

O altă direcție viitoare de cercetare pe care doresc să o dezvolt este *analiza dinamico-evolutivă a patologiei reumatismale în contextul patologiei parodontale* (prin intermediul evaluărilor imunologice specifice, interpretarea corelativă în funcție de stadiul de boală și contextul terapeutic complex).

Îmi propun ca în abordările viitoare legate de boala parodontală să pot iniția studii noi bazate pe interrelația cu *bolile metabolice - diabet zaharat și bolile cardiovasculare*.

➤ *Evaluation of the link between chronic inflammatory rheumatic disorders and temporomandibular joint (TMJ)*

O viitoare direcție de cercetare se bazează pe continuarea rezultatelor obținute în cercetările realizate în cadrul tezei de doctorat "*Modificările articulației temporo-mandibulare în bolile reumatismale*". Având ca punct de plecare aceste cercetări doresc să realizez o *analiză detaliată a morfologiei ATM* în diferite patologii sistemice, prin examene paraclinice moderne tip CBCT, scintigrafie.

Finalmente, cea de-a **treia secțiune** a tezei propune lista de referințe bibliografice accesate pe parcursul tezei de habilitare, oferind contextul internațional al cunoașterii pentru temele de cercetare abordate.

OVERVIEW OF PERSONAL, PROFESSIONAL, ACADEMIC AND SCIENTIFIC ACHIEVEMENTS

The university career is a higher stage of development in the professional activity of any individual whose principles are well correlated with the desire and need for self-transcendence, which is achieved through a continuous and intense training, designed to broaden and deepen the parameters of knowledge. The profession I have the privilege to practice offers me the unique chance, but at the same time the challenge, to carry out my activity in three essential fields: *education, health, research*.

Taken separately, each of these fields offers multiple professional satisfactions, but requires, at the same time, a continuous training, a desire to improve, in order to be able to face the special quality requirements, constantly growing as well as the existing competition in each of them.

In addition to the activity carried out in the field of health, which itself involves the maintenance of certain standards of professional and human quality, the academic environment brings a variety of opportunities as well as duties.

I had the chance to develop my professional abilities in a multicultural and multifunctional environment that required me to practice certain behavioral skills in the spirit of a civilized dialogue, elegant, calm, but also firm. On the other hand, I had the duty to cultivate students, in addition to the medical notions themselves, the passion and respect for the doctor's profession, respect for the patient and his suffering, but also interest in scientific research as a source of progress and innovation.

It is natural that in this context, together with my academic development, I propose to achieve certain short as well as long term objectives, general but also specific objectives related to each of my periods of evolution, aiming to continuously improve my professional development and to upgrade my medical, teaching and research chances.

Thus, in the development of my university career, I focused on three defining coordinates, respectively the didactic/ academic activity, the scientific research activity and the medical assistance activity, having pertinent objectives, general but also specific.

PROFESSIONAL AND ACADEMIC ACHIEVEMENTS

ACADEMIC ACHIEVEMENTS

The educational activity is a dynamic, extremely challenging, but also stimulating activity, which requires significant professional knowledge as well as instructive knowledge. The permanent interaction with the student implies a permanent adaptation to different personalities and human typologies, in order to attract, stimulate, train them in medical and research activity. This permanent interaction also constructively leaves its mark on my personality and development. The main coordinate promoted by a teacher must be the professional training of the specialist in his development.

The promotion of an instruction/education adapted to each developmental stage must bring to attention both the classical information but also the new one, in an accessible professional language, accompanied by conclusive demonstrations.

Different educational activities such as seminars and laboratories must promote active-participatory methods, to train the student in the teaching-learning process, to establish a heuristic dialogue and to be doubled by practical activities.

Furthermore, the student which is considered the future specialist must not only be edified and motivated, but also must be confronted with the perspectives of the future in which he must know how to ask and answer questions, to develop his interpersonal communication skills, to face professional confrontations (exams, competitions). For this, he must find in the daily educational activity (theoretical and practical) the support of his complex professional development.

At the same time, in this context, the student must find the support for establishing the level of values, a successful professional evolution; in addition, students also need landmarks and standards. Thus, a correct and impartial evaluation offered by the teacher to every the student at any time must form the basis of the subsequent ranking methodology.

I have started my didactic activity dedicated to student education in 2000 and currently I am working within the disciplines of *Ergonomics* and *Dental Instruments and appliances for dental medicine*.

My carrier in education was developed during several years and comprise several main steps:

2000 - 2004	<u>Junior assistant</u> Department of Implantology, Removable Restorations, Technology; Complex Oral Rehabilitation and Ergonomics; Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi
2004 - 2012	<u>Assistant professor</u> Department of Implantology, Removable Restorations, Technology; Discipline: Ergonomic; Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi.
2012 – 2018	<u>Lecturer</u> Department of Implantology, Removable Restorations, Technology; Discipline: Ergonomic; Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi.
2018 -	<u>Associate Professor</u> Department of Implantology, Removable Restorations, Technology; Discipline: Ergonomic; Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi.

Considering my teaching commitment in the Dental Medicine Faculty, I developed various activities, according to my academic degree, as follows:

Junior assistant – Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi:

- clinical training in *Prosthetic* with students from the 3rd and 4th years of study in Faculty of Dental Medicine;
- clinical training in *Ergonomy* 2nd year of study in Dental Medicine Faculty;
- laboratory training in *Ergonomy* - 2nd year of study College of Dental Technicians and Dental Assistants.

Assistant Professor - Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi:

- clinical training in *Ergonomy* 2nd year of study Dental Medicine Faculty; lines of study in Romanian, and English;
- laboratory training in *Ergonomy* 2nd year of study College of Dental Technicians and Dental assistant;
- clinical training in *Dental Instruments and appliances for dental medicine* - 2nd year of study, Dental Medicine Faculty; lines of study in Romanian and English;
- laboratory training in *Dental Instruments and appliances for dental medicine* - 2nd year of study College of Dental Technicians.

Lecturer - Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi:

- courses and clinical training in *Ergonomy* 2nd year of study, Dental Medicine Faculty; lines of study in Romanian and English;
- courses and laboratory training in *Ergonomy* 2nd year of study, College of Dental Technicians;
- courses and clinical training in *Dental Instruments and appliances for dental medicine* 3rd year of study, Dental Medicine Faculty; lines of study in Romanian, French and English;
- courses and laboratory training in *Dental Instruments and appliances for dental medicine* – 1st year of study, College of Dental Technicians.

Associate Professor- Faculty of Dental Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi:

- courses and clinical training in *Ergonomy*, 2nd year of study, Dental Medicine Faculty; lines of study in Romanian and English;
- courses and laboratory training in *Ergonomy*, 2nd year of study, College of Dental Technicians;
- courses and clinical training in *Dental Instruments and appliances for dental medicine*, 3rd of study, Dental Medicine Faculty; lines of study in Romanian and English;
- laboratory training in *Dental Instruments and appliances for dental medicine*, 1st year of study, College of Dental Technicians.

As a multidirectional potential that addresses a large number of disciplines, Ergonomics requires a particular methodology that allows the student to understand its objectives, means and results. In the meantime, the educational process in the area of ergonomics must develop its own performance for the practical application of its principles and methods during the future activity as a dentist.

The lectures were individually adapted for dental students, medical assistance and dental technicians with detailed aspects of clinical and preclinical grounds, for each specialization, making use of the graphic and video materials specific to the course topic. In my teaching activity I tried to promote student-centered active-participatory methods, to stimulate student participation and involvement in classes by including in the presentation of practical works some application aspects.

I also endeavored an interactive practical works through pros and cons, which allows students to think freely, to be able to make logical correlations in the future with other disciplines in the field of dentistry.

The courses and laboratories are focused on approaching the ergonomic concept in dentistry, with an ambitious role – to make these activities more efficient.

In order to be accessible to all students, the courses and laboratories are regularly uploaded online on the e-learning platform available at the website of our 'Grigore T. Popa' University of Medicine and Pharmacy, Iasi.

In order to support the didactic activity, I participated as an author in the elaboration and publication of 3 books for dental medicine students from the roumanian, english and french section:

1. Norina Consuela Forna & **Cristina Iordache** *Ergonomia în Medicina Dentara*, Note de curs pentru studenti, Iași 2012, editura “Gr.T.Popa” UMF Iași, ISBN-978-606-544-04-5;
2. Norina Consuela Forna & **Cristina Iordache**, *Èrgonomie dans la medicine dentaire*. Notes de cours, Iași 2012, editura “Gr.T.Popa” UMF Iași, ISBN-978-606-544-118-7;
3. Norina Consuela Forna & **Cristina Iordache** *Ergonomics in dental medicine*, Lecture notes, Iași 2014, editura “Gr.T.Popa” UMF Iași, ISBN – 978-606-544-231-3.

I encouraged students in participating in clinical, academic and research activities. In this regard, I have guided 34 license theses for dental medicine from the Romanian and French sections. Also, I promoted and guided the active participation of students in scientific student manifestations and workshops.

A comprehensive involvement in the teaching activity is foreseen in the near future by the elaboration of practical guides adapted to the training stage on different levels (student, resident, specialist doctor), the ergonomics finding its insertion in each specialty of dentistry. These guides will be developed in Romanian, French, English.

I consider very useful for professional training to make these practical guidelines and recommendations expressed concisely, but eloquently, whose subjects deal with the problems of posture of the spine both in a professional context and in everyday life. Topics such as musculoskeletal rebalancing of vertebral segments, rebalancing, relaxation and toning of peripheral muscles of the upper and lower limbs responsible for performing in good condition and with efficiency the professional act, dysfunctional syndromes related to professional dental activity will be found among publications. In this context, the interdisciplinary collaboration will be promoted and materialized, for a good and correct evaluation and presentation of the aspects.

PROFESSIONAL DEVELOPMENT

Degrees

In 1999 I have graduated the prestigious “Grigore T. Popa” University of Medicine and Pharmacy of Iasi, Romania (Diploma Seria R, Nr 0111824/septembrie 1999). I got my professional degree and expertise working in the field of general dentistry as a *trainee (2000-2003)*, thereafter *as specialist in 2003* (confirmed by the Degree issued by the Ministry of Health Nr. 431/12.05.2003). In 2008 I became senior specialist in General Dentistry (confirmed by the Degree issued by the Ministry of Health nr.1971/03.XII.2008) and in 2011 I completed already the second specialty becoming junior specialist in Dento-alveolar surgery after validating another exam (confirmed by the Degree issued by the Ministry of Health Nr nr.1535/ 03.01.2011).

Skills and competences

In all these years, I continued developing my professional education, by involving in post-graduate training courses, scientific and research-related projects. I have participated at various (20) international and national courses with international participation; of special interest, I have to mention the Training Course TRAINERS "*Evaluation and Interdisciplinary Treatment of Patients in Need of General and Oral Rehabilitation*", developed on the European project POSDRU/87/1.3/5/62208 “Training Center for Specialists and Resources in Oral Rehabilitation”, January 21 - February 28, 2013, Iasi.

SCIENTIFIC ACHIEVEMENTS**• PhD research**

In ceea ce privește activitatea de cercetare, debutul acesteia a fost reprezentat de teza de doctorat. Regarding the research activity, its beginning was represented by the doctoral thesis.

I have been admitted to be PhD training at the 'Grigore T. Popa' University of Medicine and Pharmacy Iași, Faculty of Dental Medicine in 2000 and in 2007 I was awarded the title of Doctor in Medical Sciences (Doctor's Degree, Order of the Minister of Education and Research no. 2398/15.10.2007) with the thesis entitled "*Modifications of the Temporomandibular Joint in Rheumatic diseases*", coordinator professor Burlui Vasile.

Rheumatic diseases are actually recognized as pathologic entities affecting the musculoskeletal system by immuno-inflammatory as well as mechanical/ degenerative mechanisms, characterized by high levels of morbidity, chronic, fast and disabling evolution, significant impairment of the quality and life expectancy, and high economical burden for individual and society.

The main aim of my doctoral thesis was to provide a complex epidemiological, clinical and imagistic description of TMJ involvement in different rheumatic disorders. This interdisciplinary approach by summing and interplay of knowledge of dental science and rheumatology has facilitated this scientific debate intended for a better understanding of the pathology TMJ by estimating *the prevalence* of TMJ damage during the evolution of the main inflammatory and degenerative rheumatic diseases (i), emphasizing the *clinical, biological and imagistic characteristics* (ii), evaluating the importance of local, dental-periodontal, occlusal as well as the systemic factors relevant for arthritis and osteoarthritis at the TMJ level (iii).

As required, my doctoral thesis has been divided into two main parts: general knowledge and personal contributions. *The first part* was based on a multifaceted presentation of actual issues of clinical anatomy of temporomandibular joint (TMJ) as well as new insights into the pathogenesis of immune-mediated inflammatory and degenerative rheumatic conditions, epidemiology, clinical and imaging data on the arthritis and osteoarthritis of TMJ. *The second part* of the thesis comprising four chapters of my own contributions was directed to provide relevant data about epidemiological indicators including the prevalence of TMJ damage in rheumatic diseases, to organize the clinical aspects of TMJ involvement in different pathological musculoskeletal conditions, to identify potential relations between local and general parameters defining disease activity, severity and progression, to highlights the contribution of modern imaging techniques such as ultrasound and computer tomography in the assessment of TMJ pathology.

A section of *discussion and conclusions* was designed for each chapter, while final conclusions summarize my viewpoint on the major aspects of TMJ involvement and relevant data for daily practice in dentistry as well as in the field of rheumatology. The current research was conducted on consecutive patients with different inflammatory and degenerative rheumatic disorders hospitalized in the Department of Rheumatology, Clinical Rehabilitation Hospital in Iași, Romania. A total of 348 patients fulfilling predefined inclusion and exclusion criteria were enrolled in this prospective observational study classified as follows: 152 patients diagnosed with Rheumatoid Arthritis (1987 modified American College of Rheumatology diagnostic criteria), 55 patients with Ankylosing Spondylitis (The 1995 New York criteria), 44 patients with Psoriatic Arthritis (EESG diagnostic criteria), 22 patients with Juvenile Idiopathic Arthritis (European League Against of Rheumatism diagnostic criteria) and 42 patients with osteoarthritis (American College of Rheumatology 1982 criteria); 33 healthy age and sex-matched controls were also evaluated.

Statistical analysis was performed by using the SAS 4.3 software; both descriptive statistics (mean, standard deviation, percentage, frequencies) and analytical statistics (the Probability Calculator function, χ^2 test, Pearson correlation rank test as well as one-way ANOVA Breakdown analysis) were used, with a statistical significant "p"<0.05.

- **Postdoctoral research**

After my PhD degree, I was interested in research in *three main directions*, as follows:

1. **Research in immune mediated rheumatic disorders and oral health – a complex interplay.**

Multidisciplinary research focused on the complex interplay and dual approach of parodontal disease (chronic periodontitis) and immune mediated rheumatic pathology (not only rheumatoid arthritis and spondylarthritis, but also systemic lupus erythematosus, systemic sclerosis and Sjogren's syndrome) aiming to identify correlations between specific rheumatic-related parameters and variables of oral pathology as well as the impact of biological therapy on the articular and dental components.

I had the opportunity to publish with my team preliminary results in ISI journals as well as journals indexed in other international database on:

- *Chronic periodontal disease and inflammatory chronic rheumatic conditions;*
- *Sjogren syndrome and oral health;*
- *Temporomandibular joint involvement in rheumatology.*

2. **Ergonomics and Musculoskeletal Disorders in Dentistry.**

Health care professionals working in dentistry are at risk to develop various musculoskeletal issues typically related to sub-optimal work-environment ergonomics; obviously, improper settings of work will be involved in abnormal working postures, particularly sitting ones, improper repetitive movements performed in vicious positions and repetitive strain injuries resulting in discomfort, excessive musculoskeletal loading, and early and significant fatigue. Both soft tissue (muscles, ligaments, tendons), nerves and bones/ joints, as well as intervertebral discs are commonly involved leading to different mechanical conditions such as cervical and lumbar pain with and without cervical and lumbar root problems, carpal tunnel syndrome, various tendinopathies in the upper limb, shoulder pain, rotator cuff tendinopathies.

The second research topic entitled *Ergonomics and Musculoskeletal Disorders in Dentistry* provides data on the analysis of risk factors arising from the professional act in order to quantify them, priority elements in implementing prevention protocols that will play an important role in raising awareness among students of the Faculty of Dentistry in order to reduce the professional risk.

3. **Ergonomic and aesthetic approaches in dentistry**

The third direction of research, *Ergonomic and aesthetic approaches in dentistry*, brings together a series of studies focused on aesthetics in two broad registers of dentistry - dental prosthetics and dental therapy. The research focused on both the classic aspects of aesthetics combined with functionality and the avant-garde based on the evolution of biomaterials, contemporary digital systems that provide accuracy and precision and last but not least the individualization of the therapeutic decision in their choice.

Research projects

- *Musculoskeletal pain academy*, IASP Developing Countries Project: Initiative for improving pain education competition (2011-2012) (member);

Both my professional and developmental work have led me to understand that trust in inter-academic relationships and responsibility for my activities are as important as recommendations based on scientific evidence. Furthermore, I realized that the results obtained depend not only on the quality of academic relations, but also on the organization of society as a whole. These observations determined me to get involved on the one hand in vocational training projects as well as in research projects.

In fact, my participation as a member in the project "Musculoskeletal Pain Academy", a multidisciplinary educational grant won and funded by International Association for the Study of Pain (IASP) Developing Countries Project: Initiative for Improving Pain Education 2011 helped me in my training as a researcher in the field, at the same time providing the optimal framework for the materialization of the concept of interdisciplinarity.

The project took place under the auspices of the University of Medicine and Pharmacy "Grigore. T. Popa" of Iași, within the Center "Gr. T. Popa" for Biomedical Research - European Center for Translational Research, Department of Pain Study; it was an important initiative to increase the educational level in the field of pain, materialized in the organization and implementation of a web program dedicated to musculoskeletal pain.

My decision to address the field of musculoskeletal pain was supported by the fact that pain and, particularly, musculoskeletal pain remain an actual issue of modern society, not only as a result of epidemiological indicators but also through pathophysiological and clinical aspects but also high socio-economic costs.

The multifaceted etiology of different sub-types of musculoskeletal pain (joint, muscle, bone, soft tissues) shapes the pathogenic mechanisms, clinical expression, methods of evaluation as well as the monitoring and therapeutic options in different disorders.

The educational program within the above mentioned project included several learning modules, online guidelines and recommendations as well as online discussions; we developed two main sections, one dedicated to medical staff (specialists / residents involved in the diagnosis and management of musculoskeletal pain and balneo-physiokinetherapists) and the other dedicated to patients complaining of musculoskeletal pain related to different conditions.

I was involved as a team member of the project based on my expertise gained in this field following my doctoral research.

In the special chapter dedicated to the temporo-mandibular joint we approached the following subchapters: *What is the Temporo-Mandibular Joint (TMJ)? What are the TMJ disorders that cause joint pain? Symptoms and impairment of TMJ in rheumatoid arthritis, Impairment of TMJ in ankylosing spondylitis / psoriatic arthritis / osteoarthritis, Diagnosis of TMJ dysfunction.*

I consider that my activity as a university teacher, as an integral part of the team of the "Grigore T. Popa" University of Medicine and Pharmacy, Iași, represents a mission and, at the same time, a challenge. If most professional categories have the duty to improve in only one field, we are among those who have the purpose and also the duty to multivalently and constantly enhance our knowledge, which makes obtaining exceptional results.

Indeed, to be the best in all three directions is a very difficult mission, which requires more than dedication, love of fellow human beings, but also the ability to manage with theoretical concepts and, sometimes, different abstract elements, specific to the research activity.

Achievements in the scientific publication area

Book Author – 3;

Book chapter author and co-author:

- National Book chapter author – 7;
- National Book chapter co-author – 3;
- International Book chapter coauthor – 1;

Articles published in extenso in ISI Web of Science Core Collection -indexed journals:

- First / last / correspondent author in ISI listed papers - 22;
- Coauthor in ISI listed papers - 2;
- Articles published in abstract in ISI Web of Science- 10

Articles published in extenso in international databases listed papers:

- First / last / correspondent author in international databases listed papers – 43;

- Co-author in international databases listed papers – 11;
Oral presentations at national and international scientific meetings - 59
Poster presentations at international scientific manifestations – 37.

Recognition at the national and international level

I am currently member in the following scientific professional societies:

- **International**

Romanian Dental Association for Education (ADRE)

Roumanian Society of Oral Rehabilitation (ASRRO)

Balkan Stomatological Society (BaSS)

- **National**

The College of Dentists from Romania (CMDR)

Union National of Stomatological Associations (UNAS)

International scientific visibility

Hirsch index (Clarivate Analitics) = 8

Number of publications in Clarivate Analytics DataBase = 51

Total number of citations without self citations (Clarivate Analytics) = 164

Index (Google Scholar) = 10

SECTION I. SCIENTIFIC ACHIEVEMENTS FROM THE POSTDOCTORAL PERIOD

DIRECTION 1.

RESEARCH IN IMMUNE MEDIATED RHEUMATIC DISORDERS AND ORAL HEALTH – A COMPLEX INTERPLAY

In the postdoctoral period I was particularly interested in interdisciplinary research and one of the most important direction was represented by an exhaustive assessment of the link between oral health and immune mediated rheumatic disorders comprising a broad spectrum of pathologies such as rheumatoid arthritis (RA), systemic erythematosus lupus (SLE), systemic sclerosis (SSc), Sjogren's syndrome (SSj) and entities belonging to the spondyloarthritis group (SpA).

I was interested (i) characterizing oral status in systemic autoimmune rheumatic disorders; (ii) identifying potential correlations between oral pathology and specific rheumatic parameters; and (iii) evaluating the impact of innovative biological on both articular and dental domains.

I was focused on three main topics, as follows:

- ***Chronic periodontal disease and inflammatory chronic rheumatic conditions (item I.1.1.);***
- ***Oral health in autoimmune rheumatic disorders - Sjogren syndrome (item I.1.2.);***
- ***Temporomandibular joint involvement in rheumatic disorders (item I.1.3.).***

Preliminary results were already published in several prestigious journals classified as ISI or indexed in other international databases (IDB).

I.1.1 CHRONIC PERIODONTAL DISEASE AND INFLAMMATORY CHRONIC RHEUMATIC CONDITIONS

STATE OF THE ART

Periodontal disease (PD) or periodontitis is a complex condition outlined by chronic inflammation and the subsequent damage of soft collagen-rich tissues progressing to periodontal ligament and alveolar bone loss as well as a gradual increase in tooth mobility (Fuggle et al., 2016; Genco et al., 2020; Eezammuddeen et al., 2020; de Molon et al., 2019; Rinaudo-Gaujous et al., 2019; Rutter-Loche et al., 2019; Sherina et al., 2019). It is typically initiated by an infection with oral anaerobic bacteria followed by inflammatory and immune response in the gingival and periodontal microenvironment (Genco et al., 2020; de Molon et al., 2019; Eezammuddeen et al., 2020). Autoantigens generated during citrullination induced by peptidylarginine-deaminase enzyme produced by *Porphyromonas gingivalis* (*P. gingivalis*), the keystone pathogen in the oral microbial biofilm, break the immune tolerance with induction of anti-citrullinated protein antibodies (ACPA) and promote chronic inflammatory response in both periodontal and synovial/articular tissues (Eezammuddeen et al., 2020; Erikson et al., 2019; Marrotte, 2019; de Molon et al., 2019; Mankia et al., 2019; Sherina 2019; Zamri et al., 2020)

The importance of *P.gingivalis* and other bacteria (*Tannerella forsythia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*) in the emergent periodontal inflammation as well as the link between periodontal disease and systemic disorders including cardiovascular disease, diabetes mellitus, chronic inflammatory rheumatic conditions and, even, pregnancy, was extensively debated in the last decade (Ancuța et al., 2017; Batool et al., 2016; Detert et al., 2008; Fuggle et al., 2016; Joseph et al., 2014; Payne et al., 2016).

Rheumatic diseases cover the broad spectrum of the rheumatic conditions characterized essentially by chronic pain, disability, impaired quality of life responsible for increased burden. Irrespective of their nature, inflammatory autoimmune, degenerative, mechanical or metabolic, rheumatic disorders account for a significant proportion of population, being among the most disabling disorders.

We were particularly interested in the research of several immune mediated rheumatic conditions comprising rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis among the spondyloarthritis group, systemic lupus erythematosus and systemic sclerosis belonging to connective tissue diseases and Sjogren syndrome.

Rheumatic diseases and chronic periodontitis are multifaceted chronic inflammatory conditions characterized by complex cytokine signature, with joint inflammation and damage, periodontal inflammation with subsequent periodontal ligament and alveolar bone loss and gradual increase in tooth mobility, respectively (Koziel et al., 2014; Fuggle et al., 2016).

Both entities share multifactorial pathways including similar genetic background (HLA-DR antigens) and environmental factors (smoking), unbalanced activation of proinflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-17) and proinflammatory mediators (prostaglandin E2, nitric oxide), osteoclast activation (RANKL overexpression) and dynamic articular and alveolar bone damage (Ceccarelli et al., 2019; Fuggle et al., 2016; Rangil et al., 2017; Thilagar et al., 2018).

The association between immune mediated rheumatic disorders (e.g. rheumatoid arthritis, lupus, scleroderma, spondylarthropathies) and oral health, particularly periodontal disease, is widely accepted, based on shared immune and inflammatory processes as well as local tissue (articular, gingival) damage, mediated by complex network of similar pro-inflammatory cytokine and destructive mediators (Fuggle et al., 2016; Linden et al., 2013).

Although remarkable progresses have been advanced in last decades in understanding the complex pathobiology in many rheumatic diseases, particularly immune mediated ones such as Rheumatoid arthritis (RA), spondyloarthritis (SpA), Systemic Lupus Erythematosus (SLE),

systemic sclerosis, Sjogren's syndrome, and innovative biological drugs have dramatically improved and changed the outcomes of such disorders, there are still unmet needs and the complex management remains challenging.

Rheumatoid arthritis and periodontal disease

Rheumatoid arthritis (RA) is an autoimmune condition characterized by joint inflammation and destruction associated with chronic systemic inflammation accounting for significantly impaired quality of life. It is defined by the excessive activation of proinflammatory cytokines mediators, specific autoantibodies and progressive irreversible articular damage (de Molon et al., 2019; Genco et al., 2020). Considered the hallmark of RA and, perhaps, the most important step in the pathobiology of the disease, the immune response against citrullinated peptides is driven, at least in part, by antigens derived from the periodontal tissue exposed to a dysbiotic oral microbiome during periodontitis (de Molon et al., 2019; Genco et al., 2020; Eezammuddeen et al., 2020; Sherina, 2019).

Chronic periodontitis is a complex condition outlined by chronic inflammation and the subsequent damage of soft collagen-rich tissues progressing to periodontal ligament and alveolar bone loss as well as a gradual increase in tooth mobility (Araujo et al., 2015; Batool et al., 2016; Fuggle et al., 2016; Joseph et al., 2014; Koziel et al., 2014; Payne et al., 2015).

Both entities share multifactorial pathways including similar genetic background (HLA-DR antigens) and environmental factors (smoking), unbalanced activation of proinflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-17) and proinflammatory mediators (prostaglandin E2, nitric oxide), osteoclast activation (RANKL overexpression) and dynamic articular and alveolar bone damage (Rutter-Loche et al., 2017; Äyravainen et al., 2017; Koziel et al., 2014; Fuggle et al., 2016).

Increased risk of periodontitis is already reported in patients with RA, irrespective of disease duration (Rutter-Loche et al., 2017; Äyravainen et al., 2017; Koziel et al., 2014; Fuggle et al., 2016), with a rate of 1.13 vs. controls according to a recent review (Fuggle et al., 2016); overall, it seems that RA patients are prone to develop moderate periodontitis, with worsened periodontal status and more severe and aggressive lesions if early untreated compared to established disease (Rutter-Loche et al., 2017; Äyravainen et al., 2017). On the other hand, an association between chronic periodontal inflammation and the risk to develop RA was also advanced, new data proposing that periodontitis associated with *P. gingivalis* is more likely to be present in ACPA-positive at-risk adults without arthritis (Gonzales et al., 2015; de Oliveira et al., 2019).

This association has been broadly talked in recent years, highlighting the role of gingival microorganisms (typically *P. gingivalis*), as the underlying link between dental and rheumatic pathology via citrullination (Araujo et al., 2015; Batool et al., 2016; Fuggle et al., 2016; Joseph et al., 2014; Koziel et al., 2014; Payne et al., 2015).

The role of different therapies on rheumatoid arthritis and periodontal disease outcomes

The evolving model for dynamic interrelation between RA and PD encourages the concept that standard management for RA may be effective in improving the outcomes in PD and vice versa (Äyravainen et al., 2017; Romero-Sanche et al., 2017; Rutter-Locher et al., 2017; Marrote, 2019; Sherina, 2019).

Pivotal studies have already explored the role of different synthetic and biological therapies in active RA and comorbid periodontal disease, showing *controversial results* (Bartold et al., 2020; Kobayashi et al., 2014; Kobayashi et al., 2015; Mankia et al., 2019; Rinaudo-Gaujous et al., 2019; Romero-Sanchez, et al., 2017).

Innovative biologics acting by blocking the TNF and IL-6-mediated signalling are also able to promote reliable decrease in inflammatory cytokines and antibodies with dramatic effect not only

on clinical, biological and serological activity of RA, but also on oral health. (Kobayashi et al., 2014; Sikorska et al., 2018; Smolen et al., 2017).

There is a trend to consider that TNF inhibitors, IL-6 receptor antagonist, B-cells depletive agents and, even, JAK inhibitors improve periodontal health in both RA and other arthritis (e.g., ankylosing spondylitis, psoriatic arthritis); it seems that all these drugs are ultimately effective in decreasing gingival and periodontal inflammation and, to a lesser extent, associated tissue damage (Kawalec et al., 2019; Kobayashi et al., 2015; Kobayasi et al., 2019).

Researchers even proposed a multistep approach of the sequential tissue repairing following TNF inhibitors, comprising reduced leukocytes traffic in the inflamed tissue, decreased proteolytic activity, and the normalization of osteoclast activity (Bartold et al., 2020; de Molon et al., 2019; Rinaudo-Gaujous et al., 2019; Zamri et al., 2020).

However, there are differences among anti-TNF agents as only *adalimumab* and *etanercept* significantly improved periodontal outcomes in as rapid as six months, while *infliximab* worsened gingival inflammation but prevented gingival bone loss (Rinaudo-Gaujous et al., 2019; Marrote, 2019).

Furthermore, according to a study by Kobayashi and colleagues, *tocilizumab* (TCZ) also ameliorates periodontal inflammation in RA with periodontitis as TNF inhibitors do (Kobayashi et al., 2014; Kobayashi et al., 2015; Kobayasi et al., 2019). Its beneficial effects were potentially explained by the decrease in TNF- α serum levels as well as immunoglobulin G and serum amyloid along with a consistent impact on serum inflammatory mediators and indirect influence on periodontal inflammation (Kobayashi et al., 2014; Kobayashi et al., 2015; Moller et al., 2019).

On the other hand, both *tocilizumab* and *rituximab* are able to determine an important down regulation of inflammation and damage in gingival as well as articular microenvironments in RA associated with periodontitis; this is mainly related to decrease in serum inflammatory mediators (Kobayashi et al., 2015; Coat et al., 2015).

Furthermore, one recent publication presented the role of Janus Kinase (JAK) inhibitor *tofacitinib* in two cases of RA and comorbid periodontal disease. As suggested by the authors, efficacy of tofacitinib seems to be related to the suppression of systemic inflammation promoted by high levels of IL-6 through a sustained inhibition of IL-6 signalling. Although serum concentration of IL-6 showed a significant and rapid decline, the level of IL-6 or its receptor in gingival crevicular fluid was not assessed in this study (Kobayashi et al., 2019).

Several publications have successfully demonstrated that specific therapies for chronic periodontitis (e.g. non-surgical professional scaling or root planning with or without antibiotics) may ameliorate local inflammation, improve RA activity and response to different anti-rheumatic drugs (Kawalec et al., 2019; Yang et al., 2018; Monsarrat et al., 2019).

The most recent data from the ESPERA (Experimental Study of Periodontitis and Rheumatoid Arthritis) cohort failed to demonstrate clinical improvement in established RA following aggressive and intensive periodontal treatment (Monsarrat et al., 2019).

Ankylosis spondylitis and periodontal disease

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disorder, affecting mainly the axial skeleton and, with a lesser extent, peripheral joints, entheses, eyes, bowels and skin, causing inflammation and tissue damage as a result of an autoimmune process in a genetically background (HLA-B27, genes for IL-23 and ERAP-1 (Ranganathan et al., 2017). While inflammation is the initial step in the immunopathogenesis of the disease involving the bone-cartilage interface, cartilage erosions and additional osteoproliferation (as a repair process) via TNF mediation are critical for AS (Ranganathan et al., 2017; Ratz et al., 2015).

Periodontal disease (PD) remains an inflammatory infectious condition characterized by an immunologically mediated damage of tissues surrounding and supporting the teeth accompanied by chronic gingival inflammation driven by pathogenic bacteria in the dental plaque (Kalakonda et

al., 2016; Croitoru et al., 2015). Progressive attachment loss, alveolar bone resorption, soft tissue pockets formation between the gingiva and the tooth root and/or gingival recession are typically reported as subsequent steps in the long-term course of the disease (Ranganathan et al., 2017).

Although the connection between PD and systemic conditions (including cardiovascular disease, diabetes, malignancies, autoimmune-mediated inflammatory rheumatic and non-rheumatic disorders) is classically described and accepted, the link between ankylosing spondylitis (AS), altered periodontal status and higher risk of periodontal disease is not clear (Croitoru et al., 2015; Kalakonda et al., 2016; Keller et al., 2013; Ranganathan et al., 2017; Ratz et al., 2015).

It is widely recognized that ankylosing spondylitis and PD share several local and systemic inflammatory and destructive processes addressing specific tissues: joints (sacroiliac joints, spine and peripheral joints) and entheses in AS, periodontal tissues in PD (Eke et al., 2012; Kalakonda et al., 2016; Keller et al., 2013; Ranganathan et al., 2017). In both conditions, we assist at an important immune dysregulation not only of innate, but also of acquired immune response; high concentrations of pro-inflammatory cytokines belonging to the TNF- α and IL-17/IL-23 axis are engaged in both articular and periodontal microenvironments, and ones may think about a close association between the articular and periodontal disease (Croitoru et al., 2015; Eke et al., 2012; Kalakonda et al., 2016; Ranganathan et al., 2017; Ratz et al., 2015). Moreover, it seems that the abnormal immune response occurring in AS is able, at least theoretically, to modulate the inflammatory response of oral infections with pathogens existing in the bacterial plaque that cover the teeth (Keller et al., 2013).

Data about the relationship between AS and PD, as well as the potential role of disease activity and inflammatory parameters as predictors of periodontal involvement among AS patients is still controversial (Chang et al., 2013; Keller et al., 2013; Ratz et al., 2015). While the majority of studies report a higher prevalence of impaired oral health and PD in AS compared to general population (Chang et al., 2013; Keller et al., 2013; Ratz et al., 2015), certain papers found no association between these two entities (Chang et al., 2013).

Overall, the rates of PD in AS ranges from 37.5% to 87.8% and is about 25.9 to 71.4% in healthy controls, after adjusting for general risk factors for periodontitis such as smoking, obesity, excessive alcohol intake (Chang et al., 2013; Keller et al., 2013; Ratz et al., 2015).

Chang presented in 2013 their interim analysis supporting that the prevalence and severity of PD was not increased in AS patients and anti-TNFs were not associated with the prevalence and outcomes of PD.

On the other hand, no extensive study was conducted to explore the association between these two conditions.

Psoriatic arthritis and periodontal disease

Psoriatic arthritis (PsA) represents a chronic inflammatory heterogeneous disease affecting predominantly the skin, joints, and entheses, with several distinct clinical profiles (Al Hamadi, 2016).

The pathologic process of skin and joint lesions reflects a complex interplay between immunologic and inflammatory events on a background of environmental factors (including a temporal relation with certain viral and bacterial infections) in a genetically predisposed host (Ustun et al., 2013; Skudutyte-Rysstad et al., 2014; Monson et al., 2016).

A closer look to the immunopathogenesis of the disease displays: abundant Th1-cell cytokines (e.g., TNF- α , IL-1 β , IL-10) derived from activated T cells and other mononuclear pro-inflammatory cells (monocytes, macrophages); increased proliferative activity of fibroblasts (skin, synovial) and their ability to secrete IL-1, IL-6, and platelet-derived growth factors; excessive humoral immunity (autoantibodies against nuclear antigens, cytokeratins, epidermal keratins, heat-shock proteins); abnormal bone remodelling mediated by TNF- α and matrix metalloproteinases (MMPs) (Skudutyte-Rysstad et al., 2014; Monson et al., 2016).

Both psoriatic and periodontal disease share common pathobiological pathways including excess of pro-inflammatory cytokines, such as TNF- α and IL-1- β , in target tissues (skin, joint, gingival microenvironment), exaggerated immune response to the microbiota residing at the epithelial surface (skin, periodontal tissue), abnormal bone remodeling and/or resorption (Monson et al., 2016).

Regardless of extensive interest in periodontitis and systemic disorders during the last decade, only few papers have addressed the link between PsA and chronic periodontitis, with still controversial conclusions (Batol et al., 2016; Fuegge et al., 2016; Monson, Silva et al., 2016; Monson, Porfirio et al., 2016).

While certain papers considered there is no difference in periodontal profiles, though psoriatic patients had few teeth remaining (Monson, Silva et al., 2016; Monson, Porfirio et al., 2016), others authors showed that psoriasis patients had poor periodontal status as compared to their matching controls (Monson, Silva et al., 2016; Monson, Porfirio et al., 2016; Sharma et al., 2014) and periodontitis may be associated with psoriasis (Lazadiou et al., 2013; Monson, Silva et al., 2016; Monson, Porfirio et al., 2016).

Psoriatic patients had more bone loss and loss of teeth compared to controls according to a complex periodontal assessment including alveolar bone loss on bite-wing X-rays (Monson, Silva et al., 2016; Monson, Porfirio et al., 2016).

In addition, the prevalence of periodontitis seems to be higher in patients diagnosed with psoriasis as demonstrated by clinical attachment loss and alveolar bone loss (Monson, Silva et al., 2016; Monson, Porfirio et al., 2016), particularly in moderate-to-severe disease as compared to controls (Monson, Silva et al., 2016; Monson, Porfirio et al., 2016; Skudutyte-Rysstad et al., 2014). Furthermore, the risk of severe PD in psoriasis was six times higher in smokers than in non-smokers (Antal et al., 2014; Monson, Silva et al., 2016; Monson, Porfirio et al., 2016). Also, an increased rate of psoriasis was demonstrated in patients with chronic PD (Monson, Silva et al., 2016; Monson, Porfirio et al., 2016; Skudutyte-Rysstad et al., 2014).

The relation between PsA and chronic PD is, therefore, bidirectional; increased risk for psoriasis, especially palmo-plantar pustulosis, was reported among patients with chronic periodontal disease (Ganzetti et al., 2014; Kikuchi et al., 2013; Monson, Silva et al., 2016; Monson, Porfirio et al., 2016; Nakib et al., 2013), while periodontal bone loss may increase the risk of subsequent psoriasis (Monson, Silva et al., 2016; Monson, Porfirio et al., 2016; Nakib et al., 2013).

Systemic sclerosis and periodontal disease

Systemic sclerosis (or scleroderma) is a chronic multisystem disease characterized by a dynamic and exclusively complex pathobiology directed by three essential processes: autoimmunity, widespread obliterative vasculopathy of small arteries causing ischemia-reperfusion injury, and varying degrees of inflammation and tissue fibrosis (Shah et al., 2012, Sierra-Sepúlveda et al., 2019).

The hallmark of this rare connective tissue disorder is its highly variable expression, with clinical phenotypes defined by different stages of disease expression, multiple organ involvement (lung, heart, kidney, gastrointestinal tract, and musculoskeletal system), and specific serologic biomarkers (anti-topoisomerase 1, anti-centromere, and anti-RNA polymerase III antibodies), resulting in significantly altered quality of life and survival (Shah et al., 2012, Sierra-Sepúlveda A. et al., 2019). Although recent guidelines tried to redesign therapeutic strategies to prevent progression and to minimize damage of specific organ involvement, the management of scleroderma remains a challenge in routine practice (Shah et al., 2012, Sierra-Sepúlveda A. et al., 2019). Oral health issues are commonly reported in patients with SSc (up to 80%) and comprise a broad spectrum of manifestations, from reduced mouth opening (microstomia) with abnormal interincisal distance and decreased salivary flow (xerostomia) to increased number of missing

teeth and caries, periodontal diseases with gingival recession or other types of oral infections, and even temporomandibular joint involvement (Shah et al., 2012; Sierra-Sepúlveda A. et al., 2019; Smirani, 2018; Crincoli et al., 2016; Said et al., 2016; Derbi, 2018; Yilmaz et al., 2018). A number of explanations concerning the interfaces between SSc and oral health have been proposed; it seems that orofacial manifestations are generally related to excessive and extensive fibrosis of skin and oral mucosa, as well as to local vasculopathy (Smirani, 2018; Crincoli et al., 2016; Said et al., 2016; Derbi, 2018; Yilmaz et al., 2018). Likewise, poor oral hygiene prompted not only by local conditions (microstomia) and compromised gingival vascularization but also by hand disability as a result of sclerodactyly, acro-osteolysis, and/or small joint arthritis may compromise oral health (Shah et al., 2012; Sierra-Sepúlveda A et al., 2019). Since oral disease represents an additional contributor to altered quality of life (Smirani et al., 2018) and dental treatment could be more difficult or, sometimes, unrealistic in advanced disease, routine oral assessment is indicated in scleroderma patients aiming at early detection and management of specific dental problems (Jung et al., 2017; Puzio et al., 2019).

Two major radiographic features are described in scleroderma, widening of the periodontal ligament (PDL) space (Alexandridis, 1984; Anbiaee N. et al., 2011; Anbiaee N. et al., 2012; Baron et al. 2014, Baron et al.2015, Baron et al. 2016) and mandibular erosions (Baron et al., 2014, Baron et al., 2015; Baron et al., 2016; Hopper et al., 1982; Mortazavi et al., 2016; Yalcin et al., 2019).

PDL represents the soft tissue between the inner wall of the alveolar pocket and the roots of the teeth, consisting mainly of type I collagen and connecting the cementum of teeth to the gingivae and alveolar bone (Dagenais et al., 2015; Baron et al., 2014; Baron et al., Baron et al., 2015; Baron et al., 2016; Mortazavi et al., 2016; Stoica et al., 2016).

A uniform widened PDL space at least twice as normal occurs in up to two-thirds of cases and is thought to be linked to an increased collagen synthesis in the ligament as a part of global fibrosis that characterize scleroderma and is not indicative of periodontal disease in the absence of occlusal trauma (Baron et al., 2014; Baron et al., 2015; Baron et al., 2016; Mortazavi et al., 2016). Bone erosions are identified at the sites of muscle attachment in the mandible: the masseter at the angle of the mandible, the lateral pterygoids at the condylar head, the temporalis at the coronoid process, and the digastric at the digastric region (Dagenais et al., 2015; Baron et al., 2014; Baron et al., 2015; Baron et al., 2016; Mortazavi et al., 2016). Various papers have rated the frequency of such imaging abnormalities in SSc, mainly using two-dimensional radiographs (Jung et al., 2017; Dagenais et al, 2015; Baron et al., 2014; Baron et al., 2015; Baron et al., 2016; Yalcin et al., 2019), while the performance of Cone Beam Computed Tomography (CBCT) was assessed in few case reports (Stoica et al., 2016; Tyndall et al., 2008; Yang et al., 2019). We were interested in assessing oral manifestations in SSc focusing on different aspects including periodontal disease, periodontal space widening, temporomandibular joint involvement; we performed a complex approach comprising not only clinical but also imaging studies, based on X-ray but also CBCT.

PERSONAL RESEARCH

My personal research in the rheumatology and periodontal topics comprised

- **7 ISI articles** published in local as well as international ISI journals;
- **one national book chapter** entitled „*Oral health in immune mediated rheumatic disorders*” Codrina Ancuța, Cristina Pomîrleanu, Magda Antohe, Oana Țănculescu, **Cristina Iordache**, published in “Grigore T Popa” Editure, 2021 pointing on oral health issues in different autoimmune rheumatic conditions.
- **one international book chapter** entitled ”*Rheumatoid Arthritis and Periodontal Disease: A Complex Interplay*” published in the book *New Developments in the Pathogenesis of Rheumatoid Arthritis* edited by professor Lazaros SAKKAS (Greece), 2017 (InTech, DOI:

10.5772/65863); was written in collaboration with professor Claudia Mihailov, (Rheumatologist at the University Ovidius in Constanta), and professor Codrina Irena Ancuta (Rheumatologist at our University of Medicine and Pharmacy Gr.T.Popa Iasi);

- **several oral and e-poster presentations were accepted in national and international manifestations such as:**
 - **Annual Congress of the European League Against Rheumatism (2017- Oral Health in SSc: an EUSTAR center experience; 2010-Periodontal status in PsA; 2009-Periodontal status in RA);**
 - **World Congress on Systemic Sclerosis 2018, Cone beam computed tomography CBCT for the assessment of oral manifestations in patients with SSc – preliminary results of an EUSTAR cohort;**
 - **Congress of the Asia Pacific League of Associations for Rheumatology -Periodontal disease in RA;**
 - **23rd BaSS Congress 2018 Dental Medicine of the Younger vs. Elderly Patients, (Trends in the assessment of oral manifestations of SSc: CBCT results);**
 - **1st Bass Symposium 2019 - Digital Era in Current Medical Practice (Oral manifestations in scleroderma patients – a CBCT imaging study);**
 - **Simpozionul international Teaching and Learning innovations in Medical Education, Iasi, Romania, Modificari ale ATM la pacienții cu sclerodermie (Changes at the TMJ level in patients with scleroderma).**
- I have also to mention the important recognition of my studies in the field of periodontal disease and rheumatoid arthritis; one of my abstracts submitted to the EULAR 2009, in Copenhagen, Denmark (*Periodontal status in patients with rheumatoid arthritis, FRI0171*) was selected by the *EULAR PreSS committee* for presentation to the international media; in this interesting session I was together with professor Molitor from USA who talked about his work in the same direction (*Moderate to severe adult periodontitis is associated with increased risk of seropositive rheumatoid arthritis in non-smokers: The ARIC study, FRI0129*)

<https://www.sciencedaily.com/releases/2009/06/090612115429.htm>

<http://www.irishhealth.com/article.html?id=15668>

In all the substudies developed within this general theme of crossover between oral health and rheumatic pathology I was interested in evaluating relations between specific rheumatic parameters and variables of the oral pathology and the impact of biological and targeted therapy on the articular and dental parameters.

I have particularly studied prospectively patients with different chronic inflammatory rheumatic conditions (RA, SSc, AS, PsA) and periodontal pathology, aiming to perform a descriptive assessment of oral health problems associated with rheumatic diseases and their relation with disease activity, to monitor modifications in periodontal lesions related to specific anti-rheumatic medication (biologics and targeted synthetic drugs).

The design of all studies comprised the oral and rheumatologic evaluation (disease-related parameters such as disease activity, severity, inflammatory parameters, antibody profile), the same parameters being collected in all patients at baseline and during the follow-ups.

Periodontal health status

The same experienced dentist performed a complex assessment of the oral health problems in our patients, focusing on several parameters such as plaque index (PI), gingival index (GI), bleeding on probing (BOP), probing pocket depth (PPD) and clinical attachment level (CAL). All clinical measurements were done at four sites of all teeth, respectively mesio- and disto-buccal, mesio- and disto-lingual; we used a Williams probe for PPD and CAL. Only partial (at least 8

evaluable teeth excluding 3rd molar) and fully dentate patients were accepted and included in the final analysis.

Although three main criteria are largely accepted for the clinical diagnosis of periodontitis, including CAL, BOP and PPD, a uniform definition of the diagnostic threshold has not yet been established; PPD was defined as the distance from the free gingival margin to the bottom of the sulcus or periodontal pocket, while CAL as the distance from the cement-enamel junction to the bottom of the sulcus or periodontal pocket. A patient was considered as having chronic periodontitis if at least four teeth presented a PPD ≥ 5 mm and with CAL ≥ 2 mm at the same time (1999 Consensus Classification of Periodontal Diseases) (Armitage, 1999).

Rheumatic disease status

An extensive assessment of underlying disease activity was done using internationally validated indices and scores such as DAS28 (*Disease Activity Score on 28 joints*) for rheumatoid arthritis, ASDAS-CRP (*Ankylosing Spondylitis Disease Activity score based on C reactive protein*) for ankylosing spondylitis, DAPSA (*Disease Activity in Psoriatic Arthritis*) for psoriatic arthritis and EUSTAR score for systemic sclerosis.

I will further present the main aspects and published results dedicated to periodontal inflammation in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic sclerosis, discussing also the role of TNF biologics as well as JAK inhibitors in targeting articular and periodontal disease.

Paper 1: Exploring the Role of Interleukin-6 Receptor Inhibitor Tocilizumab in Patients with Active Rheumatoid Arthritis and Periodontal Disease

By: Codrina Ancuța, Rodica Chiriac, Eugen Ancuța, Oana Țănculescu, Sorina Mihaela Solomon, Ana Maria Fătu, Adrian Doloca, **Cristina Iordache**

J. Clin. Med. 2021,10, 878.

Paper 2: Anti-Tumor Necrosis Factor Alpha Therapy and Periodontal Inflammation in Rheumatoid Arthritis: A clinical and biochemical approach

By: Ancuta C., Ancuta E, Chiriac R, Antohe M, **Cristina Iordache**

REVISTA DE CHIMIE 2017, 68 (2):369-372.

Paper 3: Efficacy of baricitinib on periodontal inflammation in patients with rheumatoid arthritis.

By: Ancuța C, Pomîrleanu C, Mihailov C, Chiriac R, Ancuța E, **Cristina Iordache**, Bran C, Țănculescu O.

Joint Bone Spine. 2020, 87 (3), 235-239.

Paper 4: Periodontal Disease in Patients with Ankylosing Spondylitis: myth or reality?

By: **Cristina Iordache**, Chiriac R, Ancuta E, Pomirleanu C, Ancuta C.

REVISTA DE CHIMIE 2017, 68 (7): 1660-1664.

Paper 5: TNF Inhibitors and Periodontal Inflammation in Psoriatic Arthritis

By Ancuta C, Ancuta E, Chiriac R, Anton C, Surlari Z, **Cristina Iordache**

REVISTA DE CHIMIE 2017, 68 (8): 1914-1918.

Paper 6: Periodontal Disease and Lipid Profile in Systemic Sclerosis: an EUSTAR Cohort Experience

By: Ancuta C, Pomirleanu C, **Cristina Iordache**, Fatu A, Popescu E, Ancuta E, Mihailov C

REVISTA DE CHIMIE 2017, 68 (4):890-893.

Paper 7: Volumetric Cone Beam Computed Tomography for the Assessment of Oral Manifestations in Systemic Sclerosis: Data from an EUSTAR Cohort

By: **Cristina Iordache**, Magda-Ecaterina Antohe, Rodica Chiriac, Eugen Ancuța, Oana Țănculescu, Codrina Ancuța

JOURNAL OF CLINICAL MEDICINE 2019, 8, 1620.

OBJECTIVES

We were interested in:

- assessing the influence on the periodontal status of weekly subcutaneous administration of tocilizumab in a local group of patients with rheumatoid arthritis and chronic periodontitis (**paper 1**);
- assessing the periodontal status in RA with and without baricitinib, a Janus kinase (JAK) inhibitor (**paper 2**);
- evaluating the periodontal status in RA patients with and without TNF inhibitors and identifying potential relations between different disease-related parameters (activity, disability, serological and inflammatory profile, treatment response) and chronic periodontitis (**paper 3**);
- assessing the relationship between periodontal disease and AS, focusing on the rate and course of PD in such patient population, factors associated with the severity of both disorders and the impact of anti-TNF treatment on inflammatory status (**paper 4**);
- evaluating the periodontal status in PsA before the initiation of biologics and after 24-weeks treatment with anti-TNFs and identifying potential relations between disease activity, inflammatory profile, therapeutic response and chronic PD (**paper 5**);
- estimating the periodontal status in SSc and defining potential relations between periodontal disease and different SSc characteristics (disease subtypes, serological, inflammatory tests), as well as serum lipid profile (**paper 6**).
- assessing oral radiologic manifestations associated with scleroderma using high-resolution CBCT and to identify potential relations with disease variables (**paper 7**).

Generally, we performed 4 observational prospective 6-months studies assessing periodontal status in different rheumatic disorders (RA, AS, PsA) and 2 cross-sectional studies in SSc. Irrespective of the study population, we applied the same algorithm meaning disease-related parameters and periodontal evaluation performed by the same skilled dentist, collected either twice (at baseline and at the follow-up visit at 6 months) for the studies where we followed the influence of medication on oral health or only once, as done in the SSc studies.

MATERIAL AND METHOD

➤ RA and periodontal status

1st study - *Exploring the Role of Interleukin-6 Receptor Inhibitor Tocilizumab in Patients with Active Rheumatoid Arthritis and Periodontal Disease*

We performed a prospective longitudinal study in fifty-one patients with moderate-to-severe RA and insufficient response to either conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs), starting TCZ according to the local recommendation for biologic and targeted synthetic therapy aligned with European League Against Rheumatism (EULAR) consensus statement and guidelines.

We performed extensive rheumatologic and full mouth assessments at baseline (before the first administration of TCZ) as well as after 3 and 6 months of therapy.

The study was approved by the local ethics committee (Sanocare Medical and Research Center, Prot. No 15/12.12.2016) and was found to conform to the guidelines of the Declaration of Helsinki. Written informed consent regarding the use of the collected data in the context of training and research was signed by all the participants before enrollment. The data used in the study were anonymized.

Statistical analysis was performed with the IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp., Armonk, New York), with p-values less than 0.05 being considered as statistically significant; data at 3 and 6 months were summarized as means \pm SD, or percentages (%) as appropriate, and correlations by Spearman rank tests; comparisons between baseline and 3 and 6 months of TCZ were assessed by Wilcoxon test.

2nd study - *Anti-Tumor Necrosis Factor Alpha Therapy and Periodontal Inflammation in Rheumatoid Arthritis: A clinical and biochemical approach*

96 consecutive RA initiating their first TNF inhibitor, recruited in a single rheumatology academic centre.

Standard assessments comprised a dual rheumatologic and dental evaluation performed by trained examiners, as follows: (i) *RA-related parameters* - disease activity (disease activity on 28 evaluable joints using erythrocyte sedimentation rate, DAS28-ESR) and disability scores (Health Assessment Questionnaire Disability Index, HAQ-DI), inflammatory (ESR and C-reactive protein, CRP) and serological parameters (rheumatoid factor, RF, and anti-cyclic citrullinated peptide antibodies, ACPA; ACPA were detected using the fluorescence enzyme immunoassay (FEIA) for anti-cyclic citrullinated peptide autoantibodies with values <7 U/ml classified as negative; 7-10 U/ml as equivocal and >10 U/ml as positive; Synevo Lab); and (ii) *periodontal status* including several parameters such as plaque index (PI), gingival index (GI), bleeding on probing (BOP), pocket (probing) depth (PD) and clinical attachment level (CAL).

The study comprised two visits, at baseline (V1), before starting TNF inhibitors, and at the end of follow-up interval (V2), after 6 months of biological therapy.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

Statistical analysis was done in IBM SPSS-19 software, $p < 0.05$.

3rd study - *Efficacy of baricitinib on periodontal inflammation in patients with rheumatoid arthritis*

In the third RA-periodontitis study, we also performed a prospective longitudinal 24-weeks follow-up, but in a small number of active RA ($n=21$) initiating baricitinib, a JAK2 inhibitor. As in the first study, we collected standard data meaning disease activity, disability, serological and inflammatory parameters, as well as the same complex dental assessment based on several indexed e.g. plaque index, gingival index, bleeding on probing, probing depth and clinical attachment level.

Since we analysed only 21 patients, the results were expressed as median and interquartile range 25–75% (IQR 25–75) or number (%), correlations by Spearman rank tests, while comparisons between baseline and 6 months of baricitinib were performed by Wilcoxon test.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

➤ AS and periodontal status

4th study *Periodontal Disease in Patients with Ankylosing Spondylitis: myth or reality?*

Prospective observational 24 weeks study in a cohort of 86 consecutive patients aged 18 years or more who meet the 1984 modified New York criteria for AS aiming to assess periodontal disease.

Patients were followed in a single academic rheumatology department and all received TNF inhibitors (adalimumab, infliximab, golimumab, etanercept) based on national recommendations for the use of biologics in active AS sub-optimally controlled by non-steroidal anti-inflammatory drugs.

Periodontal parameters and a complex rheumatologic assessment were done based on the same protocol in all AS patients:

- *Periodontal examination.* Full-mouth periodontal probing using a Williams probe was performed at 4 sites per tooth (mesio-buccal, disto-buccal, mesio-lingual, disto-lingual); probing pocket depth, clinical attachment loss, plaque index (PI), gingival index (GI) and bleeding on probing were measured in all patients.

PPD was defined as the distance from the free gingival margin to the bottom of the sulcus or periodontal pocket, and CAL as the distance from the cement-enamel junction to the bottom of the sulcus or periodontal pocket.

Chronic periodontitis was considered if at least four teeth with a PPD ≥ 5 mm and with CAL ≥ 2 mm at the same time, as recommended by the 1999 Consensus Classification of Periodontal Diseases [9];

- *Standard AS assessments* included two disease activity scores, Bath Ankylosing Spondylitis Disease Activity Score, BASDAI, and Ankylosing Spondylitis Disease Activity Score calculated using C reactive protein levels, ASDAS-CRP.

BASDAI is the old subjective activity score for AS, while ASDAS is a new composite index to assess disease activity. The 3 cut-offs for this score are <1.3 between "inactive disease" and "moderate disease activity", <2.1 between "moderate disease activity" and "high disease activity", and >3.5 between "high disease activity" and "very high disease activity".

- *Inflammatory parameters*, erythrocyte sedimentation rate (ESR) analyzed by the Westergren method (mm/hour), and C-reactive protein (CRP) by the classic method (mg/L) were performed in all patients.

Patients with severe aggressive PD requiring professional scaling were excluded from the final analysis, while those presenting with potential risk factors for PD such as diabetes, smoking, excessive alcohol intake and obesity also were not included in the study.

Periodontal evaluation, AS examination and inflammation tests were recorded twice during the study, at week 0 (before the first administration of anti-TNF agents) and at 24 weeks of therapy.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

Statistical analysis. Results were expressed as median and interquartile range 25–75% (IQR 25–75) or number (%), correlations by Spearman rank tests, while comparisons between baseline and 6 months of baricitinib were performed by Wilcoxon test. Statistics were done with SPSS software (version 19), P-values less than 0.05 being considered as statistically significant.

➤ *PsA and periodontal status*

5th study TNF Inhibitors and Periodontal Inflammation in Psoriatic Arthritis

41 consecutive PsA patients (30 women) fulfilling the 2006 CASPAR classification criteria for PsA were enrolled in a prospective short-term (24 weeks) observational study aiming to evaluate oral health, particularly periodontal disease. Patients were followed-up in the outpatient rheumatology department and qualified to initiate their first TNF inhibitor based on National Recommendation for Biologics in Active PsA refractory to synthetic drugs.

Patients were assessed according to a standard protocol comprising a complex rheumatologic (PsA activity, inflammatory prolife) and dental evaluation.

Standard assessments were performed by experienced examiners and covered a dual rheumatologic and dental, including: (i) *PsA-related parameters* - disease activity (DAS28-ESR, on 28 evaluable joints using erythrocyte sedimentation rate; and Disease activity in PsA, DAPSA score), disability scores (Health Assessment Questionnaire Disability Index, HAQ-DI) and inflammatory parameters (ESR analyzed by the Westergren method and C-reactive protein, CRP,

by the classic method); and (ii) *periodontal parameters* - bleeding on probing (BOP), probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI) and gingival index (GI).

A patient was considered as having chronic periodontitis if at least four teeth with a PPD ≥ 2 mm and with CAL ≥ 2 mm at the same time (1999 Consensus Classification of Periodontal Diseases).

No periodontal therapy or invasive dental procedures (professional scaling and prophylaxis) were permitted during the study period; additionally, all participants were instructed not to change their oral hygiene routines.

The study comprised the baseline visit (V1), before starting biological therapy, and the end of study visit, after 24 weeks (V2).

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

Statistical analysis was done in IBM SPSS-19 software, $p < 0.0$

➤ SSc and periodontal status

6th study - Periodontal Disease and Lipid Profile in Systemic Sclerosis: an EUSTAR Cohort Experience

We performed a cross-sectional observational study conducted in 31 consecutive SSc with a history of disease of more than 12 months, attending at least once the rheumatology department (acknowledged as the EUSTAR 162 centre, affiliated to the EUSTAR network).

A dual rheumatologic and periodontal assessment was done in all cases according to a standard protocol. All parameters were collected as a single point data, comprising:

- *dental evaluation* - plaque index, bleeding on probing, pocket depth, clinical attachment level/ loss; clinical measurements were done at four sites on all teeth, including mesiobuccal, distobuccal, mesiolingual and distolingual; a Williams probe was used for measurements of PD and CAL.
- *rheumatologic evaluation* - SSc subtype, clinical spectrum, inflammatory, immunological, lipid metabolism - total cholesterol, TC; low- and high-density lipoprotein cholesterol, LDL-C and HDL-C; triglycerides, TG; the atherogenic plasma index, AI), and parodontal status evaluation.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

Statistical analysis was done in SPSS-19 ($p < 0.05$), within subgroups of patients. In addition, in the SSc study analysis was performed based on skin extent and PD; multivariable regression analysis was used to evaluate the association between SSc, periodontal disease and lipid metabolism parameters.

7th study - Volumetric Cone Beam Computed Tomography for the Assessment of Oral Manifestations in Systemic Sclerosis: Data from an EUSTAR Cohort

We published data collected in a cross-sectional study enrolling forty-three consecutive scleroderma patients (fulfilling either the old 1980 American College of Rheumatology criteria or the new 2013 ACR/EULAR, European League Against Rheumatism) classification criteria for SSc, attending at least once the outpatient rheumatology department (Clinical Rehabilitation Hospital of Iasi, Romania) during a twelve-month interval (January 2017–January 2018). Additionally, forty-three sex- and age-matching controls were recruited from patients addressing osteoarthritis at the same department.

Patients underwent rheumatologic and routine oral health evaluation; in addition, all individuals were referred for dental radiographic evaluation.

Oral health status was systematically assessed and refer to:

- *Plaque accumulation*

Reflecting the oral hygiene status, plaque accumulation was recorded with a Silness and Loe plaque index; gingival index was used to measure the extent of inflammatory gingivitis (Silness, Loe, 1964). Both indexes were evaluated as degrees from 0 to 3 (Pischon et al, 2016) and also the percentage of sites with detectable plaque (PI%) and with bleeding on probing (BOP%) (Leung et al., 2011).

- *Periodontal status*

We evaluated periodontal status using periodontal probing depth (the distance from the gingival margin to the base of the gingival sulcus) and by clinical attachment level (the distance on the buccal or labial surface from the cemento-enamel junction to the base of the gingival sulcus) (Dagenais et al., 2015; Baron et al. 2014; Baron et al., 2015; Baron et al., 2016; Page et al., 2007; Savage et al., 2009). We used a custom periodontal chart that included the measurement of the gingival recession and the pocket depth in 4 points (mesiobuccal, distobuccal, mesiolingual, and distolingual) for each tooth, assessed with a periodontal probe marked in millimeter intervals (Stoica et al., 2016). The presence of periodontal disease in a given tooth was defined as either a PPD > 3 mm or a CAL \geq 5.5 (Dagenais et al., 2015; Baron et al. 2014; Baron et al., 2015; Baron et al., 2016; Leung et al., 2011; Page et al., 2007). The extent of periodontal disease in the entire mouth was calculated as the number of involved teeth, and the severity (no, mild, moderate, or severe periodontitis) was also assigned accordingly (Dagenais et al., 2015; Baron et al., 2014; Baron et al., 2015; Baron et al., 2016).

- *SSc-Related Parameters*

Specific scleroderma data comprised different variables as defined by the standard requirements promoted by EUSTAR (European Scleroderma Trials and Research Group) and included subset classification, meaning limited or diffuse cutaneous SSc based on their skin extent (LeRoy classification criteria); disease duration; clinical profile (modified Rodnan skin score 0–51, digital vasculopathy, and other visceral involvement); antibody profile (anti-topoisomerase-1, anticentromere antibodies, and anti-RNA polymerase III); disease activity (revised EUSTAR activity index (0–3)); and severity (Medsger disease severity scale; 0–4) (Sierra-Sepúlveda et al., 2019; Melsens et al., 2016, Barsotti et al., 2017; Ross et al., 2018).

The study was approved by the ethics committee board of Clinical Rehabilitation Hospital of Iasi, and subjects provided written informed consent before enrollment.

Statistical Analysis: Descriptive statistics were used for scleroderma parameters and radiologic manifestations of the patients with SSc and the controls. Nonparametric statistics (Spearman rank correlation; univariate and multivariate analysis adjusted for age, gender, and smoking status) were used to analyze the association between SSc and number of teeth with widening of the PLS and erosions. Mann Whitney U tests, Chi-squared tests, and Fisher's exact tests were used accordingly.

RESULTS

➤ RA and periodontal status

1st study - Exploring the Role of Interleukin-6 Receptor Inhibitor Tocilizumab in Patients with Active Rheumatoid Arthritis and Periodontal Disease

Baseline RA and Periodontal Assessments

Demographics, rheumatologic and periodontal characteristics, as well as RA-related drugs (concomitant glucocorticoids and immunosuppressives) taken at baseline are summarized in **Table 1**.

Table 1 Demographic, rheumatologic and periodontal characteristics at baseline

Baseline Parameters	Baseline
Demographics	
Age (years; mean ± SD)	56.3 ± 15.7
Female (n, %)	46 (90.1)
RA-related parameters	
Duration of RA (months; mean ± SD)	81.3 ± 68.9
DAS28-CRP (mean ± SD)	5.36 ± 1.67
SDAI (mean ± SD)	34.2 ± 16.3
Corticosteroids (n, %)	20 (39.21)
DMARDs (n, %)	46 (90.1)
ACPA levels (U/mL; mean ± SD)	239.7 ± 124.3
ACPA positivity (n, %)	32 (62.74)
RF levels (IU/mL; mean ± SD)	192.7 ± 85.3
RF positivity (n, %)	47 (92.15)
Serum CRP levels (mg/dL; mean ± SD)	15.3 ± 6.9
PD-related parameters	
Number of present teeth (mean ± SD)	23.7 ± 3.4
GI (mean ± SD)	0.98 ± 0.12
% sites with plaque (mean ± SD)	32.4 ± 16.9
% sites with BOP (mean ± SD)	10.2 ± 8.6
PPD (mm; mean ± SD)	2.8 ± 0.4
% sites with PPD ≥ 4 mm	12.7 ± 2.5
CAL (mm)	3.5 ± 1.2
% CAL ≥ 3 mm	12.5 ± 0.2

Most patients included in our study had seropositive established RA, with moderate-to-severe activity despite background medication. Eight patients (15.68%) received TCZ as their first biologic agent (bio-naïve), while the majority were bio-experienced patients, with failure (either insufficient response or adverse reactions) to previous biologics—15 (29.41%) to one biologic, 20 (39.21%) to two biologics, and 8 (15.68%) to three biologic agents.

We detected impaired oral health in all patients included in the final analysis, as follows: all had gingivitis (abnormal GI and increased prevalence of sites with BOP), and different degrees of chronic periodontitis (mainly level 1 and 2); advanced loss of attachment was reported in up to 23.52% of cases, while increased prevalence of sites with dental plaques in 21.56% of cases.

A closer look revealed a consistent positive correlation between the severity of chronic periodontitis, RA activity, and serum $r^2 = 0.71$ ACPA concentrations ($r_1 = 0.81$, $p_1 = 0.001$, $p_2 = 0.002$, respectively): the higher the RA activity and ACPA levels, the higher the PPD severity, with advanced CAL and tooth loss.

Changes in Rheumatologic and Periodontal Parameters with Tocilizumab

Changes in RA activity and periodontal status were reassessed after 3 and 6 months of TCZ; at follow-up visits, we reported significant improvement as compared to baseline ($p < 0.05$), although the results at 6 months were only slightly different from data obtained at 3 months ($p > 0.05$).

Changes in Rheumatologic Status

Patients displayed consistent improvements in clinical activity meaning a significant decrease in the number of tender and swollen joints, VAS pain, and morning stiffness as rapid as 3 months; as expected, clinical response was maintained 3 months later in all patients, at the final monitoring visit. Similarly, we reported a dramatic decline in inflammatory biomarkers (both ESR and CRP), as well as a considerable immunologic response, particularly for serum levels of ACPA, but also for RF (**Table 2**).

Table 2 Changes in rheumatoid arthritis (RA) related parameters at 3 and 6 months after tocilizumab

Parameter	Baseline	3 Months (V1)	6 Months (V2)	p-Value
DAS28-CRP (mean ± SD)	5.36 ± 1.67	3.39 ± 0.57	2.41 ± 0.19	*<0.05; **<0.05
SDAI (mean ± SD)	34.2 ± 16.3	18.1 ± 8.2	11.1 ± 4.3	*<0.05; **<0.05
Number of tender joints (mean ± SD)	12.31 ± 4.29	4.56 ± 1.31	3.55 ± 1.13	*<0.05; **NS
Number of swollen joints (mean ± SD)	10.01 ± 3.37	2.85 ± 4.22	1.50 ± 2.09	*<0.05; **NS
Pain VAS mm (mean ± SD)	82.7 ± 21.5	28.8 ± 23.2	16.3 ± 11.8	*<0.05; **<0.05
Serum anti-CCP titer (U/mL) (mean ± SD)	239.7 ± 124.3	192.6 ± 112.4	123.6 ± 101.6	*<0.05; **NS
Serum RF levels (IU/mL) (mean ± SD)	192.7 ± 85.3	164.8 ± 92.5	151.7 ± 89.3	*NS; **NS
Serum CRP levels (mg/dL) (mean ± SD)	15.3 ± 6.9	4.12 ± 0.92	3.92 ± 0.34	*<0.05; **NS

SD; standard deviation; DAS28-CRP, Disease activity score on 28 joints based on C-reactive protein; SDAI, Simplified Disease Activity Index; VAS, 0–10 cm visual analogue scale; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; V, visits; * V1 compared to baseline; ** V2 compared to V1; NS, non-significant (0.05).

DAS28-CRP and SDAI strongly improved during monitoring visits reaching either low disease activity or, even, remission (EULAR responders) vs. baseline, irrespective of the severity of periodontitis.

Changes in Periodontal Status

Clinical data showed improvement in periodontal inflammation after only 3 months of TCZ and maintained over 6 months, as supported by an important decrease in gingival index and sites with bleeding of probing ($p < 0.05$). However, the improvement of specific periodontal parameters such as probing pocket depth becomes evident after prolonged treatment (6 months); overall, clinical attachment loss presented only slight changes without any statistical significance; teeth count and bacterial plaque scores were also not significantly influenced by medication ($p > 0.05$) (**Table 3**).

Table 3 Changes in PD-related parameters at 3 and 6 months after tocilizumab

Parameter	Baseline	3 Months (V1)	6 months (V2)	p-Value
GI	0.98 ± 0.12	0.85 ± 0.17	0.81 ± 0.18	*<0.05; **NS
% sites with plaque	32.4 ± 16.9	30.5 ± 14.2	30.2 ± 15.8	*NS; **NS
% sites with BOP	10.2 ± 8.6	7.3 ± 6.1	6.5 ± 6.8	*<0.05; **NS
PPD (mm)	2.8 ± 0.4	2.1 ± 0.12	2.1 ± 0.09	*<0.05; **NS
% sites with PPD ≥ 4 mm	12.7 ± 2.5	7.8 ± 3.9	6.1 ± 3.6	*<0.05; **NS
CAL (mm)	3.5 ± 1.2	2.58 ± 0.30	2.55 ± 0.31	*<0.05; **NS
% sites with CAL ≥ 4 mm	12.5 ± 0.2	11.2 ± 0.4	11.3 ± 0.9	*<0.05; **NS

GI, gingival index; BOP, bleeding on probing; PPD, probing pocket depth; CAL, clinical attachment loss; * V1 compared to baseline; ** V2 compared to V1; $p > 0.05$ non-significant (NS); V1 and V2, visit 1 and 2, respectively.

No significant correlations between changes in periodontal parameters and changes in RA activity were described in our study ($p > 0.05$).

We assumed that all the modifications in the degree of local gingival and periodontal inflammation is related to IL-6 blockade as no local periodontal treatment was allowed during follow-up.

2nd study - Anti-Tumor Necrosis Factor Alpha Therapy and Periodontal Inflammation in Rheumatoid Arthritis: A clinical and biochemical approach

Baseline characteristics

RA-related parameters

Demographics, RA history (disease duration), sero-positivity (RF, ACPA), disease staging, functional status (HAQ-DI), inflammatory syndrome (ESR, CRP), disease activity (DAS28-ESR),

concomitant medication (DMARDs, corticosteroids) as well as periodontal status were recorded in all patients at baseline and summarized in **table 4**.

We enrolled patients aged between 23 and 60, with both early and established RA, with positive immune profile (RF+, ACPA+) in the majority of cases and moderate to high RF and ACPA levels.

As expected, biological therapy was proposed for patients with highly active RA (mean DAS28-ESR of 4.95 ± 1.54), with high levels of inflammation (mean ESR of 58.3 ± 21.9 , respectively more than twice the upper normal limit; mean CRP of 4.43 ± 2.89 , respectively up to 3.2 the upper normal limit) and aberrant immune response (mean RF level of 145.8 ± 122.5 , mean ACPA of 145.8 ± 116.2). Concomitant synthetic DMARDs (methotrexate, leflunomide, sulfasalazine or antimalarials) were administered in all cases, while low dose corticosteroids in about one third of RA.

Supplementary, in a limited number of RA (32) we were able to perform seriate analysis of serum TNF alpha levels (ELISA, normal values $<8.1 \text{ pg/mL}$; Synevo Lab), before and after 6 months of anti-TNFs. High levels of serum TNF were demonstrated at baseline in all patients, with a mean concentration of $16.25 \pm 5.31 \text{ pg/mL}$

Periodontal parameters

57.29 % (55) RA presented with fewer teeth than normal for age and gender-matches healthy individuals, with a mean number of evaluable teeth of 23.7 ± 9.7 . We reported an increased prevalence of sites containing dental plaques (34.9 ± 15.2), abnormal gingival index with a mean value of 0.98 ± 0.16 and 13.9 ± 8.7 % sites with bleeding on probing. Also, RA patients had a mean pocket depth was $2.75 \pm 0.51 \text{ mm}$, while important PD ($\geq 4 \text{ mm}$) was identified in 11.9 ± 2.4 % of cases. Furthermore, a significant number of cases (%) had advanced clinical attachment level, with a mean value of $2.62 \pm 0.49 \text{ mm}$ and common attachment loss. All data are shown in **table 4**.

Table 4 RA patients characteristics at baseline

Rheumatologic and periodontal	characteristics
RA-related parameters	
Age (years; mean \pm SD)	49.2 ± 25.7
Duration of RA (months; mean \pm SD)	56.5 ± 32.1
RF positivity (%) (n)	83.3 (80)
Serum RF levels (IU/mL; mean \pm SD)	145.8 ± 122.5
ACPA positivity (%) (n)	78.1 (75)
Serum ACPA titer (U/mL; mean \pm SD)	145.8 ± 116.2
ESR (mm/hour; mean \pm SD)	58.3 ± 21.9
Serum CRP levels (mg/dL; mean \pm SD)	4.43 ± 2.89
DAS28-ESR (mean \pm SD)	4.95 ± 1.54
Corticosteroids (%) (n)	37.5 (36)
DMARDs (%) (n)	100 (96)
Periodontal status	
Number of teeth present (mean \pm SD)	23.7 ± 9.7
% sites with plaque (mean \pm SD)	34.9 ± 15.2
GI (mean \pm SD)	0.98 ± 0.16
% sites with BOP (mean \pm SD)	13.9 ± 8.7
PD (mm; mean \pm SD)	2.75 ± 0.51
% sites with PD $\geq 4 \text{ mm}$ (mean \pm SD)	11.9 ± 2.4
CAL (mm; mean \pm SD)	2.62 ± 0.49
% sites with CAL $\geq 4 \text{ mm}$ (mean \pm SD)	2.51 ± 0.53

In subgroup analysis, higher inflammatory (CRP, ESR) and immune abnormalities (ACPA, but not RF) were demonstrated in RA associated with either localized or generalized aggressive PD as follows ($p < 0.05$):

- *RA with PD*: mean CRP of 6.31 ± 2.13 mg/dL, mean ESR 64.41 ± 17.62 mm/h, mean ACPA levels 256.23 ± 54.19 U/mL, while
- *RA without PD*: mean CRP of 3.27 ± 1.75 mg/dL, mean ESR 32.52 ± 0.85 mm/hour, mean ACPA 93.61 ± 14.23 U/mL.

We found statistical significant positive correlations between PD and RA activity and ACPA levels ($r=0.86$, $p<0.05$; $r=0.83$, $p<0.05$).

Changes in rheumatologic and periodontal status after TNF inhibitors

Disease activity and biochemical biomarkers

6 months of biological therapy, irrespective of the specific TNF inhibitor administered (monoclonal anti-TNF antibodies, soluble TNF receptor) resulted in significant improvement in disease activity, inflammatory and immune parameters. Thus, a significant decrease in mean DAS28-ESR levels with low to moderate final DAS28 was reported in all cases (4.95 ± 1.54 vs 2.65 ± 0.81 , $p<0.05$). Statistical significant fall in both ESR and CRP levels was reported (ESR: 58.3 ± 21.9 vs 23.12 ± 10.2 , $p<0.05$; CRP: 4.43 ± 2.89 vs 1.4 ± 0.73 , $p<0.05$), together with reduction in ACPA levels (145.8 ± 116.2 vs 101.0 ± 54.5 , $p<0.05$) (**Table 5**).

In the subgroup of patients with available serum TNF evaluation, a significant decrease was registered in the majority of patients, particularly in those achieving low disease activity status or remission; mean serum TNF was 8.84 ± 3.63 pg/mL ($p<0.05$).

Periodontal status

Although no periodontal therapy was permitted during the follow-up, and patients were instructed to maintain their dental behavior, overall a statistically significant improvement in periodontal status was demonstrated after 6 months of biological therapy with TNF inhibitors ($p<0.05$) (**Table 5**).

Our results showed significant differences in PD and CAL as compared to baseline ($p<0.05$). Mean pocket depth significantly decreased under TNF inhibitors (2.75 ± 0.51 vs 1.36 ± 0.29 , $p<0.05$), as well as the mean number of RA with PD > 4 cm (11.9 ± 2.4 vs 8.2 ± 3.5 % sites with severe PD).

The same tendency was described for clinical attachment level: significant difference as compared to baseline for the study group (2.62 ± 0.49 vs 1.92 ± 0.23 , $p<0.05$), with 2.51 ± 0.53 vs 1.4 ± 0.42 % of sites with CAL ≥ 4 mm, even clinical attachment loss.

Not surprisingly, both plaque and gingival index were not significantly influenced under biological DMARDs (% sites with plaque: 34.9 ± 15.2 vs 31.9 ± 12.4 , $p>0.05$; GI: 0.98 ± 0.16 vs 0.63 ± 0.11 , $p>0.05$).

We were also interested in assessing changes (Δ) in periodontal parameters in our RA patients treated with TNF antagonists; thus, we reported slightly changes in gingival plaques ($p>0.05$) and a Δ % sites with plaque of -3.0 ± 3.8 , accompanied by the same trend in gingival index registered as Δ GI of -0.35 ± 0.05 ($p>0.05$), and Δ % sites with BOP -3.7 ± 9.3 . However, TNF antagonists resulted in significant change in PD with a Δ PD (mm) of -1.49 ± 0.22 ($p<0.05$) and Δ % sites with PD ≥ 4 mm of -3.7 ± 6.9 ($p<0.05$), while Δ CAL (mm) (-0.5 ± 0.26) and Δ % sites with CAL ≥ 4 mm (-1.11 ± 0.11) were similarly significant ($p<0.05$).

Table 5 RA-related parameters and PD status without and with TNF inhibitors

Characteristics	Baseline	6 months	p
RA-related parameters			
DAS28-ESR	4.95 ± 1.54	2.65 ± 0.81	$p<0.05$
Serum ACPA titer (U/mL)	145.8 ± 116.2	101.0 ± 54.5	$p<0.05$
Serum RF levels (IU/mL)	145.8 ± 122.5	96.6 ± 45.8	$p<0.05$
Serum CRP levels (mg/dL)	4.43 ± 2.89	1.4 ± 0.73	$p<0.05$

ESR (mm/hour)	58.3±21.9	23.12±10.2	p<0.05
Periodontal status			
% sites with plaque	34.9 ± 15.2	31.9 ± 12.4	p>0.05
GI	0.98 ± 0.16	0.63 ± 0.11	p>0.05
% sites with BOP	13.9 ± 8.7	3.3 ± 1.8	p<0.05
PD (mm)	2.75 ± 0.51	1.36 ± 0.29	p<0.05
% sites with PD ≥ 4 mm	11.9 ± 2.4	8.2 ± 3.5	p<0.05
CAL (mm)	2.62 ± 0.49	1.92 ± 0.23	p<0.05
% sites with CAL ≥ 4 mm	2.51 ± 0.53	1.4 ± 0.42	p<0.05

3rd study - Efficacy of baricitinib on periodontal inflammation in patients with rheumatoid arthritis

We enrolled 21 RA patients under baricitinib; demographics, rheumatologic and periodontal parameters as well as concomitant RA medication are summarized below (**Table 6 and 7**).

Table 6 Demographic and rheumatologic characteristics of RA patients before and after baricitinib therapy

Characteristics	Baseline	24 months	P-values*
Gender (female/male)	18/3		
Age (years)	60.00 [53.25–64.5]		
RA duration (months)	117.16 [49.25–159.00]		
Concomitant medication			
Corticosteroids (n)	6		
Methotrexate (n)	13		
Leflunomide (n)	4		
Antimalarials (n)	2		
Without DMARDs (n)	2		
Previous biologics			
Bio-naïve RA/bio-experienced RA (n)	3/18		
Serology			
RF positive (n)	17		
RF titer (IU/mL)	265.9 [128.5–321.2]	202.3 [127.1–272.5]	0.27
ACPA positive (n)	321.17 [89.3–441.2]	175.67 [58.2–201.3]	0.01*
ACPA titer (IU/mL)			
Inflammation			
CRP (mg/dL)	4.61 [3.60–7.99]	2.57 [1.49–3.2]	0.02*
ESR (mm/hour)	48.63 [38.50–55.50]	25.00 [23.25–32.75]	0.01*
Disease activity			
DAS28-CRP	5.53 [4.91–6.00]	3.97 [3.74–4.37]	0.02*
SDAI	21.00 [18.18–27.38]	11.5 [10.00–13.75]	0.01*

RA: rheumatoid arthritis; DMARDs: Disease-Modifying AntiRheumatic Drugs; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibody; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28-CRP: Disease Activity Score including 28 joints using C-reactive protein; SDAI: Simplified Disease Activity Index; (n): number of patients; all data are presented as median and IQR values [25%–75%]; the bold values show the statistical significance.

Table 7 Periodontal status in RA patients before and after oral baricitinib

Parameter	Baseline	24 months	P-values
Teeth count (n)	22.00 [20.25–23.75]	22.00 [20.25–22.75]	NS
% sites with plaque	31.00 [29.25–33.75]	30.00 [28.25–31.75]	NS
GI	0.98 [0.95–1.10]	0.82 [0.80–0.86]	P<0.05
% sites with BOP	11.15 [10.12–12.10]	7.00 [6.50–8.1]	P<0.05
PD (mm)	2.85 [2.80–2.90]	2.00 [1.90–2.20]	P<0.05
% sites with PD ≥ 4 mm	12.7 (2.4)	8.3 (2.9)	P<0.05
CAL (mm)	3.4 [3.1–3.7]	3.00 [2.9–3.2]	NS
% sites with CAL ≥ 4 mm	12.5 [11.05–13.0]	12.00 [11.05–12.25]	NS

Values are indicated as % or median [1st and 3rd quartiles]. RA: rheumatoid arthritis; GI: gingival index; BOP: bleeding on probing; PD: probing depth; CAL: clinical attachment level; NS: not significant (P>0.05).

Patients enrolled in this study were principally seropositive (rheumatoid factor) longstanding RA subtypes, with moderate-to-severe active disease insufficiently controlled by synthetic drugs and/or failing to respond to at least one biologic.

Interestingly, impaired oral health was encountered in the majority of patients (n = 19), as follows: 15 RA had fewer teeth than normal for age and gender-matches healthy controls, 9 cases

had gingivitis (abnormal GI and increased prevalence of sites with BOP), and 19 patients had different degrees of chronic periodontitis (level 1 + 2). Furthermore, we described advanced loss of attachment in 20% cases and an increased prevalence of sites containing dental plaques in 9 cases.

Subgroup analysis showed higher inflammatory tests (CRP, ESR) and ACPA positivity (but not RF) in those RA patients with severe periodontitis irrespective of the extent of lesions (localized or generalized) vs. patients with RA and without periodontitis ($p < 0.05$). Additionally, we demonstrated a significant direct link between the periodontitis, RA activity and ACPA ($r_1 = 0.78$, $p_1 = 0.001$, $r_2 = 0.76$, $p_2 = 0.002$, respectively); that means that patients with active RA and high ACPA had more severe periodontitis (tooth loss, advanced CAL, severe PD) as compared to those with moderate activity and low serum ACPA.

Effects of baricitinib on rheumatologic and periodontal parameters

We evaluated changes in the periodontal status as well as RA activity after 24 weeks of treatment with baricitinib. As expected, all RA parameters decreased significantly: DAS28-CRP and SDAI strongly improved achieving moderate-to-low status, with a change of more than 1.2 points (EULAR-responders) as compared to baseline, irrespective of the presence and severity of periodontitis. There was a trend to better improve in RA with periodontitis, although not significantly. Similarly, we reported a consistent decline in inflammation markers (both ESR and CRP), as well as a considerable immunologic response, particularly for ACPA levels, but also for RF (Table 6).

In RA patients with chronic periodontitis we demonstrated substantial decrease in periodontal inflammation as suggested by improved GI, BOP, PD and sites with $PD \geq 4$ mm vs. baseline ($P < 0.05$) (Table 7).

Furthermore, we reported slight changes, without statistical significance, in clinical attachment level, while teeth count and bacterial plaque were also not significantly influenced by medication ($P > 0.05$) (Table 7).

Changes (Δ) in periodontal parameters after short-term baricitinib were considered: important change in PD -0.8 [$0.7-0.9$] and Δ % sites with $PD \geq 4$ mm -3.5 [$2.25-5$] together with significant modifications in GI -0.15 [$0.13-0.28$] and sites with BOP -3.8 [$3.2-4.95$]; however, we showed minor changes in periodontal parameters such as Δ CAL 0.3 [$0.4-0.5$] and Δ % sites with $CAL \geq 4$ -0.6 [$0.2-0.97$] as well as gingival plaque and % of sites with gingival plaques ($P > 0.05$).

No significant correlations between variation of periodontal parameters with variation of RA were described ($P > 0.05$).

Since local periodontal treatment was not indicated during the short-term follow-up, we considered that improvement in all parameters investigating the degree of local gingival and periodontal inflammation is related to JAK inhibition.

➤ AS and periodontal status

4th study- Periodontal Disease in Patients with Ankylosing Spondylitis: myth or reality?

Baseline data

Demographics, disease duration, inflammatory tests, disease activity scores and periodontal status at baseline are summarized below (**table 8**).

Periodontal parameters

Overall, we demonstrated impaired oral health in 71 AS (82.55%) patients; 19.76% (17 cases) presented with fewer teeth than normal for age and gender, with an average number of evaluable teeth of 22.8 ± 4.71 .

We observed an increased prevalence of sites with dental plaques (34.92%; 22 AS; 30.12 ± 9.87), abnormal gingival index (0.93 ± 0.27 mm) and bleeding on probing (31.39% meaning

27 AS; 12.75±5.31) in our cohort of consecutive active AS. The mean pocket depth was 3.42±0.78mm, while PPD≥4mm was reported in 17.55% (15 cases) with a mean value of 12.45±2.9 mm. Clinical attachment loss was noted in 31.39% (27 cases), with a mean of 2.91±0.92 mm.

Chronic periodontitis was demonstrated in 73.35 % (63 cases); about 10% of patients presented with severe aggressive periodontitis requiring scaling and were not taken into account in the final analysis.

Patients with chronic PD featured high inflammatory parameters, with a direct relation between the level of systemic inflammation and the presence and severity of periodontal involvement; thus mean CRP levels were higher in AS and periodontitis as compared to AS without PD (20.15±6.27 mg/dL vs. 12.03 ± 4.36 mg/dL, p<0.05). In addition, mean ESR was higher in AS with PD as compared to ESR in those without PD (56.12±17.15 mm/h in patients with periodontitis vs. 36.16±7.29 mm/h in those without periodontal disease; p<0.05)

CRP levels correlated with the presence and severity of periodontitis (r=0.82, p<0.05) in studied patients.

Table 8 Patients characteristics: demographics, AS-related and periodontal disease

Rheumatologic and periodontal parameters	
AS parameters	
Age (years; mean ± SD)	37.74±18.33
Disease duration (months; mean ± SD)	34.18±17.96
BASDAI (mean ± SD)	6.75±1.29
ASDAS-CRP (mean ± SD)	3.21±1.12
Periodontal status	
Number of missing teeth (mean ± SD)	7.8±3.1
Periodontal disease prevalence (% , n)	73.35 % (63)
Periodontitis severity	
• Mild (% , n)	19.04 % (12)
• Moderate (% , n)	71.42% (45)
• Severe (% , n)	9.52% (6)
Sites with plaque (% , n) (mean±SD)	34.92% (22); 30.12±9.87
Gingival index (mean ± SD)	0.93±0.27
Sites with bleeding on probing (% , n) (mean±SD)	31.39% (27) (12.75±5.31) 3.42±0.78
Probing pocket depth (mm; mean ± SD)	
Sites with probing pocket depth≥4 mm (% ,n) (mean±SD)	17.55% (15) (7.42±2.35) 2.91±0.92
Clinical attachment loss (mm; mean ± SD)	
Sites with clinical attachment loss≥4 mm (% , mean ± SD)	31.39% (27) (5.87±0.23)
Inflammatory parameters	
ESR (mm/h) (mean ± SD)	52.75±12.13
CRP (mg/dL) (mean ± SD)	18.25±5.12

AS and inflammatory parameters

The majority of patients were man (83.72 % , 72 cases), in the in third decade (mean age of 31.74±18.33 years) with a mean disease duration of 34.18±17.96 months.

All had active AS, failing to respond to NSAIDs, as we enrolled all patients starting their first biological agent according to the national recommendations; mean BASDAI was 6.75±1.29

(cut-off levels of active AS described before), while mean ASDAS-CRP was 3.21 ± 1.12 (cut off value for active disease described before).

All patients had high levels of inflammation; mean ESR of 52.75 ± 12.13 mm/h, more than twice the upper normal limit, while mean CRP was 18.25 ± 5.12 mg/dL, up to three times the upper normal limit.

End of study data

Modifications in the periodontal status, AS activity and inflammatory parameters were examined after 24 weeks, following the benefits of TNF inhibitors.

Periodontal status

We demonstrated statistically significant improvement in periodontal status after 24 weeks of treatment with TNF inhibitors ($p < 0.05$); no difference among different agents (monoclonal anti-TNF antibodies or soluble anti-TNF receptor) was reported (**table 9**).

A detailed analysis of all probing parameters found sizeable changes for probing pocket depth and clinical attachment loss ($p < 0.05$), with only discrete modification for gingival involvement (gingival index or plaque index) ($p > 0.05$) related to TNF blockade.

Thus, mean CAL at 24 weeks was smaller as compared to baseline (1.56 ± 0.29 mm vs. 2.91 ± 0.92 mm, $p < 0.05$), while mean PPD featured the same trend (1.83 ± 0.47 mm vs. 3.42 ± 0.78 mm, $p < 0.05$). Furthermore, we observed also a decrease in sites with CAL more than 4 mm (4.26 ± 0.25 vs. 5.87 ± 0.23 ; 20.93% vs 31.39%, $p < 0.05$) and patients with a PPD more than 4 mm (4.45 ± 0.37 vs. 7.42 ± 2.35 ; 10.46% vs. 17.55%; $p < 0.05$).

Local periodontal treatment was not permitted during the study.

Disease activity and inflammatory tests

After 24 weeks of continuous biological therapy, TNF inhibitors resulted in significant improve in disease activity scores in all cases ($p < 0.05$); mean BASDAI decreased to 2.89 ± 0.57 , while mean ASDAS-CRP achieved was 1.75 ± 0.89 .

Furthermore, ESR and serum concentration of CRP registered the same sizeable response under anti-TNF therapy in all AS ($p < 0.05$); mean ESR was 17.15 ± 9.33 mm/h at the end of study, while mean CRP was 7.13 ± 2.64 mg/dL (Table 2). Thus we obtained a rapid and consistent change across at 24 weeks of therapy (delta BASDAI of more than -3.89 points, delta ASDAS-CRP of -1.46 points). The same trend was reported irrespective of TNF inhibitor administered, monoclonal anti-TNF antibodies (infliximab, adalimumab or golimumab) or anti-TNF receptor (etanercept).

Table 9 AS and PD at baseline and after 24 weeks of anti-TNFs

Characteristics	Week 0	Week 24	P
AS-related parameters			
BASDAI	6.75 ± 1.29	2.89 ± 0.57	< 0.05
ASDAS-CRP	3.21 ± 1.12	1.75 ± 0.89	< 0.05
Periodontal parameters			
Sites with plaque (% , n) (mean \pm SD)	34.92% (22); 30.12 ± 9.87	23.25% (20); 27.17 ± 8.15	> 0.05
Gingival index (mean \pm SD)	0.93 ± 0.27	0.85 ± 0.23	> 0.05
Sites with bleeding on probing (% , n) (mean \pm SD)	31.39% (27); 12.75 ± 5.31	23.39% (20); 8.47 ± 3.26	< 0.05
Probing pocket depth (mm; mean \pm SD)	3.42 ± 0.78	1.83 ± 0.47	< 0.05
Sites with probing pocket depth ≥ 4 mm (% , n) (mean \pm SD)	17.55% (15); 7.42 ± 2.35	10.46% (9); 4.45 ± 0.37	< 0.05
Clinical attachment loss (mm; mean \pm SD)	2.91 ± 0.92	1.56 ± 0.29	< 0.05
Sites with clinical attachment loss ≥ 4 mm (% , mean \pm SD)	31.39% (27); 5.87 ± 0.23	20.93% (18); 4.26 ± 0.25	< 0.05
Inflammatory tests			

ESR	52.75±12.13	17.15±9.33	<0.05
CRP	18.25±5.12	7.13±2.64	<0.05

➤ PsA and periodontal status

5th study TNF Inhibitors and Periodontal Inflammation in Psoriatic Arthritis

Baseline (V1) characteristics

PsA-related parameters

Demographics, disease duration, inflammatory tests, concomitant medication (non-steroidal anti-inflammatory and immunosuppressive drugs), disease activity and disability scores as well as periodontal status at baseline are provided in **Table 10**.

As expected, moderate to severe active PsA (DAS28-ESR: 5.25±0.87; DAPSA: 22.57±8.12), with high levels of inflammation (ESR: 47.65±19.36 mm/h, meaning around twice the upper normal limit; CRP: 12.43 ± 6.37 mg/dL, respectively up to 3.75 times the upper normal limit) qualified for to receive TNF inhibitors. Concomitant NSAIDs and synthetic disease modifying anti-rheumatic drugs (e.g. methotrexate, leflunomide, sulfasalazine) were administered in the majority of cases (87.80% and 100%, respectively) at the time of investigation, either alone or in combination.

Periodontal parameters

48.78% (20) PsA patients presented with fewer teeth than normal for age and gender-matches healthy individuals, and the average number of evaluable teeth of 21.8±4.3.

An increased prevalence of dental plaques (32.85±11.7), abnormal gingival index (0.93±0.27) and bleeding on probing (14.2±7.1) were described at baseline in PsA. The mean pocket depth was 3.42±0.78 mm, with a value ≥4mm identified in 12.45±2.9 % of cases. Besides, a significant number of cases had advanced clinical attachment loss, with an average of 2.91±0.72 mm. All data are shown in **Table 10**.

Up to one third of patients enrolled in our study (29.26%, 12 cases) presented with chronic periodontitis. Further, PsA with aggressive periodontitis (localized or generalized) displayed higher levels of inflammatory parameters as compared with PsA without periodontitis: mean CRP 6.31±2.13 mg/dL, mean ESR of 59.23±12.37 mm/h in patients with periodontitis vs. mean CRP 3.74±0.63 mg/dL and mean ESR of 37.12±10.35 mm/h in patients without periodontitis (p<0.05).

CRP levels correlated with the presence and severity of periodontitis (p<0.05) in studied patients.

Table 10 PsA patients – rheumatologic and periodontal characteristics

<i>Rheumatologic and periodontal characteristics</i>	
<i>RA-related parameters</i>	
<i>Age (years; mean ± SD)</i>	53.36±18.27
<i>PsA duration (months; mean ± SD)</i>	36.45±24.57
<i>ESR (mm/h; mean ± SD)</i>	47.65±19.36
<i>Serum CRP levels (mg/dL; mean ± SD)</i>	12.43±6.37
<i>DAS28-ESR (mean ± SD)</i>	5.25±0.87
<i>DAPSA (mean±SD)</i>	22.57±8.12
<i>NSAIDs (%) (n)</i>	87.80 (36)
<i>DMARDs (%) (n)</i>	100 (41)
<i>Periodontal status</i>	

<i>Number of present teeth (mean ± SD)</i>	21.8±4.3
<i>% of sites with plaque (mean ± SD)</i>	32.85±11.7
<i>Gingival index (mean ± SD)</i>	0.93±0.27
<i>% of sites with bleeding on probing (mean ± SD)</i>	14.2±7.1
<i>PPD (mm; mean ± SD)</i>	3.42±0.78
<i>% of sites with PPD ≥4 mm (mean ± SD)</i>	12.45±2.9
<i>CAL (mm; mean ± SD)</i>	2.91±0.92
<i>% of sites with CAL ≥4 mm (mean ± SD)</i>	1.87±0.23

Changes in rheumatologic and periodontal status after TNF inhibitors (V2)

Disease activity and biochemical biomarkers

At 24 weeks of biological therapy, we demonstrated significant improvement in disease activity and inflammatory parameters regardless of the TNF inhibitor administered (monoclonal anti-TNF antibody or soluble TNF receptor). Patients in our study were treated with adalimumab, etanercept or golimumab. A rapid and consistent decrease in DAS28-ESR with low to moderate final DAS28-ESR was reported in all cases (5.25±0.87 vs. 3.1±0.56, p<0.05). The same trend was registered for DAPSA: 22.57±8.12 vs. 14.68±2.83 (p<0.05).

Both ESR and CRP levels dramatically improved under TNF inhibitors - ESR: 47.65±19.36 mm/h vs. 25.51±12.72 mm/h, p<0.05; CRP: 12.43±6.37 mg/dL vs. 5.27±1.09 mg/dL, p<0.05) (Table 2).

Periodontal status

Significant improvement in periodontal status was reported under TNF inhibitors at the end of the follow-up period (p<0.05) (**Table 11**).

We demonstrated substantial differences in PPD and CAL as compared to baseline (p<0.05); despite any specific periodontal therapy, mean PPD as well as patients with PPD≥4mm declined with biologics (3.42±0.78 vs. 1.96±0.41; 12.45±2.9 vs. 7.9±2.7%, respectively; p<0.05).

Additionally, significant difference in CAL as compared to baseline was observed at 24 weeks: 2.91±0.72 mm vs. 1.87±0.35, p<0.05); significant lower number of sites with CAL≥4mm were shown (1.87±0.23 vs. 0.95±0.26%).

However, we have not demonstrated important modifications in plaque and gingival index with TNF inhibitors (p>0.05).

Table 11 PsA and PD before and at 24-weeks of anti-TNFs

RA-related parameters			
DAS28-ESR	5.25±0.87	3.1±0.56	p<0.05
DAPSA	22.57±8.12	14.68±2.83	p<0.05
Serum CRP levels (mg/dL)	12.43±6.37	5.27±1.09	p<0.05
ESR (mm/h)	47.65±19.36	25.51±12.72	p<0.05
Periodontal status			
% of sites with plaque	32.85±11.7	31.9 ± 12.4	p>0.05
Gingival index	0.93±0.27	0.82±0.17	p>0.05
% of sites with bleeding on probing	14.2±7.1	4.7±2.1	p<0.05
PPD (mm)	3.42±0.78	1.96±0.41	p<0.05

% of sites with PPD \geq 4 mm	12.45 \pm 2.9	7.9 \pm 2.7	p<0.05
CAL (mm)	2.91 \pm 0.92	1.87 \pm 0.35	p<0.05
% sites with CAL \geq 4 mm	1.87 \pm 0.23	0.95 \pm 0.26	p<0.05

➤ SSc and periodontal status

6th study - Periodontal Disease and Lipid Profile in Systemic Sclerosis: an EUSTAR Cohort Experience

SSc-related parameters

We enrolled 31 SSc, predominantly women (83.87%), with a mean age of 42.9 years (ranging between 23 and 58), and a mean disease duration of 6.3 years (from 1.2 to a maximum of 10.7 years); the majority of patients enrolled had a diffuse SSc subtype (67.74%) and only one third were diagnosed with a limited disease. To note, all men in our study developed extensive severe diffuse SSc.

Musculoskeletal involvement with potential impact on oral hygiene in SSc revealed non-erosive arthritis in 67.74% cases, with major functional impact on hand dexterity in up to one third of patients (32.25%) and significant impaired quality of life as demonstrated by an average HAQ (Health Assessment Questionnaire) of 2.1 (1.5-3). Only 12.90% of SSc had myositis, with decreased muscle endurance and influence on the ability to perform routine daily activities. Patients with hand deformity and contractures were typically classified in the diffuse SSc subset.

Limited oral aperture (microstomia) with decreased inter-incisal distance was demonstrated in 58% cases.

An average high ESR as well as CRP level were registered, while immunological abnormalities account for about one out of five anti-centromere antibody positivity and more than half SSc with anti-topoisomerase-1 specificity.

General data about SSc-related characteristics are summarized in **Table 12**.

Table 12 Demographics and SSc-related variables in our patients

General SSc data	
Demographics	
Age (years)	42.9 (23-58)
Gender (%); F: M ratio	83.87% F; 26 F : 5 M
Disease-related	
Disease duration (years)	6.3 (1.2-10.7)
<i>Disease subset</i>	
• Diffuse cutaneous SSc (%)	67.74
• Limited cutaneous SSc (%)	32.25
Disease activity (MEDSGER)	1.25 (0-2)
Disease severity	4.5 (3-6)
Skin score (modified RODNAN, mRSS)	17 (10-37) 70.96
Pulmonary fibrosis (computer tomography) (%)	22.58
Pulmonary hypertension (%)	100
Raynaud phenomenon (%)	64.51
Digital ulcers ever (%)	12.90
Myositis (%)	67.74
Non-erosive arthritis (%)	6.45
Renal involvement (%)	9.67
Calcinosis (%)	

Periodontal disease in SSc

35.48% of all participants were regular attendees of dental practice.

Overall, up to 70.96 % of SSc developed oral manifestations and had reduced oral health-related quality of life. We demonstrated a low resting salivary flow rate and PH (25.80% cases), a reduced maximal mouth opening (54.83% cases) and a small inter-incisal distance (32.5 mm). 64.51% of SSc experienced one or more caries and more than half of patients (51.61%) presented with periodontal disease.

Key clinical manifestation of periodontal disease featured in SSc included gingival inflammation in 81.25% cases, 50% patients displaying sites with detectable plaque, 53.75% with bleeding on probing, 31.25% with periodontal pockets (classic pocket depth >3 mm), while clinical attachment level ≥ 5.5 mm in 18.75% SSc of patients with periodontitis. Severe aggressive periodontitis was described in one third of SSc patients with periodontal disease. Subgroup analysis based on skin extent and periodontal status showed that patients with diffuse SSc presented more frequently with periodontitis than those with limited disease ($p < 0.05$); besides, they developed more aggressive periodontal disease ($p < 0.05$).

As mentioned, we were interested in evaluating also the lipid metabolism parameters. An abnormal lipid pattern meaning low serum HDL- and high LDL-cholesterol, increased serum triglycerides, significant modification in total cholesterol level was noticed in our patients. These abnormalities significantly correlated with diffuse SSc and skin involvement, disease duration, anti-SCL70 positivity, disease activity (EUSTAR) and severity (MEDSGER) scores, as well as the presence of PD ($p < 0.05$) (**Table 13 a, b**).

Table 13 a, b. Oral manifestations and correlation with lipid profile in studied SSc

Oral manifestations	
Overall dental pathology (%)	70.96
Decreased saliva production (%)	25.80
Microstomia (%)	54.83
Inter-incisal distance (mm)	32.5
Caries (one or more) (%)	64.51
Periodontal disease (%)	51.61
• Gingival inflammation (%)	81.25
• Sites with dental plaques (%)	50
• POB (%)	43.75
• PD (%)	31.25
• CAL (%)	18.75

Lab parameters	
Antibodies positivity	
Anti-centromere, ACA (%)	22.58
Anti-topoisomerase 1 positivity, anti-SCL70 (%)	58.06
Total anti-nuclear antibodies, ANA (%)	87.09
Inflammatory syndrome	
CRP (mg/dL)	6.2 (1-14)
ESR (mm/hour)	29 (15-64)
Cholesterol (mg/dL)	173.91 (118-278)
HDL-cholesterol (mg/dL)	43.18 (34-71)
LDL-cholesterol (mg/dL)	132 (120-192)
Triglycerides (mg/dL)	151.4 (117-231)

7th study - Volumetric Cone Beam Computed Tomography for the Assessment of Oral Manifestations in Systemic Sclerosis: Data from an EUSTAR Cohort

SSc-Related Characteristics

We analysed 43 patients with systemic sclerosis enrolled in the CBCT study; the main demographic and SSC-related parameters were: mainly women (72%, $n = 31$), with a mean (SD) age of 43.95 (11.36) years and a mean (SD) disease duration of 8.7 (4.5) years; 67.74% ($n = 29$) had diffuse disease, and 53.48 % ($n = 23$) were anti-topoisomerase 1 positive SSc; and the mean (SD) disease severity was 4.8 (2.1) (**Table 14**).

Table 14 Systemic sclerosis (SSc)- related parameters, clinical, oral and radiographic features

Parameter	No (%) or mean \pm SD
Demographics	31 (72)
Female	43.95 (11.36)
Age	10 (23.25)
Smoking status	
SSc-related measures	29 (67.74)
Diffuse cutaneous SSc	8.7 (4.5)
Disease duration	18 (10.1)
Modified RODNAN (0-51)	1.5 (0.7)
Facial skin score (0-3)	
Serology	23 (53.48)
Anti-SCL70	10 (23.25)
Anti-centromere B	
Dental issues	9.3 (4.5)
Missing teeth per subject	7.2 (3.4)
Teeth with periodontal disease	

Oral Health

We demonstrated a reduced maximal mouth opening in 69.76% patients ($n = 30$) and a mean (SD) inter-incisal distance of 32.5 (7.2) mm, smaller than normal ($p < 0.05$).

The mean (SD) number of evaluable teeth was 23.5 (4.2) in SSc and 29.6 (2.1) in controls, respectively, with a trend to have more missing teeth in patients with SSc; moreover, these individuals were significantly more likely to be edentulous than matching controls (Table 18).

At $n = 27$, 62.8% of SSc experienced one or more caries, and more than half of patients (53.48%, $n = 23$) presented with periodontal disease.

Significantly higher plaque accumulation was found in SSc, up to 50% of patients displaying sites with detectable plaque: 0.75 (0.39–1.51) vs. 0.39 (0.24–0.61) in controls ($p < 0.05$). Furthermore, gingival inflammation was found in 67.44% ($n = 29$) cases, while 55.81% of scleroderma patients ($n = 24$) presented with bleeding on probing.

For $n = 14$, 32.55% SSc had periodontal pockets and 27.9% ($n = 12$) had a CAL \geq 5.5 mm; mean (SD) PD was significantly different in scleroderma compared with controls: 5.21 (0.25) mm vs. 3.15 (0.37) mm, $p < 0.05$. Severity of periodontitis was also meaningfully different in SSc vs. controls ($p < 0.05$), with severe disease described in up to one third of scleroderma and related periodontal disease (**Table 15**).

Table 15 Associations between scleroderma- related parameters and oral radiographic abnormalities (univariate analysis)

Parameter	PDL widening		Erosions	
	RR	p	RR	P
Demographics	1.1	$p > 0.05$	1.2	$p > 0.05$
Female	1.43	$p > 0.05$	1.1	$p > 0.05$
Age	1.06	$p > 0.05$	1.06	$p > 0.05$
Smoking status				

SSc-related measures	1.25	p>0.05	1.02	p>0.05
Diffuse cutaneous SSc	2.36	p<0.05	0.98	p>0.05
Disease duration	3.12	p<0.05	1.3	p>0.05
Modified RODNAN (0-51)	2.71	p<0.05	1.02	p>0.05
Facial skin score (0-3)	1.21	p>0.05	1.17	p>0.05
SSc activity	3.09	p<0.05	0.92	p>0.05
SSc severity	1.21	p>0.05	3.51	p<0.05
Interdental distance				
Dental issues	1.02	p>0.05	0.87	p>0.05
Missing teeth per subject	1.15	p>0.05	1.12	p>0.05
Teeth with periodontal disease				

Imaging Studies

Panoramic radiographs were performed in all cases to allow a basic assessment of the mandibular erosions and to select teeth suitable for further CBCT evaluation. Both panoramic radiographs and CBCT sections showed the widening of the PDL space, several remaining roots, and dental caries; in addition, mandibular erosions, even condylar lysis, were described, particularly using CBCT exams.

PDL Space Widening

Panoramically reconstructed CBCT demonstrated widening of the PDL in at least one tooth in 46.51% SSc ($n = 20$) vs. 13.95% ($n = 6$) controls ($p < 0.05$). Mean (SD) periapical PDL width was 0.35 (0.16) mm, about twice the normal thickness, and 0.17 (0.04) mm in controls ($p < 0.05$)

Although both anterior and posterior teeth were involved, a wider PDL was commonly found in the posterior region ($p < 0.05$). Nevertheless, the molars and premolars presented with the most significant differences between scleroderma and controls ($p < 0.05$).

Multivariate analysis adjusting for age, gender, and current smoking status confirmed the important difference between the two groups (OR 7.26; 95% CI 3.87–13.65). Moreover, there were significantly more teeth with widened PDL in scleroderma patients than in controls as suggested by univariate and multivariate statistics: 1.21 (2.31) vs. 0.28 (0.25) ($p < 0.05$), with relative risk (RR) 8.51; 95% CI 5.37–12.61), respectively. No calcification within the PDL space was demonstrated.

Figure 1 (a,b,c,d) presents examples of PDL space measurements.

Figure 1 Measurements of periodontal ligament space on cone beam computed tomography (CBCT): (a) clinical attachment level (CAL) and apical PDL space measurements; (b) 8-point cervical third measurements; (c) 4-point middle third measurements; and (d) 4-point apical third measurements.

Associations with PDL Space Widening and Erosions

Subgroup analysis in scleroderma subjects with and without PDL widening and with and without erosions based on univariate analysis including clinical parameters and oral radiographic abnormalities were, further, done.

Significant correlations between number of teeth with PDL widening and MEDSGER disease severity score ($r = 0.702, p = 0.028$), RODNAN skin score ($r = 0.821, p = 0.01$), disease subset (diffuse vs. limited, $r = 0.782, p = 0.041$ vs. $r = 0.451, p = 0.05$, respectively), anti-topoisomerase I antibodies ($r = 0.568, p = 0.012$), age ($r = 0.872, p = 0.01$), and disease duration ($r = 0.811, p = 0.01$) were demonstrated.

Moreover, the relative risk of PDL space widening in relation with different determinants of scleroderma severity are listed in **Table 16**.

Table 16 Associations between the number of teeth with PDL space widening and SSc severity

Parameter	RR	95% CI	P
Gender	2.17	0.91-14.28	p>0.05
Age	1.00	0.89-1.73	p<0.05
Smoking status	5.31	4.27-9.12	p>0.05
SSc duration	3.26	1.20-7.53	p<0.05
SSc subtype	4.51	2.39-8.14	p<0.05
RODNAN	0.93	0.89-3.76	p<0.05
SSc severity	1.25	1.58-3.89	p<0.05
SSc activity	2.36	1.02-3.41	p>0.05
Anti-topoisomerase 1	5.22	2.3-7.67	p<0.05

For multivariate analysis adjusting for age, disease duration, gender, and smoking status, there were a significant association between the number of teeth with widened PLD and MEDSGER disease severity ($p < 0.05$) (**Table 17**).

Table 17. Correlations between of teeth with PDL space widening and number of number of teeh with periodontal disease

Parameter	RR	95% CI	P
Gender	2.17	0.91-14.28	p>0.05
Age	1.00	0.89-1.73	p>0.05
Smoking status	5.31	4.27-9.12	p>0.05
SSc duration	3.26	1.20-7.53	p<0.05
SSc subtype	4.51	2.39-8.14	p<0.05
RODNAN	0.93	0.89-3.76	p<0.05
SSc severity	1.25	1.58-3.89	p<0.05
SSc activity	2.32	1.45-3.22	p>0.05
Anti-topoisomerase 1	5.19	2.24-7.32	p<0.05
Number of teeth with periodontal disease	1.19	0.87-1.45	p>0.05

DISCUSSION

➤ *RA and periodontal status*

1st study - Exploring the Role of Interleukin-6 Receptor Inhibitor Tocilizumab in Patients with Active Rheumatoid Arthritis and Periodontal Disease

We aimed to assess the influence of the IL-6 receptor inhibitor on periodontal status in active RA associated with periodontitis, assuming that TCZ might be able not only to improve clinical and biochemical RA-related parameters but also to ameliorate chronic periodontitis as a result of decreased IL-6 in the periodontal microenvironment via declining systemic inflammation.

Although our target is to demonstrate the ability of TCZ to modulate periodontal inflammation and subsequent damage, firstly, we emphasized its role in controlling RA activity. We reasonably confirmed a consistent response to TCZ in real-life settings, which was achieved in as rapid as three months and continued after six months of therapy, irrespective of background medication and clinical scenario (mono- or combined therapy, bio-naïve or bio-experienced patients); it is more than clear that even in the short-term, IL-6 blockade displays significant clinical, biological, as well as serologic disease improvement. Although we found no consistent difference in clinical response in seropositive vs. seronegative RA, we noticed a significant impact on ACPA serum concentration after six months, which is an improvement that parallels the decrease in periodontal inflammation, suggesting a role of IL-6 in both systemic and local inflammation (synovial and periodontal) and the potential implications via citrullination. Therefore, our results stand by as a proof of the effectiveness of subcutaneous TCZ in managing inflammatory and immune pathways in RA (Yang et al., 2018).

We also focused on the magnitude of compromised oral health in RA; most patients in our initial group presented a high rate of mild and severe periodontal disease, validating/ reinforcing the already known risk of periodontitis in such patients, particularly in established, longstanding disease (Genco et al., 2020; Eezammuddeen et al., 2020; Sherina, 2019; Bartold et al., 2020). We have included in the final analysis only those cases with overt periodontal disease, meaning that up to 75% had at baseline altered periodontal status in a group of consecutive patients starting TCZ for their active disease. Indeed, recent reviews and meta-analyses have already discussed periodontal disease in various RA settings (independent of age, disease duration, serology profile, and disease activity) compared to general population (de Molon et al., 2019; Eezammuddeen et al., 2020; Rinaudo-Gaujous et al., 2019; Mankia et al., 2019; Äyravainen et al., 2017; Lee et al., 2020; Qiao et al., 2020; Choi et al., 2016).

We identified excessive gingival involvement confirmed by an increased percentage of sites with plaques and inflammation and abnormal periodontal status (e.g., increased probing depth, clinical attachment loss) supporting data from the literature (Kobayasy et al., 2015; Kobayasy et al., 2014; Qiao et al., 2020; Lee et al., 2020; Kobayasy et al., 2014; Jung et al., 2018; Romero-Sanchez et al., 2017; Mayer et al., 2020; Tachibana et al., 2020). Moreover, we recognized positive correlations between the severity of periodontitis, inflammatory parameters (especially CRP), serology (ACPA status and titers), and RA activity; indeed, recent studies suggest a worse periodontal status in active untreated RA, and higher CRP if RA is associated with severe periodontitis (Koziel et al., 2014; Mankia et al., 2019; Gonzales et al., 2015; Kobayasy et al., 2015; Kobayasy et al., 2014; Äyravainen et al., 2019; Lee et al., 2015). Finally, it seems that ACPA-positive patients had severely impaired periodontal health, while disease activity correlated with periodontitis degree as well (Koziel et al., 2014; Kobayasy et al., 2015; Kobayasy et al., 2014; Äyravainen et al., 2019; Lee et al., 2015).

Finally, we demonstrated that short-term tocilizumab significantly reduced gingival as well as periodontal inflammation as supported by decreased levels of gingival index, bleeding on probing, and probing pocket depth, paralleling the articular improvement. Indeed, only minor

changes in clinical attachment loss were detected in our enrolled patients, and the supragingival plaque remained stable after 3 and 6 months of biological treatment ($p > 0.05$).

A closer look at recent data definitely emphasizes the dual effects of early and aggressive RA treatment with biologic and non-biologic drugs (Janus kinase inhibitors, JAK inhibitors) on articular as well as comorbid periodontal disease (Rinaudo-Gaujous et al 2019; Kobayasy et al., 2015; Kobayasy et al., 2014; Lee et al., 2015; Jung et al., 2018; Romero-Sanchez et al., 2017). It is widely accepted that TNF and IL-6 receptor inhibitors are able to ameliorate oral health in active RA, as reflected by clinical, biological, and even serological RA biomarkers (Rinaudo-Gaujous et al., 2019; Kobayasy et al., 2015; Jung et al., 2018; Romero-Sanchez et al., 2017; Mayer et al., 2009; Savioli et al., 2012). Although there are controversial effectiveness signals with TNF inhibitors in improving chronic periodontitis (Eezammuddeen et al., 2020; Koziel et al., 2014; Mankia et al., 2019; Jing et al., 2018; Romero-Sanchez et al., 2017), all papers about anti-IL-6 therapy clearly demonstrated articular, systemic, and also periodontal benefits with TCZ without any periodontal specific treatment (Kobayasy et al., 2015; Kobayasy et al., 2014).

An interesting trial compared periodontal condition in patients with RA and periodontitis before and after biological therapy in two cohorts: one under tocilizumab and the other receiving medication with TNF inhibitors. After 6 months, both tocilizumab and TNF inhibitors demonstrated a consistent improvement of oral health with significantly reduced periodontal inflammation (gingival index, bleeding on probing, and probing depth) compared to baseline, with similar results in both cohorts unless there was a greater decrease in gingival index and less gingival inflammation with tocilizumab; however, plaque levels remained the same irrespective of medication, while periodontal clinical attachment loss decreased only after TCZ but not after TNF inhibitors (Kobayasy et al., 2015; Kobayasy et al., 2014). These observations were partially supported by the results of another study about an excessive inflammatory response against oral pathogens essentially based on high levels of IL-6 (Kobayasy et al., 2015; Kobayasy et al., 2014; Nibali et al., 2011).

Recent meta-analyses reviewed the most important studies on TNF and non-TNF biologics in patients with RA and PD (Rinaudo-Gaujous et al., 2019; Qiao et al., 2020). The critical difference between the class of TNF inhibitors and TCZ or B-cell depletive agent rituximab is that infliximab, an anti-TNF monoclonal antibody, may negatively address gingival inflammation although it may also improve alveolar bone destruction (Rinaudo-Gaujous et al., 2019; Koziel et al., 2014; Rinaudo-Gaujous et al., 2019; Äyräväinen et al., 2017) resulting in a dissociated response for patients with severe periodontitis (Rinaudo-Gaujous et al., 2019), while both tocilizumab and rituximab associate with significant a down regulation of gingival inflammation and damage in RA associated with periodontitis (Kobayasy et al., 2015; Kobayasy et al., 2014; Nibali et al., 2011; Coat et al., 2015).

Additional research is necessary to clearly differentiate between the direct effects of TCZ on local periodontal inflammation and IL-6 or its receptor levels in the gingival crevicular fluids and periodontium of patients and the indirect effect via dramatically decreasing systemic inflammation, which may impact also oral health (Kobayasy et al., 2015; Kobayasy et al., 2014). Indeed, numerous studies indicated a rapid and significant decline in typical inflammatory parameters (ESR and CRP), but also in serological RA biomarkers (RF, ACPA) as well as inflammatory cytokines (TNF, IL-6) and mediators (serum-amyloid A, matrixmetalloproteinases 1, 3), supporting the indirect role of TCZ in periodontitis (Kobayasy et al., 2015; Kobayasy et al., 2014).

2nd study - *Anti-Tumor Necrosis Factor Alpha Therapy and Periodontal Inflammation in Rheumatoid Arthritis: A clinical and biochemical approach*

Our study has clearly demonstrated rapid and sustained efficacy of anti-TNFs in active RA sub-optimally controlled by synthetic DMARDs; short-term TNF inhibition resulted in significant

decrease of disease activity (as supported by DAS28-ESR) and improved inflammatory (ESR, CRP) and serologic (ACPA) parameters as well.

It is widely recognized that TNF antagonists reasonably control inflammatory pathways in moderate-to-severe active RA, and our results generally support the evidences in integrative literature reviews (Bryrkoglu et al, 2013; Monssarat et al, 2013; Ortis et al, 2009; Savioli et al, 2010).

Furthermore, we identified significant association between TNF antagonists (only infliximab, adalimumab, etanercept were evaluated at the time of this study) and the periodontal status (plaque index, gingival index, pocket depth, clinical attachment loss) in short-term (24 weeks) follow-up. Actually, in the current study, we observed that RA patients tend to have more gingival plaques, possible related to different degrees of hand disability, as well as high prevalence of gingival inflammation, as shown by GI; however, TNF inhibition had no significant effect neither on PI nor on GI ($p>0.05$), although modestly ameliorated such periodontal parameters. The decrease in GI and BOP may be related to decrease in gingival inflammation with TNF agents.

The other parameters defining the periodontal status including pocket depth and clinical attachment loss improved significantly from baseline, supporting the role of anti-TNF therapy in suppressing periodontal inflammation and delaying local alveolar damage. Thus, the difference in PD and CAL during follow-up was thought to be related to decrease in local (periodontal microenvironment) of pro-inflammatory mediators / cytokines levels induced by TNF blockade.

A closer look to the RA-periodontal disease relation and the benefits of TNF antagonists in both conditions revealed conflicting data (Ortis et al., 2009; Savioli et al., 2010; Kadkhoda et al., 2016). Treatment with a TNF inhibitor was shown in a several previous research papers to control both RA and periodontitis Ortis et al., 2009; Savioli et al., 2010; Kadkhoda et al., 2016). On the other hand, different authors noticed only modest influence of TNF inhibition in periodontal disease in the absence of surgical procedures or other periodontal specific therapeutic protocols (Ortis et al., 2009; Savioli et al., 2010; Kobayasi et al., 2014; Kadkhoda et al., 2016; Monsarrat et al., 2013).

Interestingly, a recent report advanced the hypothesis that tocilizumab, a recombinant humanized antihuman interleukin-6 receptor monoclonal antibody, may ameliorate periodontal inflammation in RA with periodontitis (Kobayasi et al., 2014). In fact, the study has demonstrated that patients in both TNF inhibitor and tocilizumab groups present with a significant improve in rheumatologic parameters and decrease in periodontal inflammation as assessed by probing depth and clinical attachment loss, while gingival index as well as bleeding on probing were modestly influenced (Kobayasi et al., 2014). Moreover, none of these two drugs was associated with significant changes in plaque index (Kobayasi et al., 2014).

As in our study, IL-6 and TNF blockade may not only decrease RA activity but also ameliorate systemic inflammation, which subsequent recover of periodontal inflammation (Ancuta et al., 2009; Kobayasi et al., 2014).

Furthermore, TNF inhibition is responsible for consistent decrease in serum inflammatory mediators and antibody profile as well, providing an excellent impact on all RA related characteristics and positively influencing oral health.

3rd study - Efficacy of baricitinib on periodontal inflammation in patients with rheumatoid arthritis

We performed this study aiming to evaluate the influence of tsDMARDs on periodontal health in RA patients; we assumed that baricitinib, a JAK inhibitor blocking the subtypes JAK1 and JAK2, might decrease the levels of pro-inflammatory mediators in the periodontal microenvironment via the decline in systemic inflammation.

Before emphasizing the benefits of baricitinib on periodontal condition, we focused on oral health status in our RA cohort.

Firstly, we confirmed compromised oral health in the majority of cases, particularly a high rate of moderate-to-severe periodontal disease, confirming the already known risk of periodontitis in established RA (Äyräväinen et al., 2017; N.R. Fuggle et al., 2016; I.A. Choi et al., 2016; Kobayashi et al., 2015; Mankia et al., 2019). Although we discussed only about longstanding RA, several other studies have already noticed excessive periodontal disease nevertheless of RA settings (age, disease duration, serology profile, activity) *vs.* general population (Äyräväinen et al., 2017; Fuggle et al., 2016; Mankia et al., 2019; Gonzales et al., 2015). We identified abnormal periodontal parameters (increased PD, CAL) as well as high levels of gingival involvement confirmed by increased percentage of sites with plaques and inflammation, supporting data from literature (Rutter-Loche et al., 2017; Äyräväinen et al., 2017). Moreover, we recognized positive correlations between the severity of periodontitis, inflammatory parameters (especially CRP), serology (ACPA status and titres) and RA activity; indeed, recent studies suggest worst periodontal status in active untreated RA, and higher CRP if RA is associated with severe periodontitis (Rutter-Loche et al., 2017; Äyräväinen et al., 2017; Fuggle et al., 2016; K. Mankia et al., 2019; Gonzales et al., 2015). Finally, it seems that ACPA-positive patients had severely impaired periodontal health, while disease activity correlated with periodontitis degree as well (Rutter-Loche et al., 2017; Äyräväinen et al., 2017; Koziel et al., 2014; Fuggle et al., 2016; Mankia et al., 2019; Gonzales et al., 2015).

Secondly, we registered a rapid and consistent response to baricitinib, regardless of patient's previous medication (bio-naïve or bio-experienced RA); short-term JAK inhibition is able to result in significant improvement in clinical, biologic and, surprisingly, serologic RA activity (especially for ACPA, and here one can comment about the implications via citrullination at the periodontal and synovial microenvironment). Our results reasonably confirm the efficacy of baricitinib in controlling inflammation pathways in active established RA (P. Kawalec et al., 2019).

Thirdly, short-term course of baricitinib significantly reduced gingival and periodontal inflammation as suggested by improvement in GI, BOP, PD, paralleling the articular improvement. However, only minor changes in CAL were noticed, while the bacterial PI remained stable after 24 weeks of baricitinib ($P > 0.05$). That means a positive reaction of gingiva related to baricitinib, despite the fact that bacterial plaque index remained the same; that is really encouraging.

All patients continued background medication, their dental hygiene behaviour remained unchanged, and no periodontal therapy was practiced; accordingly, we concluded that the decrease in GI and BOP might be related to decrease in gingival inflammation induced by baricitinib.

Recent reports offer suitable arguments to reinforce that early aggressive RA management with csDMARDs and/or biologics not only promote sustained remission, but also impact periodontal damage (Rutter-Loche et al., 2017; Äyräväinen et al., 2017; Jung, et al., 2018; Romero-Sanchez et al., 2017; Kawalec et al., 2019). It seems that regular treatment with biologics or non-biologics may retrieve periodontal status in RA with periodontitis (Rutter-Loche et al., 2017; Äyräväinen et al., 2017; Savioli et al., 2014; Mayer et al., 2009; Kadkhoda et al., 2016; Sikorska et al., 2018; Kobayashi et al., 2014; Kobayashi et al., 2015; Coat et al., 2015). Additionally, innovative biologics acting by blocking the TNF and IL-6-mediated signalling are also able to promote reliable decrease in inflammatory cytokines and antibodies with dramatic effect not only on clinical, biological and serological activity of RA, but also on oral health (Jung, et al., 2018; Romero-Sanchez et al., 2017; Savioli et al., 2014; Mayer et al., 2009; Kadkhoda et al., 2016; Sikorska et al., 2018; Kobayashi et al., 2014; Kobayashi et al., 2015).

A closer look for evidences concerning TNF inhibitors in improving chronic periodontitis showed inconsistent results (Rutter-Loche et al., 2017; Äyräväinen et al., 2017; Savioli et al., 2014; Mayer et al., 2009; Kadkhoda et al., 2016; Sikorska et al.,

2018; Kobayashi et al., 2014; Kobayashi et al., 2015; Coat et al., 2015). Several papers clearly demonstrated the efficacy of TNF blockade in controlling both RA and periodontitis (Savioli et al., 2014; Mayer et al., 2009; Kadkhoda et al., 2016; Sikorska et al., 2018; Kobayashi et al., 2014; Kobayashi et al., 2015; Coat et al., 2015), but others recognized only uncertain advantages unless concomitant specific periodontal treatment, even surgical procedures (Savioli et al., 2014). Interestingly, it seems that infliximab, a monoclonal antibody targeting TNF, enhances gingival inflammation, while improving alveolar bone destruction (Rutter-Loche et al., 2017; Äyräväinen et al., 2017; Rinaudo-Gaujous et al., 2019); besides, infliximab dissociates response of severe periodontal destruction biomarkers (e.g. matrix metalloproteinase 3) in RA (Rinaudo-Gaujous et al., 2019). In contrast, both tocilizumab and rituximab promote a significant down regulation of gingival inflammation and gingival damage in RA associated with periodontitis related to decrease in serum inflammatory mediators (Kobayashi et al., 2014; Coat et al., 2015).

The influence of intensive periodontal treatment on RA is similarly controversial. Several publications (Ortis et al., 2009; Yang et al., 2018; Calderaro et al., 2017; Monsarrat et al., 2019) have successfully demonstrated that specific therapies for chronic periodontitis (e.g. non-surgical professional scaling or root planning with or without antibiotics) may ameliorate local inflammation, improve RA activity and response to different anti-rheumatic drugs. However, other reports (Monsarrat et al., 2019) fail to demonstrate successful RA outcomes with periodontal treatment; indeed, ESPERA trial emphasized improved periodontal health with periodontal treatment in RA, but no effect on clinical parameters assessed by DAS28 (Monsarrat et al., 2019).

Data about JAK inhibitors in periodontitis are scarce; only one recent publication already mentioned the role of tofacitinib in two cases of RA and comorbid periodontal disease (Kobayashi et al., 2019). As suggested, efficacy of tofacitinib seems to be related to the suppression of systemic inflammation promoted by high levels of IL-6 through a sustained inhibition of IL-6 signalling (Kobayashi et al., 2019). Unfortunately, the level of IL-6 or its receptor in gingival crevicular fluid was not assessed, although serum concentration showed a significant and rapid decline.

In short-term we registered a significant decrease in clinical, biologic and serologic RA activity; we also noticed improvement of periodontal condition especially related to decrease in gingival inflammation (as supported by decreased in gingival index, bleeding on probing, sites with bleeding), but also on probing depth. That means a positive reaction of gingiva related to baricitinib, despite the fact that bacterial plaque index remained the same.

However, we failed to describe any significant correlations between variation of periodontal and rheumatologic parameters.

➤ *AS and periodontal status*

4th study Periodontal Disease in Patients with Ankylosing Spondylitis: myth or reality?

We performed this cross-sectional observational study taking in mind the potential relationship between PD and AS and the possible favorable impact of TNF inhibitors on the course of both disorders in a cohort of consecutive patients.

We demonstrated compromised oral health among patients diagnosed with AS, particularly a high rate of periodontal disease (73.35%). Abnormal periodontal parameters, meaning increased PPD and CAL values, as well as high levels of gingival involvement as supported by high frequency of sites with plaques and inflammation were reported in such patients.

According to the severity, the majority of AS with PD had mild to moderate periodontal involvement (90.46%), those with severe disease being excluded from the final analysis. Furthermore, we identified positive correlations between the severity of PD, inflammatory parameters (especially CRP) and the activity of the rheumatic condition.

In the second step of the study, the analysis performed after 24 weeks of TNF inhibitor indicated a significantly improved periodontal status in the majority of AS patients, paralleling the improvement of BASDAI and ASDAS-CRP scores. In addition, a significant decrease in inflammatory parameters (ESR and CRP) was registered in all cases, as a good indicator of the efficacy of biologic therapy.

We reported a decline in all parameters reflecting the periodontal pathology (gingival and plaque index, PPD and CAL) suggesting a potential benefit of TNF antagonists in controlling not only systemic, but also local, articular, enthesal and gingival inflammation.

Despite extensive knowledge about the association between chronic periodontitis and systemic diseases, such as immune mediated rheumatic pathology (rheumatoid arthritis), diabetes mellitus, cardiovascular disease (Mayer et al., 2013; Ancuta et al., 2016; Ancuta et al., 2017; Batool et al., 2016; Fuggle et al., 2016), even adverse pregnancy outcomes, inconsistent data present the correlation between AS and periodontal disease and the impact systemic therapies directed against AS on periodontal inflammation and damage (Croitoru et al., 2015; Ratz et al., 2015).

A systematic review of literature aiming to evaluate the potential association between AS and periodontitis was recently published by Ratz et al., 2015, concluding on significant risk of AS associated with periodontitis (Ratz et al., 2015).

Dissimilarities in reporting the magnitude of impaired periodontal health among different papers are largely based on periodontitis and gingivitis definitions and diagnostic thresholds used (e.g. community periodontal index ≥ 3 or ≥ 2 , PPD ≥ 4 mm or ≥ 3 mm, which allow a large proportion of subjects with gingivitis to be subsequently classified as having periodontitis) [4, 5, 15]. However, irrespective of thresholds for periodontitis, different authors (Croitoru et al., 2015; Ratz et al., 2015; Pischon et al., 2010) demonstrated comparable rate of chronic periodontitis, ranging from 41.7% to 47.92% (Croitoru et al., 2015; Ratz et al., 2015) of the AS patients, significant higher than in controls, 29.2% and 31.25% (Croitoru et al., 2015; Ratz et al., 2015). Moreover, patients with AS had significant 6.81-fold increased odds ratio (95% CI 1.96 to 23.67) of PD (defined as mean attachment loss >3 mm) compared to controls as reported by Pischon et al, 2010.

Our data in the Romanian cohort of consecutive patients confirm a high prevalence of periodontitis during active AS.

Although various parameters (e.g. disease activity, age, gender, education, smoking, alcohol consumption, body mass index) were proposed as predictors for developing periodontitis during AS, stepwise logistic regression, including AS status, age, gender, education, smoking, alcohol consumption and body mass index, only AS status, age and education remained significant predictors of periodontal disease (Croitoru et al., 2015; Ratz et al., 2015).

Interestingly, Chang et al (Chang et al., 2013) failed to demonstrate an association between periodontal disease, AS and the use of TNF- α inhibitors in a Korean population. The prevalence of PD was comparable in healthy controls and AS (59% vs. 68%, $p>0.05$), with no significant difference in all probing measurements (PI, BOP, PPD, CAL) between groups. Moreover, only male gender was significantly ($p<0.05$) associated with PD when performing the initial AS assessment; however, other variables including the current use of TNF antagonists was not important ($p>0.05$). Likewise, biological therapy did not affect periodontal treatment outcomes in AS with PD. In conclusion, the prevalence and severity of PD was not increased among AS (Chang et al., 2013).

This study is not our first experience in evaluating oral health, particularly periodontal disease, in patients with chronic inflammatory rheumatic disorders; we have already published data about rheumatoid arthritis and periodontitis (Ancuta et al., 2016; Ancuta et al., 2017), psoriatic arthritis (another disease included in the spondylarthropathies group as AS) and

periodontitis [unpublished data], focusing on factors associated with severity and impact of specific biologic therapies on both articular and dental status.

We demonstrated high rate of periodontal disease not only among rheumatoid arthritis, psoriatic arthritis, but also in ankylosing spondylitis, with positive outcomes even after a short course (24 weeks) of TNF inhibitors.

Patients with inflammatory rheumatic pathologies are largely characterized by elevated ESR and CRP; in addition, those presenting with concomitant chronic periodontitis had higher levels of systemic inflammation (Croitoru et al., 2015; Ratz et al., 2015; Ancuta et al., 2016; Ancuta et al., 2017). We found a robust direct correlation between CRP levels and periodontal health at baseline in our patients, meaning that increased serum CRP concentrations are demonstrated in AS with severe periodontitis. The correlation was maintained throughout the end of the study.

Further studies in larger cohorts of AS patients are recommended to correctly assess the prevalence of periodontitis, to demonstrate predictors of impaired periodontal health and to confirm the dual role of TNF inhibitors on both periodontal and articular status.

➤ *PsA and periodontal status*

5th study TNF Inhibitors and Periodontal Inflammation in Psoriatic Arthritis

We prospectively assessed periodontal status in patients with moderate to severe active PsA and we evaluated the relationship between clinical periodontal parameters, CRP levels and disease activity in patients with PsA treated with TNF inhibitors.

Firstly, we showed that participants in the current study have impaired oral health and significantly higher number of missing teeth (described in up to half of analyzed PsA) and more periodontal disease as expected for age and sex-matched healthy individuals; we reported a high frequency of gingival plaques and gingival inflammation, but high PPD and CAL as well. Furthermore, up to one third of PsA had chronic periodontitis, and even severe periodontal involvement. Interestingly, a direct correlation between serum CRP levels as an indicator of active psoriasis-related inflammation, and periodontal disease was identified.

Secondly, we confirmed the benefits of biological therapy in PsA as supported by a rapid and sustained effect in active disease, refractory to synthetic immunosuppressive; a short-term (24 weeks) treatment with TNF inhibitors (adalimumab, etanercept, golimumab) resulted in significant decline in disease activity and inflammatory parameters (ESR, CRP).

Thirdly, we demonstrated an improvement of periodontal status (plaque index, gingival index, pocket depth and clinical attachment loss) during anti-TNF therapy, indirectly suggesting that controlling systemic inflammation could also influence local, gingival inflammation even during short-term (24 weeks) follow-up.

Though common inflammatory pathways of systemic and local (articular, gingival) inflammation and the key role of oral pathogens in modulating host inflammatory and immune response are widely recognized in rheumatoid arthritis and, to a lesser extent, in psoriatic arthritis, insufficient data is actually known about the interrelation between PsA and periodontal disease (Kalakonda et al., 2016; Linden et al., 2013; Mayer et al., 2013; Monson et al., 2016; Monson et al., 2016).

We were able to talk about impaired periodontal health with an increased frequency of severe periodontitis in our PsA patients; however, data from literature is still controversial [8-23]. Certain studies failed to recognize a statistically significant prevalence of periodontitis in PsA as compared with healthy control subjects (Keller et al., 2012; Monson et al., 2016; Monson et al., 2016). One potential explanation is the long-term use of medication known to have protective effects on periodontal damage in PsA cases enrolled in different studies (Keller et al., 2012; Monson et al., 2016; Monson et al., 2016; Skudutyte-Rysstad et al., 2014).

Conversely, different other papers (Monson et al., 2016; Monson et al., 2016; Padel et al., 2013; Preus et al., 2010; Skudutyte-Rysstad et al., 2014) reported important association between

moderate to severe psoriasis and oral health, particularly periodontal disease; patients with psoriasis have significantly fewer teeth and radiographic bone loss compared to controls (Monson et al., 2016; Monson et al., 2016; Skudutyte-Rysstad et al., 2014); the prevalence of moderate to severe periodontitis was also higher (Monson et al., 2016; Monson et al., 2016).

Besides, a recent work demonstrated a significant association between PsA and severe chronic periodontitis (Monson et al., 2016); although higher CAL, as the standard for evaluating the severity of periodontitis assessing the past disease activity, was demonstrated in PsA, PPD (reflecting current disease activity) presented with high but not statistically significant values (Monson et al., 2016; Skudutyte-Rysstad et al., 2014).

Furthermore, parameters overlapping the accuracy of data analysis such as smoking, obesity and systemic diseases including diabetes and cardiovascular disease were not allowed in our protocol.

Additionally, we demonstrated an important improvement of PPD and CAL during biological therapy for active PsA, advancing the role of TNF inhibitors in suppressing not only articular inflammation and subsequent damage, but also periodontal inflammation and local, alveolar damage. It is reasonable to assert that a decrease in proinflammatory cytokines level in the periodontal microenvironment, induced by TNF blockade is also responsible for a positive outcome for periodontal parameters such as PPD, CAL, gingival index and bleeding on probing.

TNF inhibitors typically account for decrease in acute phase reactants (e.g. CRP) levels in PsA. We identified not only a strong positive correlation between CRP level and periodontal health (high CRP levels associated with more severe periodontitis) at baseline, but at 24 weeks of follow-up (V2).

Finally, we provided sufficient arguments for significant burden of periodontitis in patients with active PsA and the role of TNF inhibitors in controlling both PsA-related parameters and periodontal health in short term administration.

Further studies in larger cohorts of PsA patients as well as comparison with periodontal disease within other inflammatory immune rheumatic diseases, particularly rheumatoid arthritis patients are necessary in order to characterize periodontal health in patients with PsA and to validate the influence of biologic drugs in improving periodontitis in such patient population.

➤ *SSc and periodontal status*

6th study - Periodontal Disease and Lipid Profile in Systemic Sclerosis: an EUSTAR Cohort Experience

We assumed that patients with SSc are at risk to develop impaired oral health, including periodontitis, based on multiple general and/or disease-specific predisposing factors; we further assessed the prevalence of PD in a cohort of SSc as well as the potential relations with various SSc-related characteristics and lipid metabolism tests.

PD manifestations described in our cohort, e.g. gingival inflammation, plaques and bleeding, comprised: up to one third of cases displayed periodontal pockets, one out of five significant clinical attachment loss, even alveolar bone loss. Although periodontitis was reported in both diffuse and limited SSc patients, aggressive oral signs and symptoms were found particularly in diffuse SSc settings.

There is no substantial association with age, disease duration or hand disability.

Recently published data from the Canadian Systemic Sclerosis Oral Health Study III (Canadian Scleroderma Research Group) indicated that a diminished inter-incisal distance correlates with overall disease severity, decreased salivary production (concomitant oral sicca syndrome), gastro-esophageal reflux and the association of tooth loss with poor upper extremity function (Baron et al., 2014; Baron et al., 2015).

Lastly, local defective vascularity and alteration of gingival microcirculation (SSc related vasculopathy) may also account for high prevalence of oral abnormalities in SSc (Yuen et al., 2011; Yues et al., 2014).

We found abnormal serum lipids, particularly in diffuse SSc and patients with severe aggressive PD: elevated LDL-cholesterol along with decreased HDL-cholesterol fractions were usually detected.

Though we have previously reported abnormal lipid pattern in different SSc settings (Ancuta et al., 2010; Ancuta et al., 2015; Ancuta et al., 2016; Au et al., 2011; Farag et al., 2015), information about lipid metabolism in SSc is still controversial (Nordin et al., 2013; Nussinovitch et al., 2010; Schiopu et al., 2014; Tsifetaki et al., 2010; Vettori et al., 2010). Decreased HDL-cholesterol was detected in patients with limited cutaneous disease, while abnormal values in other studies performed in SSc (Hettema et al., 2008; Missala et al., 2012). Also, increased lipoprotein concentrations without further differences in detailed lipid profile in comparison with healthy controls were found in both limited and diffuse SSc (Nordin et al., 2013; Nussinovitch et al., 2011; Schiopu et al., 2014; Tsifetaki et al., 2010; Vettori et al., 2010).

It is widely recognized that PD may be associated with various lipid metabolism abnormalities (Griffiths et al., 2010); according to some researchers, PD changes the lipoproteins promoting a proatherogenic profile (with increased LDL-cholesterol and triglycerides, together with impaired HDL-cholesterol) (Griffiths et al., 2010), predisposing to early atherosclerosis (Griffiths et al., 2010; Missala et al., 2010).

A closer look to lipid changes in patients with chronic periodontal inflammation confirmed higher LDL-cholesterol and triacylglycerol levels, smaller lipoprotein and higher dense LDLs, particularly if aggressive periodontitis (Griffiths et al., 2010).

Several studies have recently suggested some benefits of periodontal therapy on lipoprotein metabolism, indicating deleterious effects on circulating inflammatory mediators, with subsequent influence cholesterol fractions (LDL, HDL), and, thus, on subclinical atherosclerosis (Griffiths et al., 2010; Yuen et al., 2012). LDL-cholesterol is usually reduced after periodontal therapy, while HDL-cholesterol replaced by a more anti-atherogenic fraction (Griffiths et al., 2010).

Our results visibly advise about the link between PD and lipid modifications in SSc patients, especially in severe PD cases. Interestingly, those patients are predisposed to develop PD and abnormal lipid profile, suggesting a potential linkage between SSc and (subclinical) atherosclerosis via gingival inflammation and lipid metabolism (Griffiths et al., 2010; Hettema et al., 2008).

Further research is necessary in order to assess the true prevalence of clinically manifest or subclinical premature atherosclerosis in SSc with or without concomitant periodontal disease.

7th study - Volumetric Cone Beam Computed Tomography for the Assessment of Oral Manifestations in Systemic Sclerosis: Data from an EUSTAR Cohort

We performed a systematic 3-D analysis of the radiographic orofacial abnormalities associated with SSc, aiming to describe specific CBCT findings and to identify potential correlations with disease characteristics, activity/severity, or prognostic factors. We designed a case-control study within a local EUSTAR SSc-cohort and matching controls focused on a comprehensive evaluation of periodontal ligament and erosions as the most common radiographic manifestations in scleroderma.

We reported an increased rate of PDL space widening with a tendency for significantly more teeth with widened PDL space in scleroderma as compared to controls irrespective of the evaluation method (number of teeth with abnormal PDL or individual evaluation per one tooth): 46.51% SSc with PDL widening in at least one tooth vs. 13.95% controls. Moreover, wider PDL space was generally detected in the posterior teeth in more than one quadrant, although anterior

region was also involved. Our results are within the range of reported data in literature by using conventional panoramic radiographs (38–66%) (Jung et al., 2017; Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015, Baron et al., 2016; Yalcin et al., 2019; Savage et al., 2009; Jepsen et al., 2018; Jagadish et al., 2012).

A systematic review of the literature addressing the impact of scleroderma on oral health has identified only a few studies having as endpoint the radiographic findings; moreover, the majority considered bi-dimensional panoramic radiographic assessment, and none of them focused on interrelations between imaging parameters and disease characteristics (Jung et al., 2017; Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015, Baron et al., 2016; Yalcin et al., 2019; Savage et al., 2009; Jepsen et al., 2018; Jagadish et al., 2012).

A closer look to the Canadian Systemic Sclerosis Oral Health Study offered a relevant picture of oral manifestations related to SSc; this was an ambitious study focused on SSc interferences with oral conditions within a large cohort of patients selected from several rheumatology centers. Compared with controls, patients with SSc are significantly more likely to have more teeth (molars and premolars) with PDL space widening as well as mandibular erosions. Furthermore, the evaluation of radiographs by two blinded experts increased accuracy of the results (Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015; Baron et al., 2016).

We performed a panoramic approach of oral SS-related features by two-dimensional radiographs and also by high-resolution volumetric CBCT. Although the oral pattern of involvement in scleroderma on standard films is widely recognized, data on 3-D assessments are scarce. In fact, only one study with a comparable design is still ongoing in a French cohort aiming to characterize precisely the oral manifestations associated with SSc and to identify specific radiological (3-D CBCT), clinical, and/or biological signs.

We used Adobe Photoshop for PDL space widening assessment on panoramic images; compared to the Canadian SSc Oral Health Study, where results were analyzed by two radiologists, in our study, data were read by only one radiologist, and this may have a potential bias for the accuracy of the results (Dagenais et al., 2015; Baron et al., 2014; Baron et al., 2015; Baron et al., 2016).

PDL remains an active tissue, with an increased remodeling capacity (Baron et al., 2014; Baron et al., 2015; Baron et al., 2016). Widening of the PDL space may be related to SSc as a result of excessive and extensive fibrosis of the ligament correlating with disease severity (Shah et al., 2013; Ylmaz et al., 2018) and also may develop in occlusal/orthodontic trauma, periodontal/periapical disease, pulpo-periapical lesions, bisphosphonate-related jaw osteonecrosis, malignancies (osteosarcoma, chondrosarcoma, and non-Hodgkin lymphoma) or in radiation-induced bone defect (Mortazavi et al., 2016). In dental occlusion trauma, PDL involvement is usually related to excessive or para-axial biting forces and is generalized or located and associated with angular bone defects and teeth mobility, while in malignancies, PDL space widening is limited to the adjacent teeth and the lamina dura is involved. In contrast, in patients with scleroderma, the lamina dura frequently remains intact and a uniform enlarged PDL space occurs in more than one quadrant, usually in the posterior teeth (Alexandridis et al., 1984; Anbiaee et al., 2011, Anbiaee et al., 2012; Baron et al., 2014, Baron et al., 2015; Baron et al., 2016; Mortazavi et al., 2016; Hopper et al., 1982).

In about one out of four SSc (23.25%) we also demonstrated an increased frequency of mandibular erosions, particularly condylar erosions in the area of the lateral pterygoids muscle attachment to the bone. Our results are within the range reported from previous 2-D studies (7–10%); in fact, only one paper described a higher prevalence of mandibular angle involvement (83.33% cases) (Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015; Baron et al., 2016; Mortazavi et al., 2016; Matsuda et al., 2018; Seifert et al., 1975).

The difference was significant only for the condylar erosions in patients with SSc compared with controls ($p < 0.05$).

It was demonstrated that mandibular findings in scleroderma include resorption of the angle, condyle, coronoid process, ascending ramus, and antegonial notch. However, complete condylar osteolysis and secondary mandibular resorption are only rarely documented (Dagenais et al., 2015; Baron et al., 2014; Baron et al., 2015; Baron et al., 2016; Jagadish et al., 2012). Abnormal muscle contraction with subsequent abnormal pressure on the bone via atrophic muscles at their attachment site (Baron et al. 2014, Baron et al. 2015, Baron et al. 2016, Jepsen et al., 2017), bone ischemia due to vasculitis and deposition of collagen in vascular wall, as well as rigidity and pressure from overlying skin are among the mechanisms likely involved in the emerge and persistence of bone erosions in SSc (Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015; Baron et al., 2016; Jagadish et al., 2012).

Calcifications within the periodontal ligament were not reported in our study. An interesting paper published several years ago reported calcifications within the PDL space of most maxillary teeth seen on 3-D CBCT analysis as well as pulp calcifications in some incisors and premolars with subsequent root canal obliterations (Jung et al., 2013).

Finally, we explored associations between SSc parameters and oral radiographic changes in our scleroderma patients. To the best of our knowledge, only the Canadian Oral Health Study systematically assessed and reported such correlations; our analysis confirms published data and enhance the expertise in oral health in different scleroderma scenarios. Interestingly, although widening of the PDL space is related to disease severity, reflecting extensive fibrosis and aberrant collagen turnover, no relation with periodontal disease and missing teeth were described. However, we did not report any correlation between PDL space widening and smoking as previously described, although the influence of nicotine on fibroblast phenotype and activity within PDL space is recognized (Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015; Baron et al., 2016).

CONCLUSIONS

As a final remark, we may assert that periodontal disease is commonly reported in patients with various immune mediated inflammatory rheumatic conditions:

- we concluded that tocilizumab decreased gingival inflammation since no periodontal therapy was permitted and the dental hygiene behavior remained unchanged in our enrolled patients (**paper 1**).
- *RA*, particularly active severe ACPA-positive disease subtypes, is essentially accompanied by comorbid periodontal disease; TNF blockade is efficient in active disease and potentially able to modulate the inflammatory process in the periodontal tissue (**paper 2**);
- *baricitinib* also resulted in significant improvement of periodontal inflammation in active *RA* patients, possible related to inhibition of both IL-6 and JAK-mediated cytokine signalling. (**paper 3**);
- in short-term we registered a significant decrease in clinical, biologic and serologic *RA* activity; we also noticed improvement of periodontal condition especially related to decrease in gingival inflammation (as supported by decreased in gingival index, bleeding on probing, sites with bleeding), but also on probing depth. That means a positive reaction of gingiva related to baricitinib, despite the fact that bacterial plaque index remained the same. (**paper 3**);
- to the best of our knowledge, this was the first report to compare periodontal condition in patients with *RA* and chronic periodontitis before and after baricitinib therapy (**paper 3**);
- patients with active *AS* are at risk to develop periodontal disease, predominantly those with high levels of systemic inflammation; benefits of anti-TNFs in the particular settings of *AS* and concomitant periodontitis should be validated through further studies in larger cohorts of patients (**paper 4**);

- chronic periodontitis may also develop in patients with PsA and should be commonly evaluated, particularly in those with active disease; efficacy of TNF inhibitors meaning significant response in articular and periodontal parameters, suggest common inflammatory pathways in both entities (**paper 5**);
- patients with SSc are at risk to develop impaired oral health, particularly chronic PD, as well as abnormal lipid profile (low serum HDL- and high LDL-cholesterol). The link between gingival inflammation, periodontal destruction and changes in lipid metabolism might represent one pathobiological pathway driving atherosclerosis (**paper 6**).
- volumetric CBCT performance in assessing PDL space widening and mandibular erosions in patients with SSc shows promising results; PDL space widening as well as mandibular erosions are commonly reported in scleroderma and correlated with different disease characteristics especially severity, skin extent, and antibody profile; future studies could investigate the pattern of PDL widening at different root heights and in different oral disease context (**paper 7**).

1.1.2 ORAL HEALTH IN SJOGREN SYNDROME

STATE OF THE ART

The second topic in this interdisciplinary approach was based on Sjogren Syndrome (SSj) and the importance of salivary and oral assessment in the diagnosis and follow-up of the disease as well as in guiding the therapeutic plan. We assume that both entities, SSj and PD share multiple pathogenic interferences such as xerostomia and altered saliva composition, xerostomia and oral infections, xerostomia and dental caries, xerostomia and altered periodontal status (Shah et al., 2020).

Sjogren's syndrome remains an autoimmune rheumatic disease widely characterized by different degrees of oral and ocular dryness, with or without various extra-glandular manifestations including peripheral chronic arthritis, peripheral vasculopathy and a wide spectrum of visceral involvement; the disease occurs on a background of specific serology, meaning the anti-Ro/SSA and/or -La/SSB antibodies positivity (Bayetto et al, 2010; Soyfoo et al, 2012; Vitali et al, 2002).

A wide spectrum of clinical and serological manifestation ranging from different degrees of oral and ocular dryness (xerostomia and serophtalmia, respectively) and extra-glandular features (arthralgia or arthritis, peripheral vasculopathy with Raynaud phenomenon, pulmonary, gastrointestinal, neurological and renal pathology, vasculitis, cytopenia) with a background of specific immune abnormalities comprising anti-Ro/SSA and/or anti-La/SSB antibodies are essentially recognized in pSSj and result in significant impaired health-related quality of life (De Langhe et al., 2017; Serrano et al., 2020).

Oral health issues are generally identified in primary SSj: xerostomia, increased susceptibility to develop caries and oral (bacterial and fungal) infections, as well as early dental loss due to caries (Serano et al., 2020; Sutcliffe et al., 2021) despite good oral hygiene (Isine et al., 2016, Sutcliffe et al., 2021) are documented among such patients, requiring a complex diagnostic and management focused on different strategies such as salivary flow stimulation, chemical control of dental plaque, restorative treatment, dental implants (Sutcliffe et al., 2021); however, periodontal disease and periodontal care are still controversial in patients with pSSj (De Langhe et al., 2017; Serrano et al., 2020).

It is widely accepted that oral health impairment secondary to pSSj is multifactorial; immune-mediated salivary secretory dysfunction with chronic xerostomia and hyposalivation, changes in saliva components and quality, changes in oral microbiota (high bacterial count of

species such as *Lactobacillus acidophilus*, *Streptococcus mutans*, *Candida albicans*) remain major determinants of altered oral health in SSj (Medeiros et al., 2018; Serrano et al., 2020).

Furthermore, salivary secretory anomalies, reduced whole saliva flow rates, abnormal pH and buffer capacity as well as potentially altered saliva composition with modified concentrations of various electrolytes and organic constituents are characteristically reported in patients with pSSj, result in impaired salivary protective properties and support the occurrence of several oral-health related issues (Isine et al, 2016; Medeiros et al 2018; Sutcliffe et al., 2021).

An early and complex diagnostic and management approach is required, comprising specific strategies such as salivary flow stimulation, chemical control of dental plaque, restorative treatment, dental implants (Castagnola et al., 2017; Isine et al., 2016; Shah et al., 2020) aiming to maintain health-related quality of life.

Together with my rheumatologists partners, we realized a complex assessment of patients with Sjogren syndrome (split in primary and secondary SSj) including clinical parameters, laboratory assessments-autoantibody panel, imaging studies (X-rays, ultrasound – musculoskeletal and salivary gland, CT), salivary tests; a complex oral health assessment completed the evaluation protocol for enrolled patients.

We have already published Romanian **ISI journal** preliminary data about the role of specific chemical modifications of saliva during SSj emphasizing its role in promoting the cariogenic risk.

Specific Sialochemical and Sialometric Changes and Cariogenic Risk in Patients with Primary Sjogren's Syndrome

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REVISTA DE CHIMIE 2017, 68 (9): 2135-2138.

OBJECTIVES

The aim of our study was to evaluate the salivary flow rates and composition and to assess potential impact on oral health, particularly cariogenic issues, in patients with autoimmune salivary secretory dysfunction such as primary Sjogren's syndrome (pSSj).

METHODS

We performed a prospective observational study in consecutive pSSj (fulfilling the 2002 American-European consensus classification criteria) and healthy age-matched controls.

The standardized protocol comprised salivary and dental assessments as follows: (i) resting unstimulated (RFR) and stimulated (RFS) whole salivary flow rates, pH and composition (inorganic, organic constituents) and (ii) the number of decayed, missing and filled tooth surfaces (DMFS index) and the Silnes & Loe plaque index (PI).

Salivary flow rates and pH

In order to avoid potential influence of circadian rhythm on saliva secretion and composition, the fluid was collected between 09:00-10:00 a.m.; the rate of resting salivary flow (RFR) was calculated by whole saliva collection after spitting out of the water and initial swallow (graduated measuring jar every 30 sec. for six minutes. The flow rate was calculated as collected volume/ collection time (ml/ min) (normal values 0.5-0.7 mL/min).

Saliva production was stimulated by chewing paraffin wax (mechanical method) for 30 sec., whole saliva was collected by spitting into a graduated measuring jar for 6 minutes; the total salivary volume was divided by six in order to calculate mL of saliva per minute (paraffin stimulated salivary flow, RFS) (normal values 1.00-1.20 mL/min).

Salivary composition

Saliva components include inorganic (anions, cations, gases) and organic evaluated from whole stimulated saliva centrifuged and analysed. Normal amylase activity 11.900- 304.700U/L,

total protein 1.1-1.8 g/L, chloride concentrations 5-40 mmol/L, potassium 6.4-37 mmol/L, sodium 2-21 mmol/L.

Carries assessment

The decayed, missing (due to caries only) and filled (restored) surfaces (DMFS) index basically counts each affected dental surface in an attempt to assess the prevalence of dental caries prevalence and the requirement of dental treatment based on in-field clinical exam. Silness-Loe plaque index measures the status of oral hygiene and is based on recording both soft debris and mineralized deposits on the teeth. Each of the four surfaces of the teeth (buccal, lingual, mesial and distal) is given a score from 0-3 and then used to calculate the plaque index for the tooth.

Statistical analysis (descriptive, analytical tests) was done in SPSS package, $p < 0.05$. The Newman-Keuls statistical test commonly applied to compare different parameters.

RESULTS

Demographic data, smoking status, oral hygiene habits, number of annual dental visits were comparable among study groups ($p > 0.05$).

pSS patients (all woman) were aged between 45 and 62 years, had a mean disease duration of 4.5 years, and were classified as having significant oral dryness/ xerostomia. Cariogenic indexes (DMFS and PI), salivary flow rates (unstimulated and stimulated), salivary pH and differences between study groups are summarized in **Table 18 and 19** respectively, while data about sialochemical salivary analysis in **Tables 20 and 21**.

Table 18 Cariogen indexes, salivary flow rate and salivary pH

	Group	Average	Std dev
DMFS	control	10.61	1.55
	SS	47.17	1.25
PI	control	0.38	0.50
	SS	2.17	0.71
RFR (ml/min)	control	0.50	0.07
	SS	0.11	0.05
RFS (ml/min)	control	0.741	0.214
	SS	0.513	0.387
pH	control	6.26	0.15
	SS	4.58	1.05

Table 19 Newman Keules test for study group

Cariogenic indicators	P
DMFS	0.000110
PI	0.000119
RFR	0.000139
RFS	0.000104
pH	0.000055

Salivary flow rates and pH

Salivary flow rates were significantly lower in pSSj for both unstimulated and stimulated tests ($p < 0.05$), with a drop in pH as compared to healthy controls ($p < 0.05$, 0.11 ± 0.05 vs. 0.50 ± 0.07 for RFR; 0.513 ± 0.387 vs. 0.741 ± 0.214 for RFS, respectively). Patients with pSSj presented with a drop in salivary pH (4.58 ± 1.05) compared to their controls (6.26 ± 0.15), with significant lower p H ($p < 0.05$).

Sialochemical analysis

A detailed analysis of inorganic and organic saliva composition was done in all pSSj and controls, including data about cations (sodium and potassium concentrations), anions (chloride concentrations), total protein and amylase activity.

Abnormal inorganic and organic saliva composition was reported in all cases comprising higher sodium (139.75 ± 4.27 mmol/L vs. 32.44 ± 10.40 mmol/L), lower potassium (05 ± 0.42 mmol/L vs. 4.39 ± 0.60 mmol/L) and chloride concentrations, 99.75 ± 3.61 mmol/L vs. 100.12 ± 4.10 mmol/L higher amylase activity (44633.3 ± 16615.1 U/L vs. 1506 ± 0.198 g/L vs. 1233 ± 0.198 g/L) and lower total protein ($p < 0.05$). Differences in inorganic and organic salivary components were statistically significant as shown by Newman-Keuls test ($p < 0.05$) (**Table 20**).

Table 20 Saliva composition in study group

	Group	Average	Std dev
Na (mmol/l)	control	32.44	10.40
	SS	139.75	4.27
K (mmol/l)	control	4.39	0.60
	SS	4.05	0.42
Cl (mmol/l)	control	100.12	4.10
	SS	99.75	3.61
Amylases (U/l)	control	114456.3	97342.3
	SS	44633.3	16615.1
Total protein (g/l)	control	1.506	0.198
	SS	1.233	0.114

Oral findings

Statistically significant higher cariogenic scores, particularly DMFS, were demonstrated in all pSSj ($p < 0.05$).

We reported significantly higher ($p < 0.05$) DMFS and PI in all studied pSSj compared to their matched controls (47.17 ± 1.25 vs. 10.61 ± 1.55 for DMSF, 2.17 ± 0.71 vs. 0.38 ± 0.50 for PI respectively). Differences among study groups were statistically significant for all parameters (cariogenic indexes, salivary flow rate and pH) as demonstrated by applying the Newman-Keuls test (**Table 21**).

Higher number of missing teeth vs. controls, higher number of filled (due to carries) tooth surfaces were demonstrated in pSSj ($p < 0.05$).

Moreover, a direct correlation between DMFS and xerostomia and hyposalivation was also demonstrated - significant oral dryness and severely impaired salivary flow rate are associated with more carries and higher DMFS ($p < 0.05$).

Table 21 Newman Keuls test for inorganic and organic salivary compounds

Saliva compounds	p
Na	0.000120
K	0.000112
Cl	0.001441
Amylases	0.006539
Total protein	0.298832

DISCUSSION

Oral health pathologies are quite frequent in pSSj, particularly oral dryness, low salivary flow, acidic pH, modified composition, caries and/or periodontal disease (Boutsi et al., 2000; Thomson et al., 2006; Christensen et al., 2001; Lynge et al., 2015; Isine et al., 2016; Pedersen et al., 1999; Rius et al., 2015). While that dental does not correlate with age and oral hygiene

habits in such patients, it seems that the severity of xerostomia and decreased salivary flow inversely correlate in pSSj (Lynge et al., 2015).

Major determinants of dental caries in pSSj include abnormal pH (acidic salivary environment), electrolytes and organic composition and low salivary flow rates (Lynge et al., 2015).

Also, specific sialometric and sialochemical salivary could be considered as oral biomarkers predicting SSj severity: thus, high sodium and chloride correlated with decreased salivary flow, excessive glandular deposits of lymphocytes, high concentrations of specific autoantibodies (anti-Ro/SSA, - La/SSB) (Lynge et al., 2015).

In our patients, we performed a detailed sialochemical and sialometric analysis doubled by a complex oral health assessment, focusing on cariogenic issues. All pSSj were characterized by significantly reduced salivary secretion (unstimulated, stimulated whole salivary flow rates) ($p < 0.05$).

Several other quantitative and qualitative changes in salivary parameters were reported: abnormal pH and abnormal organic and inorganic composition ($p < 0.05$). Similar trends were described also in other systemic pathologies defined by secretory dysfunction.

Remarkably, we identified high cariogenic indexes in our pSSj meaning more injured teeth (number of decayed, missing and filled surfaces, soft debris and mineralized deposits) suggested by a high DMFS and PI ($p < 0.05$).

Abnormal salivary sodium and chloride as well as potassium concentrations detected in pSSj may reflect impaired ductal salt reabsorption. Our main finding in electrolyte composition comprised high sodium, low chloride and potassium, suggesting further analysis in order to clarify the above mentioned inconsistency.

Generally, our sialochemical and sialometric results in patients with primary SSj encourage similar findings described in other studies, with an exception: the chloride concentration.

We recommend a multidisciplinary approach (dentist-rheumatologist-primary care physician) for a complex and correct management of such patients.

CONCLUSIONS

In conclusion, patients with pSSj are at increased risk to develop cariogenic issues due to both quantitative and qualitative salivary changes.

A decreased salivary secretion remains the mainstay of SSj and is thought to be accountable for enhanced susceptibility of oral mucosa to various physical, chemical and microbial aggressions.

I.1.3 TEMPOROMANDIBULAR JOINT IN RHEUMATIC CONDITIONS

STATE OF THE ART

Temporomandibular joint (TMJ) is commonly involved in various immune-mediated rheumatic disorders including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and spondyloarthropathies such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), leading to significant disability as well as impaired quality of life (O'Connor et al., 2017; Covert et al., 2021; Goupille, 1993).

Up to 98% of patients with RA, 63% of patients with PsA, about 32% of those diagnosed with AS, and up to 72% JIA will develop TMJ arthritis during the course of their disease, presenting with a variable clinical spectrum that range from asymptomatic to clinically significant arthritis characterized by severe pain, articular noises, mandibular deviation during maximum

extrusion, joint stiffness, difficulties in opening the mouth (O'Connor et al., 2017; Covert et al., 2021; Goupille, 1993; Niibo et al., 2016).

The magnitude of TMJ involvement depends on the type of rheumatic pathology and seems to be related to disease activity and severity status. Therefore, it is clearly that inflammatory parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as immune abnormalities including the level of rheumatoid factor (RF) and plasma tumour necrosis factor- α (TNF- α) are related to the severity of TMJ disease, particularly in RA patients (Kristwnsen et al., 2014; Mercuri et al., 2017; Schett et al., 2016).

Both RA and spondyloarthropathies are characterized by complex pathobiology meaning cytokine imbalances with the preponderance of systemic as well as articular inflammatory mediators (TNF- α , IL-6, IL-1, prostaglandins), subsequent inflammation, immune (T and B cells, macrophages) and non-immune (osteoclast, synoviocytes, chondrocytes) cell activation, (neo)angiogenesis and, as a final step, structural damage (erosive lesions in RA, as well as destructive and proliferative lesions in spondyloarthropathies) (Kristwnsen et al., 2014; Mercuri et al., 2017; Schett et al., 2016).

It is currently accepted that TNF- α is associated not only with severe active and advanced joint damage, but also with TMJ inflammation and pain. Furthermore, TNF- α is able to endorse the release and activation of destructive mediators including matrix enzymes (O'Connor et al., 2017; Mercuri et al., 2017; Schett et al., 2016).

IL-1 α and IL-1 β are widely recognized as potent pro-inflammatory and destructive cytokines, promoting a broad spectrum of local as well as systemic events e.g. vasodilatation, cellular trafficking, induction of matrix-metalloproteinases. Moreover, high serum concentrations of IL-1 β are typically related to both inflammation and damage in RA with TMJ arthritis (O'Connor et al., 2017; Mercuri et al., 2017; Schett et al., 2016).

Finally, another interleukin (IL-6) seems also to be important for TMJ pathology as certain authors reported correlation between IL-6 levels, the degree of acute synovitis and acute perforation of the TMJ joint disc as supported by arthroscopic assessment. However, no relation was demonstrated between pain, joint dysfunction and the total protein concentration in synovial fluid (O'Connor et al., 2017; Mercuri et al., 2017; Schett et al., 2016).

Serum levels of different proinflammatory cytokines such as IL-1 β , IL-6, IL-8 and TNF- α are significantly increased in patients with TMJ involvement, without any correlation with signs and symptoms (Cricoli et al., 2015; O'Connor et al., 2017; Mercuri et al., 2017; Schett et al., 2016). Moreover, higher synovial fluid concentrations of IgA, IgG and β -glucuronidase were described in patients with clinically significant TMJ involvement (e.g. severe pain, mandibular stiffness) as compared to general population (Akhlaghi et al., 2019).

Despite consistent evidence of TMJ involvement in chronic inflammatory rheumatic conditions, signs and symptoms of TMJ pathology are typically underestimated by rheumatologists and even by patients, especially when treatment is focused on other peripheral joints (Akhlaghi et al., 2019; Cricoli et al., 2015; O'Connor et al., 2017; Kristwnsen et al., 2014).

Imaging studies play a key role in the diagnosis of TMJ disorders, assessing not only the severity and structural damage progression, but also monitoring efficacy of therapy. Although commonly used, panoramic X-ray remains inappropriate for an early and complete diagnosis of TMJ involvement. Modern imaging techniques such as ultrasound and cone beam computed tomography (CBCT) are actually used for both diagnosis and therapeutic follow-up. (Covert et al., 2021; Ola Mohamed et al., 2018).

Another direction settled in this interdisciplinary collaboration was focused to the involvement of temporomandibular joint (TMJ) in chronic inflammatory rheumatic disorders, particularly RA,

JIA, PsA and SSc; we proposed a complex assessment based on clinical, immunological and imaging studies (radiology, ultrasonography, IRM and cone beam CT) of the TMJ; in addition, we used various health related quality of life questionnaires.

Results were published in the Romanian Journal of Oral Rehabilitation (RJOR), Romanian Journal of Medical and Dental Education (ADRE) and Romanian Journal of Functional and Clinical, Macro - and Microscopical Anatomy and of Anthropology indexed in several international databases, and other journals including ISI indexed (Journal of Clinical Medicine, Revista de Chimie).

PERSONAL RESEARCH

My personal research in ergonomics and work-related spine pathology topics comprised 7 articles published in ISI and IBD journals:

1. **Cristina Iordache**, Vascu B, Ancuta E, Chiriac R, Pomirleanu C, Ancuta C, Immunobiological assessments of temporomandibular joint disease in patients with immune-mediated rheumatic conditions: a cross sectional study of 273 cases, Revista de Chimie 2017, 68 (12): 2987-2991.
2. **Cristina Iordache**, Magda-Ecaterina Antohe, Rodica Chiriac, Eugen Ancuța, Oana Țănculescu, Codrina Ancuța, Volumetric Cone Beam Computed Tomography for the assessment of oral manifestation in systemic sclerosis Data from an EUSTAR Cohort, J. Clin. Med. 2019, 8, 1620; doi:10.3390/jcm8101620.
3. **Cristina Iordache**, Ghiorghe Cristina-Angela, Ancuța Codrina, Epidemiology of temporomandibular joint involvement in rheumatic pathology, Roumanian journal of Oral Rehabilitation, 2017, 9(3), p 16-24.
4. **Cristina Iordache**, Murariu Alice, Boariu Diana, Chiriac Rodica, Ancuța Codrina Temporomandibular joint involvement in rheumatoid arthritis patients – correlations with disease activity and quality of life, Romanian Journal of Oral Rehabilitation 10, (3), 2018, 109-115.
5. **Cristina Iordache**, Ana Maria Fătu, Surlari Zenovia, Elena Luca, Antohe Magda*, Ancuța Codrina Temporomandibular joint in rheumatoid arthritis – a complex imaging approach, Romanian Journal of Medical and Dental Education Vol. 7, No. 2, 2018, 107 -112.
6. **Cristina Iordache**, Fătu Maria Ana, Pomârleanu Cristina, Scurtu Daniel, Ancuța Codrina Temporomandibular joint in juvenile idiopathic arthritis: an imaging study and ergonomic considerations, Roumanian journal of Oral Rehabilitation, 2017, 9 (1), p 60-67.
7. **Cristina Iordache**, Cristina Angela Ghiorghe*, Magda Ecaterina Antohe, Irina Esanu, Codrina Ancuta Temporomandibular joint involvement in rheumatoid arthritis and ankylosing spondylitis: a cross- sectional study, Roumanian journal of Oral Rehabilitation, 2017, 9(4), p 40-46.

We will further present several of our results published in ISI and IBD journals:

Paper 1: Immunobiological assessments of temporomandibular joint disease in patients with immune-mediated rheumatic conditions: a cross sectional study of 273 cases

By: **Cristina Iordache**, Vascu B, Ancuta E, Chiriac R, Pomirleanu C, Ancuta C, Revista de Chimie 2017, 68 (12): 2987-2991.

Paper 2: Volumetric Cone Beam Computed Tomography for the assessment of oral manifestation in systemic sclerosis Data from an EUSTAR Cohort

By: **Cristina Iordache**, Magda-Ecaterina Antohe, Rodica Chiriac, Eugen Ancuța, Oana Țănculescu, Codrina Ancuța, J. Clin. Med. 2019, 8, 1620; doi:10.3390/jcm8101620

Paper 3: Temporomandibular joint involvement in rheumatoid arthritis patients – correlations with disease activity and quality of life,

By: **Cristina Iordache**, Murariu Alice, Boariu Diana, Chirieac Rodica, Ancuța Codrina
Romanian Journal of Oral Rehabilitation 10, (3), 2018, 109-115

Paper 4: Temporomandibular joint involvement in rheumatoid arthritis and ankylosing spondylitis: a cross-sectional study

By: **Cristina Iordache**, Cristina Angela Ghiorghe*, Magda Ecaterina Antohe, Irina Esanu, Codrina Ancuta,

Roumanian journal of Oral Rehabilitation, 2017, 9(4), p 40-46.

OBJECTIVES

The aims of our research in TMJ pathology among rheumatic conditions were:

- to assess inflammatory and immune parameters in patients with TMJ arthritis related to rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) and to identify potential relation with severity and dysfunction of TMJ pathology (**Paper 1**);
- to assess oral radiologic manifestations associated with scleroderma using high-resolution CBCT and to identify potential relations with disease variables. (**Paper 2**);
- to assess symptoms and signs of temporomandibular joint involvement in patients with rheumatoid arthritis and to offer a complex outlook of the TMJ evaluation in routine practice in rheumatic patients (**Paper 3**);
- to identify potential relations between TMJ pathology (signs and symptoms) and disease activity, disability and impairment of quality of life in patients with inflammatory rheumatic conditions. (**Paper 4**);

MATERIALS AND METHODS

1st study: Immunobiological assessments of temporomandibular joint disease in patients with immune-mediated rheumatic conditions: a cross sectional study of 273 cases

We performed a **cross-sectional observational study in a cohort of 433 consecutive RA, 32 JIA, 258 AS, and 103 PsA** attending at least once the Rheumatology Department from January 2005 to July 2007.

TMJ disorder was identified by applying specific questionnaires enquiring about main complaints (e.g. pain and stiffness in the TMJ, articular sounds, bruxism, mouth opening derangement, restricted movements).

The assessment protocol included: (i) *inflammatory parameters* (ESR and CRP) performed in all patients; (ii) *immunological tests - rheumatoid factor* (RF by latex and Waaler Rose reactions; normal range 8-512 UI/mL), *anti-cyclic citrullinated peptide antibodies* (ACPA; ELISA; normal < 4.5 U/mL) in RA, *anti-nuclear antibodies* (ANA by ELISA, cut off value 1/80 U/mL) in RA and JIA; *Interleukin-1* (IL-1) in RA (ELISA, normal ≤10U/mL); (iii) *disease activity and disability scores* (DAS28-ESR and DAS28-CRP for RA; DAPSA for PsA; BASDAI and ASDAS-CRP for AS).

Data were compared with biological assessments registered in healthy controls.

The study was approved by the ethics committee board of Clinical Rehabilitation Hospital of Iasi, and subjects provided written informed consent before enrollment.

Statistical analysis was done in SAS 4.3 program (descriptive and analytical statistics including chi-squared, Pearson's correlation, Breakdown one way ANOVA in all the groups described above).

2nd study: Volumetric Cone Beam Computed Tomography for the assessment of oral manifestation in systemic sclerosis Data from an EUSTAR Cohort

We performed a **cross-sectional study** in a cohort of forty-three consecutive patients fulfilling either the old 1980 ACR (American College of Rheumatology) criteria or the recent 2013 ACR/EULAR (European League Against Rheumatism) classification criteria for SSc, attending at least once the outpatient rheumatology department (Clinical Rehabilitation Hospital of Iasi, Romania) during a twelve-month interval (January 2017–January 2018). Additionally, forty-three sex- and age-matching controls were recruited from patients addressing osteoarthritis at the same department.

Patients underwent rheumatologic and routine oral health evaluation; in addition, all individuals were referred for dental *radiographic evaluation*. All patients had a detailed radiologic analysis meaning conventional radiographs and an upper and lower jaw volumetric CBCT, focusing on the width of the periodontal ligament space and the **presence of mandibular erosions**.

The study was approved by the ethics committee board of Clinical Rehabilitation Hospital of Iasi, and subjects provided written informed consent before enrollment.

Statistical Analysis: Descriptive statistics were used for scleroderma parameters and radiologic manifestations of the patients with SSc and the controls. Nonparametric statistics (Spearman rank correlation; univariate and multivariate analysis adjusted for age, gender, and smoking status) were used to analyze the association between SSc and number of teeth with widening of the PLS and erosions. Mann Whitney U tests, Chi-squared tests, and Fisher's exact tests were used accordingly. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) v.20 IBM statistics (IBM Corp., Armonk, NY, USA) with p-values < 0.05 being considered statistically significant.

The study was approved by the ethics committee board of Clinical Rehabilitation Hospital of Iasi, and subjects provided written informed consent before enrollment.

Statistical analysis was done in SAS 4.3 program, $p < 0.05$; differences among groups were calculated using the Probability calculator for descriptive statistics, the χ^2 test, the Pearson "r" correlations and Breakdown one way ANOVA tests.

3rd study: Temporomandibular joint involvement in rheumatoid arthritis patients – correlations with disease activity and quality of life

We performed a **prospective observational study** in consecutive patients with different inflammatory and degenerative rheumatic conditions and secondary TMJ involvement, aiming to realise a complex (epidemiological, clinical, biological and imaging) characterization of TMJ pathology.

The final analysis *included 152 patients* fulfilling the 1987 ACR diagnostic criteria for rheumatoid arthritis and having TMJ involvement.

A multifaceted (rheumatologic and stomatologic) assessment was performed comprising the following parameters:

- *demographics*: gender, age, age of onset of RA as well as TMJ involvement;
- *RA-related parameters*: (i) *clinical* (tender and swollen joints on 28 evaluable joints, morning stiffness, pain on a 0-100 mm visual analogue scale) and *immunoinflammatory parameters* (rheumatoid factor, erythrocyte sedimentation rate - ESR and C reactive protein - CRP); (ii) disease activity score by DAS-28-ESR; (iii) *disability and quality of life* by *Health Assessment Questionnaire (HAQ-DI)*.

- *TMJ-related parameters* TMJ complaints were recorded by means of a questionnaire examining: *tenderness or pain in the joint area (arthralgia)* (ranging from slight tenderness to extreme pain on a VAS scale), *tenderness or stiffness in the TMJ, jaw and neck, muscle pain during use of the jaw* (chewing, etc.), *difficulty in opening the mouth*, a feeling that the jaw was stuck or locked, headaches .

We evaluated: *pain* (uni- or bilateral TMJ pain reported by patient or at palpation, with or without irradiation, mainly inflammatory subtype, associated with stiffness); *crepitations and articular sounds* mainly at mandible mobilization; masseter, temporal, pterigoidian muscular spasm. dental, gingival and occlusal status - partial or total edentation, with or without prosthesis; degree of dental mobility; gingival retractions; malocclusion.

The study was approved by the ethics committee board of Clinical Rehabilitation Hospital of Iasi, and subjects provided written informed consent before enrollment.

4th study: Temporomandibular joint involvement in rheumatoid arthritis and ankylosing spondylitis: a cross - sectional study

We performed a **cross-sectional observational study** in a cohort of consecutive patients with inflammatory rheumatic disorders (IRD) and TMJ-related arthritis, attending at least once the outpatient rheumatology department from January 2005 to July 2007.

152 patients with rheumatoid arthritis (RA; ACR 1987 diagnostic criteria) and *55 with ankylosing spondylitis* (AS; 1984 modified New York criteria) met the eligibility criteria (IRD with TMJ involvement at the time of examination) and were recruited for this study; supplementary, *33 healthy controls* also featured signs and symptoms related to TMJ involvement and were qualified to be included in the study.

TMJ complaints were recorded by using a regular questionnaire examining the following items:

- spontaneous muscle pain (visual analogue scale 0-10),
- muscle pain during use of the jaw (chewing) (present/absent),
- articular pain (present/absent),
- difficulty in opening the mouth (present/absent).

For RA we calculated disease activity by DAS28-ESR (Disease Activity Score on 28 evaluable joints using erythrocyte sedimentation rate) and *disability by HAQ* (Health Assessment Questionnaire)

AS activity was assessed by the *BASDAI score* (Bath Ankylosing Spondylitis Disease Activity Index), while disability was quantified by *BASFI* (Bath Ankylosing Spondylitis functional index)

The study protocol has the approval of the Ethics Committee and subject have signed the informed consent before enrolment in the study.

Statistical analysis was done in SAS 4.3 program (descriptive and analytical statistics including chi-squared, Pearson's correlation, Breakdown one way ANOVA in all the groups described above), $p < 0.05$

RESULTS

1st study: Immunobiological assessments of temporomandibular joint disease in patients with immune-mediated rheumatic conditions: a cross sectional study of 273 cases

Inflammatory and serologic abnormalities in RA

Acute-phase reactants were positive in more than half of RA with TMJ involvement (ESR 54.61%, CRP 56.58%).

Serology for RF and ACPA was positive in up to 80%: 72.37% RA were seropositive for RF, with high titres in more than half (63.16%); however, ACPA positivity was reported only in 40% of RA cases.

Serum IL-1 was randomly checked in 33 RA: 55% had very high levels, particularly if associated with severe active disease and secondary TMJ involvement (**Table 22**).

Table 22 Immuno-biological assessments in RA

ESR (mm/h)	Normal ESR		Moderate increased ESR		High ESR			
	N	%	N	%	N	%		
	8	5.26	61	40.13	83	54.61		
CRP (mg/dl)	Normal CRP			High CRP				
	N		%		N		%	
	66		43.42		86		56.58	
RF (UI/mL)	Absent		Positive		Important positive			
	N	%	N	%	N	%		
	42	27.63	14	9.21	96	63.16		
ACPA (UI/mL)	Absent			Present				
	92		60.53		60		39.47	
IL-1 (UI/mL)				33		100%		

Statistically significant correlation between duration and severity of TMJ arthritis and increased ESR ($r=0.278$, $p=0.001$), high RF levels ($r=0.274$, $p=0.001$), increased IL-1 concentrations ($r=0.264$, $p=0.001$) were demonstrated.

The link between RA synovitis (activity and severity) and CRP levels is well acknowledged; however, the association with TMJ arthritis severity was described only in several papers. We reported a positive correlation between TMJ pain and dysfunction and CRP levels.

Inflammatory abnormalities in AS

Up to 70% of patients with AS enrolled in our study had moderate to high ESR and about one third (30.90%) abnormal CRP levels (**Table 23**). In addition, patients with clinically symptomatic TMJ involvement had higher ESR vs. AS without TMJ pain (89.50% vs. 66.67%; $\chi^2 = 4.49$, $p=0.03$).

Inflammatory and serologic abnormalities in PsA

We demonstrated abnormal ESR in all subjects included in the final analysis, with 80% displaying high inflammation and one out of five only moderate increased ESR. In 67.27% cases we reported increased CRP, while one third was in the normal range (**Table 24**).

Table 23 Acute-phase reactants in AS

ESR (mm/h)	Normal ESR		Moderate increased ESR		High ESR			
	N	%	N	%	N	%		
	7	12.73	38	69.09	10	18.18		
CRP (mg/dl)	Normal CRP			High CRP				
	N		%		N		%	
	38		69.09		17		30.91	

Table 24 Acute-phase reactants in PsA patients

ESR (mm/h)	Normal ESR		Moderate increased ESR		High ESR	
	N	%	N	%	n	%

	0	0	9	20.45	35	79.55
CRP (mg/dl)	Normal CRP			High CRP		
	n		%		%	
	18		32.73		67.27	

Inflammatory and serologic abnormalities in JIA

ANA positivity was reported in about 30% of JIA particularly if polyarticular involvement. All JIA had raised ESR, 81.82% moderate increased ESR. Conversely, only 18.18% had high CRP concentrations (Table 25).

Table 25 Immunobiological assessments in JIA

	0	0	18	81.82	4	18.18
	0	0	18	81.82	4	18.18
CRP (mg/dl)	Normal CRP			High CRP		
	n		%		%	
	18		81.82		18.18	
ANA (UI/mL)	Normal CRP			High CRP		
	n		%		%	
	14		63.64		36.36	

Biological assessments in controls

Healthy controls with no inflammatory rheumatic pathology were widely (up to 90%) with normal ESR and CRP levels; however 9% had moderate increased ERS.

Comparative ESR analysis

Higher ERS levels were described in patients with TMJ arthritis related to PsA and RA as compared to those with AS and JIA (Table 26), with the highest ESR in PsA (60.98%) (Figure 2).

Table 26 ESR in studied group

RA (152)	46.54	19.82	12.0	105.0	43.36	49.72	1.61	.0001
AS (55)	33.75	14.69	13.0	105.0	29.77	37.72	1.98	.0000
PsA (44)	60.98	24.78	28.0	127.0	53.44	68.51	3.74	
JIA(22)	36.73	8.66	28.0	67.0	32.89	40.57	1.85	.0000
Controls (33)	14.27	4.11	6.00	23.00	12.82	15.73	.72	.0000

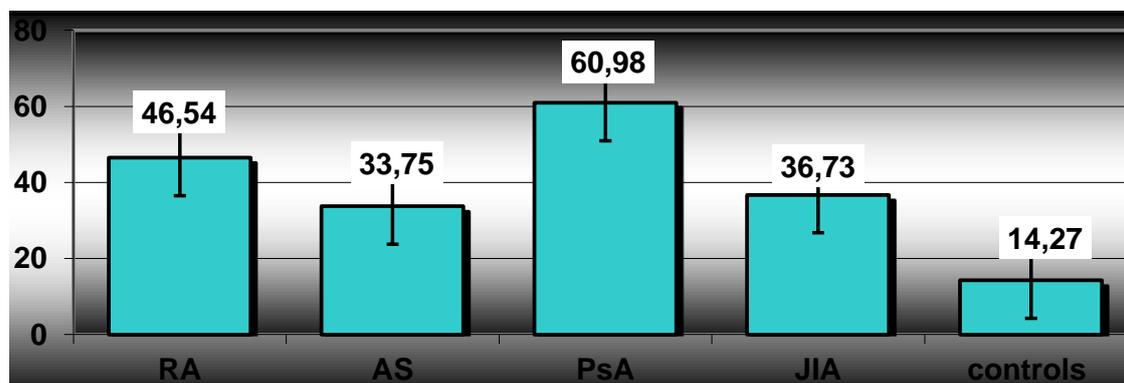


Figure 2 ESR in study groups and healthy controls

Detailed ESR analysis according to normal, moderate and high level categories was further proposed (Table 27, Figure 3).

Table 27 Detailed ESR analysis in rheumatic pathology

	Normal ESR		Moderate high ESR		High ESR	
	n	%	n	%	N	%
RA	8	*5.26	61	**40.13	83	*54.61
AS	7	*12.73	38	69.09	10	*18.18
PsA	0	*0	9	**20.45	35	79.55
JIA	0	*0	18	81.82	4	*18.18
Controls	30	90.91	3	**9.09	0	*0
p		.0000		.0003 .0000		.003 .0000.

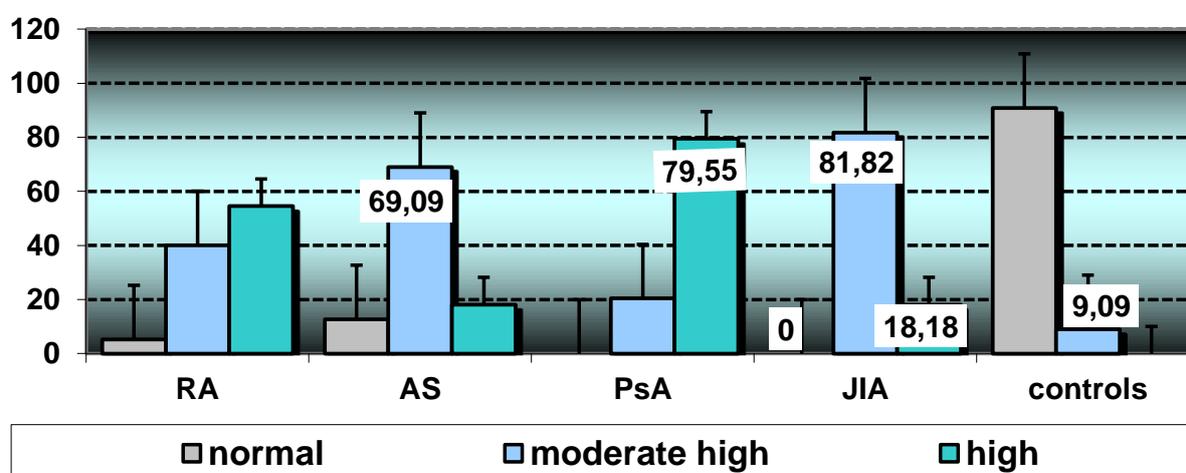


Figure 3 ESR in patients with TMJ involvement related to rheumatic disorders

Comparative CRP analysis

Finally, comparative data regarding CPR in various rheumatic disorders with TMJ arthritis are summarized in Table below, demonstrating significantly higher concentrations in RA and PsA; such patients are associated with potentially severe TMJ damage ($p < 0.05$) (Table 28).

Table 28 CRP in study groups

RA (152)	6.35	3.25	0.00	17.60	.26	5.83	6.87
AS (55)	5.93	1.90	3.50	14.20	.26	5.42	6.45
PsA (44)	6.58	1.77	4.50	12.60	.27	6.04	7.12
JIA (22)	*5.61	1.59	4.20	10.20	.34	4.91	6.32

2nd study: Volumetric Cone Beam Computed Tomography for the assessment of oral manifestation in systemic sclerosis Data from an EUSTAR Cohort

SSc-Related Characteristics

We enrolled 43 subjects with scleroderma as follows: mainly women (72%, $n = 31$), with a mean (SD) age of 43.95 (11.36) years and a mean (SD) disease duration of 8.7 (4.5) years; 67.74%

(n = 29) had diffuse disease, and 53.48 % (n = 23) were anti-topoisomerase 1 positive SSc; and the mean (SD) disease severity was 4.8 (2.1) (**Table 29**).

Table 29 Systemic sclerosis (SSc) related parameters, clinical, oral and radiographic features

Parameter	No (%) or Mean ± SD
Demographics	
Female	31 (72)
Age	43.95 (11.36)
Smoking status	10 (23.25)
SSc-related measures	
Diffuse cutaneous SSc	29 (67.74)
Disease duration	8.7 (4.5)
Modified RODNAN (0–51)	18 (10.1)
Facial skin score (0–3)	1.5 (0.7)
Serology	
Anti-SCL70	23 (53.48)
Anti-centromere B	10 (23.25)
Dental issues	
Missing teeth per subject	9.3 (4.5)
Teeth with periodontal disease	7.2 (3.4)
PDL space widening	
Patients with uniform PDL space widening	20 (46.51)
Apical PDL space widening (mm)	0.35 (0.16)
Erosions	
Patients with mandibular erosions	10 (23.25)
Number of subjects with condylar erosions	8 (18.60)

PDL = periodontal ligament.

Erosions

Additionally, erosions of the mandible were described in 23.25% (n = 10) of scleroderma cases (**Table 29, Figures 4 and 5**), with the majority of patients presenting with at least one condylar erosion; the mean (SD) number of sites with bone erosions was 0.42 (0.5).

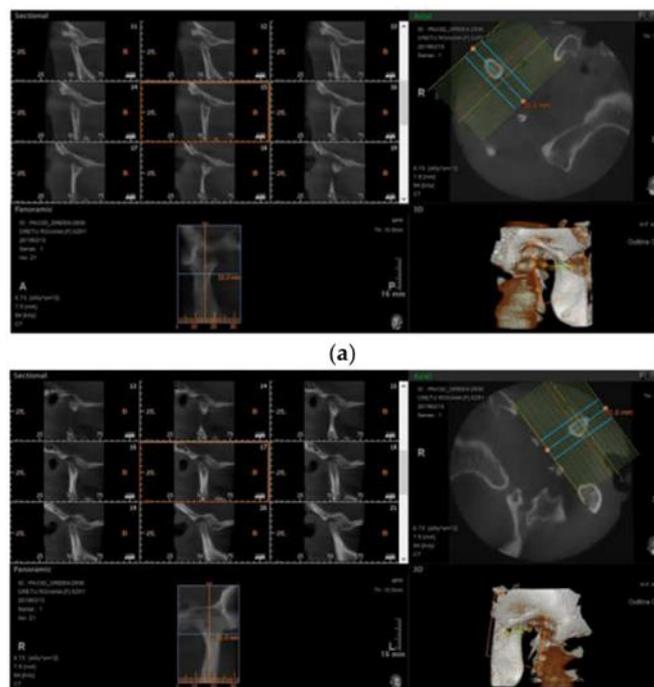


Figure 4 CBCT aspects of the (a) right and (b) left temporomandibular joint (TMJ).



Figure 5 CBCT aspects of the (a) right and (b) left TMJ.

Overall, patients with SSc had more mandibular erosions, irrespective of the locations (condyle, coronoid process, or otherwise) vs. controls (23.25%, $n = 10$ vs. 6.97%, $n = 3$, $p < 0.05$) as demonstrated by multivariate analysis (OR 5.32; 95% CI 1.87–11.74). However, the difference was significant only for the condylar erosions in patients with SSc compared with control (18.60%, $n = 8$ vs. 23.2%, $n = 1$; $p < 0.05$). It may be only because the changes in the condyles are easier to detect compared to the others, especially in the early stages. In addition, changes due to stomatognathic system dysfunction (malocclusion, edentulism, maxillo-mandibular malrelationship) may also be superimposed.

Associations with PDL Space Widening and Erosions

Subgroup analysis in scleroderma subjects with and without PDL widening and with and without erosions based on univariate analysis including clinical parameters and oral radiographic abnormalities were, further, done (**Table 30**).

Table 30 Associations between scleroderma-related parameters and oral radiographic abnormalities (univariate analysis)

Parameter	PDL Widening		Erosions	
	RR	p	RR	p
Demographics	1.1	$p > 0.05$	1.2	$p > 0.05$
Female	1.43	$p > 0.05$	1.1	$p > 0.05$
Age				
Smoking status	1.06	$p > 0.05$	1.06	$p > 0.05$
SSc-related measures				
Diffuse cutaneous SSc	1.25	$p > 0.05$	1.02	$p > 0.05$
Disease duration	2.36 *	$p < 0.05$	0.98	$p > 0.05$
Modified Rodnan (0–51)	3.12 *	$p < 0.05$	1.3	$p > 0.05$
Facial skin score (0–3)	2.71 *	$p < 0.05$	1.02	$p > 0.05$
SSc activity	1.21	$p > 0.05$	1.17	$p > 0.05$
SSc severity	3.09 *	$p < 0.05$	0.92	$p > 0.05$
Interdental distance	1.21	$p > 0.05$	3.51 *	$p < 0.05$
Dental issues				
Missing teeth per subject	1.02	$p > 0.05$	0.87	$p > 0.05$
Teeth with periodontal disease	1.15	$p > 0.05$	1.12	$p > 0.05$

RR, relative risk; PDL, periodontal ligament; * $p < 0.05$.

Significant correlations between number of teeth with PDL widening and MEDSGER disease severity score ($r = 0.702$, $p = 0.028$), RODNAN skin score ($r = 0.821$, $p = 0.01$), disease subset (diffuse vs. limited, $r = 0.782$, $p = 0.041$ vs. $r = 0.451$, $p = 0.05$, respectively), anti-topoisomerase I antibodies ($r = 0.568$, $p = 0.012$), age ($r = 0.872$, $p = 0.01$), and disease duration ($r = 0.811$, $p = 0.01$) were demonstrated. Moreover, the relative risk of PDL space widening in relation with different determinants of scleroderma severity are listed in **Table 31**.

For multivariate analysis adjusting for age, disease duration, gender, and smoking status, there were a significant association between the number of teeth with widened PLD and MEDSGER disease severity ($p < 0.05$) (**Table 32**).

Table 31 Associations between the number of teeth with PDL space widening and SSc severity

Parameter	RR	95% CI
Gender	2.17	0.91–14.28
Age	1.00 *	0.89–1.73
Smoking status	5.31	4.27–9.12
SSc duration	3.26 *	1.20–7.53
SSc subtype	4.51 *	2.39–8.14
RODNAN skin score	0.93 *	0.89–3.76
SSc severity	1.25 *	1.58–3.89
SSc activity	2.36	1.02–3.41
Anti-topoisomerase 1	5.22 *	2.3–7.67

RR, relative risk; 95% CI. 95% confidence interval; * $p < 0.05$.

Table 32 Correlations between the number of teeth with PDL space widening and number of teeth with periodontal disease

Parameter	RR	95% CI
Gender	2.17	0.91–14.28
Age	1.00	0.89–1.73
Smoking status	5.31	4.27–9.12
SSc duration	3.26 *	1.20–7.53
SSc subtype	4.51*	2.39–8.14
RODNAN skin score	0.93 *	0.89–3.76
SSc severity	1.25 *	1.58–3.89
SSc activity	2.32	1.45–3.22
Anti-topoisomerase 1	5.19 *	2.24–7.32
Number of teeth with periodontal disease	1.19	0.87–1.45

* $p < 0.05$.

Erosions were predominantly found in patients with aggressive scleroderma, especially related to the attachment of lateral pterygoids at the condylar head and masseter muscle at the angle of mandibula. Total resorption of the condylar head was reported only in one case (**Figure 6**).



Figure 6 CBCT-condylar lysis and condylar remodeling

3rd study: Temporomandibular joint involvement in rheumatoid arthritis patients – correlations with disease activity and quality of life

RA related parameters

Patients included in our study were, as expected, mainly women (135 RA), with a mean age of 47.44±18.43 years old (18-83), with both early (under 2 years from diagnosis) and established disease subtypes; the majority had seropositive RA (up to 85%) and 79% cases were classified in the 2nd and 3rd radiological stage.

A closer look to individual RA parameters revealed that 84.87% of cases presented with more than six swollen joints, while the great majority (94.74%) more than six tender joints. Moreover, 98% RA had at the study visit more than 10 affected joints (Ritchie index).

Therefore, it was not surprisingly that the majority has moderate disease activity (DAS28-ESR of 3.2-5.2), about one third (31.58%) active disease (DAS28-ESR>5.1), while only 2% were in remission (DAS28<1).

Physical function and quality of life were also significantly impaired: 38.82% RA had a HAQ score between 2.5 and 3 (severe disability); 46.71% moderate impairment (HAQ of 1-2.5), and 14.47% only mild impaired quality of life and disability (HAQ score<1).

TMJ involvement

- *Pain and stiffness* - Joint pain (spontaneous, at palpation, when moving the joint), muscle pain and morning stiffness were the most prevalent symptoms and signs of TMJ involvement in our cohort; more than half of RA featured TMJ stiffness (63.82%), TMJ pain (61.84%), pretragal pain at palpation (52.63%); one third (34.87%) had pain at palpation of the external auditory channel, while 32.25% had an anterior cervical radiation of pain and 29.61 in the cervical region.
- *Muscle pain and spasm* Muscle pain during use of the jaw (chewing, etc.) as well as palpation was reported in 53.29% for masseter muscle, 29.61% in temporal muscle and 40.13 in the pterigoidian one. Moreover, muscle spasm was also demonstrated – 11.84% for masseter, 57.24% for temporal and 28.95 for pterigoidian muscles.
- *TMJ sounds, bruxism and opening derangement*- Both TMJ sounds and bruxism were reported in our patients. Opening mandible derangement as well as restricted movement were also described in RA, including reduced mouth opening.
- *Dento-periodontal status* We were also interested in assessing the prevalence of dento-periodontal lesions in our patients, as the mutual disadvantage between the two segments of the stomatognathic system is widely recognized. Data are summarized in figure 4. Once,

descriptive statistics performed, we applied also several analytic tests (chi-squared, Pearson's correlations). We demonstrated that TMJ involvement significantly associated with more than 6 swollen joints ($\chi^2 = 4.78$, $p = 0.029$), more than 10 painful joints ($\chi^2 = 5.87$, $p = 0.015$); severe HAQ ($\chi^2 = 12.97$, $p = 0.0003$); high Ritchie index ($\chi^2 = 4.96$, $p = 0.02$).

4th study: Temporomandibular joint involvement in rheumatoid arthritis and ankylosing spondylitis: a cross - sectional study

RA and TMJ involvement

A total of 152 RA and TMJ arthritis were analysed. As expected, the majority were women (88.82%, 135 cases), mean age of 55.14±12.81 years (range between 20 and 83); about 79% had moderate to severe radiological damage; 94.74% of cases had more than 6 tender joints, while 84.87% more than 6 swollen joints; in addition, according the articular index Ritchie (including TMJ) known to define the aggressiveness of the disease, almost all patients (98%) presented with more than 10 affected joints. Data are summarized in Table 40.

According to the Steinbroker's classification, our patients had mild functional impairment in about 11.84% cases and moderate disability in 47.379% (inflammation), while 40.79% had severe joint damage with consecutive limited function (**Table 33**).

Table 33 Individual RA parameters

Stage I		Stage II		Stage III		Stage IV	
N	%	n	%	N	%	n	%
10	6.58	47	30.92	73	48.03	22	14.47
Swollen joint count				Tender joint count			
< 6		> 6		< 6		> 6	
N	%	n	%	N	%	n	%
23	15.13	139	84.87	8	5.26	144	94.74
< 10 joints (Ritchie index)				>10 joints (Ritchie index)			
N		%		N		%	
3		1.97		149		98.03	
Steinbroker functional capacity stage I		Steinbroker functional capacity Stage II		Steinbroker functional capacity Stage III & IV			
N	%	n	%	n	%		
18	11.84	72	47.37	62	40.79		

One third of our RA (31.58%) was in HDA at the moment of their rheumatologic appointment, more than half (66.45%) showed MDA, while only a very small percentage of patients (1.97%) fall into REM.

We arbitrarily considered mild disability if HAQ < 1, moderate for HAQ between 1 and 2.5, while severe disability correspond to a HAQ between 2.5 and 3. 38.82 % of our patients presented with significantly impaired quality of life (HAQ more than 2.5) and 46.71% with moderate disability.

Pain at digital palpation of the jaw muscles and TMJ are widely considered related to both inflammation and articular destruction; 52.63% of RA described pain at pretragus region palpation, while 34.13% at external auditory canal level. Pain was commonly described in the masseter muscle (53.29%) as well as medial pterygoid muscle (40.13%), and only in 29.61% was related to temporal muscles.

Muscle spasm was frequently identified in the temporal muscle (57.24%), 28.95% medial pterygoid and 11.84% of masseter muscle.

Further analysis revealed a significant association of TMJ pain with the number of involved joints (> 4 swollen joints; $\chi^2=4.78$, $p=0.029$; and > 10 tender joints, $\chi^2=5.87$, $p=0.015$), disability (HAQ >2.5; $\chi^2=12.97$, $p=0.0003$) as well as Ritchie index ($\chi^2=4.96$, $p=0.02$). Moreover, the absence of pain in TMJ was typically reported in those RA patients in remission according to DAS28-ESR.

• **AS and TMJ involvement**

We enrolled 55 patients with AS and TMJ-related arthritis. 80% were males, with mean age of 44.36±12.04 years (ranging between 20 and 80 years) and mean disease duration of 15.49±8.68 years (ranging from 2 to 44 years).

All patients had axial disease, and more than half (31 cases, 56.36%) developed peripheral arthritis. TMJ arthritis was reported typically in the third and fourth decade of our patients. Up to 55% cases presented severe sacroiliac joint involvement (ankylosis, stage IV), and about one third (34.55%) significant narrowing of the articular space (stage III sacroiliitis).

AS activity and severity were evaluated according to the internationally validated indexes BASDAI and BASFI, as summarized in **Table 34**. About half of cases (45.45%) had moderate disease activity, with BASDAI values of 5 or 6, 38.18% were in low disease activity, while 14.55 in high activity. In addition, BASFI covered moderate (49.09%) and high (30.9%) functional disability in a substantial proportion of patients.

Table 34 BASDAI and BASFI scores in AS patients

BASDAI (0-10)			BASFI (0-100)		
	n	%		n	%
Normal	1	1.82	Normal	4	7.27
Mild disease activity (3-4)	21	38.18	Mild disability (30-40)	7	12.73
Moderate disease activity (5-7)	25	45.45	Moderate disability (50-70)	27	49.09
High disease activity (8-10)	8	14.55	High disability (80-100)	17	30.91

Signs and symptoms of TMJ arthritis in AS are further described. 45.45% cases had unilateral TMJ involvement. The majority of AS patients (89.09%) had TMJ pain, 67.27% felt pain at palpation of the external auditory canal, 52.73% at palpation of pretragus region, 49.43% at mastication; finally, 32.73% AS featured also TMJ stiffness.

Extended analysis showed further associations between TMJ signs and symptoms and AS activity and functional scores (**Table 35**).

Table 35 BASDAI, BASFI and TMJ signs and symptoms

BASDAI	Pain at mastication	3.50	.02
	Pain at palpation of the external auditory canal	4.37	.008
	Pretragus region pain	3.23	.03
	Pain when closing mouth	3.24	.03
	Noises when opening mouth	2.87	.045
	Pain in the temporal muscle	6.67	.0007
	Spasm of the temporal muscle	2.91	.04
BASFI	Pain at mastication	6.19	.001
	Pain at palpation of the external auditory canal	3.41	.02
	Noises when opening mouth	3.17	.03
	Pain in the temporal muscle	3.70	.02

- *TMJ in controls*

33 subjects belonging to the control group were also analysed; 11 male (33.33%) and 22 female (66.67%), with mean age of 55.15±10.41 years (between 32 and 78). We included in the control group patients attending the rheumatology department for one of the following rheumatic conditions: sciatica (45.45%), acute low back pain (21.21%), cruralgia (12.12%), as well as chronic low back pain and fractures (forearm).

TMJ signs and symptoms were detected unilaterally in 21.22% cases; the majority of patients recruited in the control group (87.88%) presented pain at palpation of the pretragus region, 40% at the external auditory canal. All cases had *TMJ stiffness*. *Muscle pain* was also commonly registered at palpation of the masseter muscle (75.76%) and medial pterygoid muscle (42.42%), while muscle spasm involved frequently the temporal muscle (81.82%).

DISCUSSION

1st study: Immunobiological assessments of temporomandibular joint disease in patients with immune-mediated rheumatic conditions: a cross sectional study of 273 cases

It is widely accepted that patients with inflammatory chronic rheumatic conditions such as RA, AS, PsA, even JIA are characterized by high levels of TMJ involvement (O'Connor et al., 2017; Crincoli et al., 2015; Elslame et al., 2016; Mercuri et al., 2017; Niibo et al., 2016; Poveda et al., 2008). However, comparative immuno-biological assessments in a national cohort were never performed.

We systematically evaluated acute phase reactants in a consistent cohort of patients with chronic inflammatory rheumatic diseases, as well as immunological tests according to the diagnosis (RF and ACPA in all RA, IL-1 levels in a subgroup of RA, ANA for JIA).

We demonstrated that patients TMJ arthritis related to rheumatic disorders are commonly characterized by higher concentrations of inflammatory parameters vs. healthy controls.

RA patients tend to have more frequent and severe symptoms, signs and radiological TMJ damage vs. PsA and AS (O'Connor et al., 2017); however, we showed high ESR as well as CRP in both PsA and RA. On the other hand, AS and JIA had lower levels of systemic inflammation.

Moreover, we revealed statistically significant correlations between the duration and severity of TMJ involvement and high ESR, CRP, abnormal RF, positive ACPA and high IL-1 in RA. Data are not consistent in AS, PsA and JIA.

A detailed analysis of literature, also demonstrated associations between inflammation (ESR, CRP), immune tests (particularly RF), severity and RA duration and activity and severity of TMJ involvement in RA (O'Connor et al., 2017; Elslame et al., 2016; Voog et al., 2003).

Interestingly, patients with PsA and skin psoriasis are commonly describing TMJ issues (sounds, bruxism, mouth-opening derangements) (Crincoli et al., 2015), with a direct relation with duration and severity of rheumatic pathology; however, it seems that the extent and severity of skin involvement is not related to particular TMJ involvement (O'Connor et al., 2017).

2nd study: Volumetric Cone Beam Computed Tomography for the assessment of oral manifestation in systemic sclerosis Data from an EUSTAR Cohort

We performed a systematic 3-D analysis of the radiographic orofacial abnormalities associated with SSc, aiming to describe specific CBCT findings and to identify potential correlations with disease characteristics, activity/severity, or prognostic factors.

A systematic review of the literature addressing the impact of scleroderma on oral health has identified only a few studies having as endpoint the radiographic findings; moreover, the majority considered bi-dimensional panoramic radiographic assessment, and none of them focused on

interrelations between imaging parameters and disease characteristics (Jung et al., 2017; Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015, Baron et al., 2016; Yalcin et al., 2019; Savage et al., 2009; Jepsen et al., 2018; Jagadish et al., 2012).

On the other hand, we reported an increased frequency of mandibular erosions in about one out of four SSc (23.25%), particularly condylar erosions developed in the area of the lateral pterygoids muscle attachment to the bone (see figure). Our results are within the range reported from previous 2-D studies (7–10%); in fact, only one paper described a higher prevalence of mandibular angle involvement (83.33% cases) (Dagenais et al., 2015; Baron et al., 2014; Baron et al., 2015; Baron et al., 2016; Matsuda et al., 2018; Seifert et al., 1975).

However, the difference was significant only for the condylar erosions in patients with Ssc compared with controls ($p < 0.05$).

It is well established that mandibular findings in scleroderma include resorption of the angle, condyle, coronoid process, ascending ramus, and antegonial notch. However, complete condylar osteolysis and secondary mandibular resorption are only rarely documented (Dagenais et al., 2015; Baron et al., 2014, Baron et al., 2015, Baron et al., 2016; Jagadish et al., 2012). Abnormal muscle contraction with subsequent abnormal pressure on the bone via atrophic muscles at their attachment site, bone ischemia due to vasculitis and deposition of collagen in vascular wall, as well as rigidity and pressure from overlying skin are among the mechanisms likely involved in the emerge and persistence of bone erosions in SSc (Dagenais et al., 2015; Baron et al., 2014; Baron et al., 2015; Baron et al., 2016; Jagadish et al., 2012).

We described a significant negative correlation of mandibular erosions and interincisal distance, suggesting that abnormal local intraoral stress may be responsible for bone lesions; in addition, there was no relation with disease activity and severity. Condylar erosions were associated with clinical signs and symptoms of TMJ involvement, but this was not valuable for erosions with other location.

Our study has some limitations, e.g., the number of recruited patients, the evaluation of radiographs by only one expert, and associated multiple oral pathologies.

The quality of the images obtained is of paramount importance. There is a greater probability of correctly identifying and measuring fine structures like lamina dura and PDL when the image is acquired using the smallest voxel resolution parameters. On the other hand, a compromise has to be made in order to reduce patient exposure to X-rays by a shorter scanning time, using protocols that offer the same performances. In our study, the 0.4 mm voxel size was used for TMJ images, allowing a qualitative analysis, and 0.12 mm voxel size was used for PDL space measurements, allowing a quantitative evaluation

3rd study: Temporomandibular joint involvement in rheumatoid arthritis patients – correlations with disease activity and quality of life

Various papers highlighted increased prevalence of TMJ symptoms and signs in patients with inflammatory rheumatic disorders such as rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis.

We evaluated a cohort of consecutive RA patients attending one academic rheumatology department applying a validated questionnaire enquiring about TMJ involvement: tenderness or pain in the joint area (arthralgia); muscle pain, ranging from slight tenderness to extreme pain (VAS scale); joint and/or muscle pain during use of the jaw (chewing, etc.); joint stiffness; difficulty in opening the mouth. In addition, we were also interested in assessing the dental and periodontal status in our RA patients.

The results of the present study showed that TMJ involvement was unusually reported in different RA subtypes. Interestingly, the presence of TMJ issues was significantly associated with several individual RA parameters defining disease activity such as tender and swollen joints and also with disability and impaired life quality as suggested by high HAQ scores.

Indeed, we haven't performed a dynamic analysis of TMJ involvement in RA and we haven't assessed the value of different drugs (either synthetic or biologic medication) on TMJ pathology in our cohort. But we clearly emphasized the importance of TMJ contribution for the clinical picture of our patients as well as additional disability and compromised health-related quality of life in RA.

4th study: Temporomandibular joint involvement in rheumatoid arthritis and ankylosing spondylitis: a cross - sectional study.

Comparative analysis of RA, AS and controls

A complex clinical as well as lab assessment of the TMJ, dento-periodontal and specific evaluation of the RA and AS was carried out and materialized our research database.

Pain, a cardinal symptom of musculoskeletal pathology with precise connotations in IRD was systematically analysed highlighting TMJ involvement in our patients.

We studied the potential impact of TMJrelated arthritis on disease activity and disability in patients with RA or AS.

Definitely, patients with inflammatory rheumatic disorders and TMJ involvement experience significant levels of activity and functional impairment, with subsequent influence on health-related quality of life. Therefore, we found that about 90% of RA subjects and near 80% of those diagnosed with AS had moderate to high level of disability (**Table 36**).

Table 36 Functional capacity in studied patients with AR, AS and controls

Study groups	Level of disability					
	I		II		III	
	N	%	N	%	N	%
RA	18	11.84*	72	47.37	62	40.79*
AS	13	23.64	16	29.09*	26	47.27
Controls	10	30.3	10	30.3	13	39.39

Mild disability (level I) was described significantly more frequent in the control group (p =0.006, 0.008); moderate health impairment (level II) was found significantly more frequently in AR patients (p=0.02, 0.001), and higher degree of disability (level III) was also significantly more common in AR (p = .045).

In order to establish significant variations in the TMJ damage index according to the factors included in the study, we proceeded to ANOVA one way analysis; table below summarizes variables with statistical significance (Snedecor F coefficient, p<0,05) (**Table 37**).

Table 37 HAQ and clinical TMJ signs and symptoms (ANOVA)

HAQ	TMJ pain	F	p
	Pain at mastication	3.47	.03
	VAS TMJ pain	10.75	.00004
	Pain radiating to the cervical posterior region	3.52	.03
	Progressive course	4.42	.01
	TMJ stiffness	11.32	.00003
	Pain at palpation of the pretragus region	5.81	.004
	Pain when opening the mouth	7.12	.001
	Pain when closing the mouth	5.79	.004

	TMJ sounds when opening the mouth	4.99	.008
	Pain at masseter muscle palpation	4.70	.01

CONCLUSIONS

We concluded that:

- TMJ involvement is traditionally described in chronic inflammatory rheumatic disorders, mainly in patients with higher levels of inflammation as detected in RA and PsA. Disease activity and severity, as well as biological and serological assessments (RF, ACPA, IL-1) represent significant determinants of the severity of TMJ arthritis (**paper 1**);
- volumetric CBCT performance in assessing PDL space widening and mandibular erosions in patients with SSc shows promising results. Furthermore, PDL space widening as well as mandibular erosions are commonly reported in scleroderma and correlated with different disease characteristics especially severity, skin extent, and antibody profile. Future studies could investigate the pattern of PDL widening at different root heights and in different oral disease context (**paper 2**).
- TMJ issues are commonly described among patients with different RA settings, comprising orofacial pain (joint and muscle pain), stiffness, sounds and opening derangement. Moreover, the stomatognathic system status may also be impaired during RA, particularly in patients with established and advanced disease. TMJ pathology remains a major cause of altered quality of life in patients with chronic inflammatory rheumatic conditions such as RA (**paper 3**).
- TMJ involvement is commonly reported in patients with rheumatoid arthritis and ankylosing spondylitis and account for high levels of disability and impaired healthrelated quality of life. Pain (articular, jam muscle), TMJ stiffness, restricted motions, TMJ sounds as well as opening derangements remain major clinical signs and symptoms of TMJ arthritis as a result of both inflammatory and destructive damage of the articular and soft tissue lesions. TMJ arthritis significantly correlates with disease activity and disability not only in rheumatoid arthritis but also in ankylosing spondylitis, requiring a complex management (**paper 4**).

DIRECTION 2

ERGONOMICS AND MUSCULOSKELETAL DISORDERS IN DENTISTRY

STATE OF THE ART

It is well defined that the musculoskeletal system remains the support of movement, the main expression of life in this context; thus, a broad range of articles have already addressed the significance of the musculoskeletal system, its physiological role but also its potential involvement in different inflammatory, degenerative and mechanic rheumatic and non-rheumatic disorders.

Its integrity as well as a harmonious development ensures balance, movement, contact with the external environment, offering personality to the human being. Furthermore, professional personality, but also artistic and sports are the main strengths of the locomotor system permanently guided and controlled by the nervous system.

On the other hand, clearly our professional behavior is able to shape our personality and dentistry may be considered an environment in which locomotor activity is expressed at high levels. Accuracy, strength, performance, insufficient or inappropriate equipment, inappropriate work area design and work in a restricted space, continuous manual activity, direct injuries,

vicious positions maintained for long periods of time (such as sitting for extended times with a flexed and twisted back) as well as repetitive movements from working with dental instruments are several factors that express activity in this field (Kumar et al., 2020; Nissi et al 2020; Ohlendorf et al.,2020; Sultana et al., 2017).

All segments of the musculoskeletal system may be, potentially, involved, but especially the cervical and lumbar spine as well as the upper limb, particularly the hand, but also shoulder.

Scientific research in recent years highlighted the fact that dentistry is able to induce occupational hazards leading to a complex pathology that categorically influences the quality of life of dentists, efficiency and results of their professional activity.

According to the World Health Organization (WHO), musculoskeletal disorders (MSDs) comprise a broad spectrum of chronic conditions involving muscles and tendons as well as peripheral and axial joints, intervertebral discs, peripheral nerves and vascular system related leading to a chronic and progressive impact of the quality of life.

Generally speaking, the group of MSDs comprise a spectrum of inflammatory and degenerative conditions clinically expressed as upper and lower back pain related to herniated disc or spine osteoarthritis, neck pain with or without cervical root problems, carpal tunnel syndrome, tenosynovitis, bursitis, tendinitis and synovitis, shoulder pain related to rotator cuff tendinopathies and repetitive strain injuries. Chronic pain, muscle spasm, vicious spine posture, impaired spine mobility and fatigue are the main signs and symptoms related to musculoskeletal involvement, with subsequent impaired quality of work and, even, quality of life. (Ohlendorf et al., 2020).

MSD developing among different professional categories including dentists represent a very exciting field of MSD considered as multifactorial disorders; abnormal posture and repetitive movements eliciting for a wide range of complaints that occur among dentists have increased over the last decade, leading to significant work-related health issues, particularly expressed at the musculoskeletal level. Overall, musculoskeletal disorders in dentists are commonly reported and related to high rates of temporary or permanent disability, reduction in the production capacity, with a negative impact on the quality of life (QoL) and absenteeism (Berdouses et al., 2020; Lietz et al., 2018; Saliba et al., 2016).

- *Prevalence of musculoskeletal disorders in dentists*

There is no doubt about the *high prevalence of MSD among dentists ranging from 64 to up to 98%* (Aljanakh et al., 2015; Kalluri et al., 2018; Lietz et al., 2018; Nokhostin et al., 2016). The most common sites for MSDs are typically the spine - cervical and neck pain (19.8–85%), but also lumbar spine (36.3–60.1%) and all the joints of the upper limb – shoulders (17%), elbows, with the highest prevalence in wrists, and hands (60–69.5%) (Berdouses et al., 2020; Haas et al., 2020; Meisha et al., 2019; Moodley et al., 2018). Higher rates of musculoskeletal complains were reported by older and more experienced dentists (Meisha et al., 2019), while dental hygienists commonly present with hand and wrist pain (Harris et al., 2019). A more detailed analysis showed that the rates of neck and shoulder work-related issues were very high for all types of dental workers, as follows: 66% of dental hygienists, 41% of dentists, 30% of assistants and 30% of students reported neck pain, whereas 53%, 30%, 24% and 11%, respectively, reported shoulder pain (Harris et al., 2019; Kalluri et al., 2018; Moodley et al., 2018; Ng et al., 2016).

Overall, all the categories of oral health professionals starting from dental hygienists, periodontists, orthodontists, endodontists dental surgeon, dental assistants, dental laboratory technicians, and ending with students and trainees in dentistry will somehow suffer from work-related musculoskeletal pathology (Lietz et al., 2018). Lietz et al conducted a meta-analysis of MSD prevalence among oral health practitioners and reported 11% to 98% involvement.

Interestingly, a more detailed analysis has also focused on specific musculoskeletal signs and symptoms in various categories of dental practitioners; thus, it seems that *dental hygienists and periodontists* are predisposed to develop neck, shoulder, and wrist pain largely due to the static

postures combined with forceful, repetitive movements adopted while performing procedures (Harris et al., 2019). In addition, due to the repeated forward positioning of head and bending of low back during clinical procedures, *orthodontists* seems to be more predisposed to develop low back pain, while a significant proportion of *dental surgeons* (67.5%) had different musculoskeletal problems, especially in their neck and cervical spine (51.9%), wrist (93.0%), waist (11.1%) and shoulder (7.4%) (Kalluri et al., 2018; Meisha et al., 2019; Nokhostin et al., 2016).

It seems that MSDs complaints are commonly reported early in the career of a dentist, with a high prevalence occurring in students during training as the number of practice hours increased. (Kalluri et al., 2018). Furthermore, there is a direct correlation between the prevalence of work-related musculoskeletal issues and the practitioner age (Berdouses et al., 2020; Ohlendorf et al., 2020; Lamia, 2017), with higher prevalence among female practitioners, particularly for neck and wrist pain (Lamia, 2017). However, the explanation was that increased MSDs frequency may be related to the fact that women were more concerned about their health compared to men and tended to report health problems more often (Puriene et al., 2008).

- *Causes of musculoskeletal disorders in dentists*

Several risk factors for the development of MSD's as work-related pathology are already recognized (Petrović et al., 2016; Hodacova et al., 2015); static posture and abnormal incorrect postures in dental practitioners during working hours (87.5%), repetitive movements (68.8%), muscle imbalances and individual characteristics including a sedentary lifestyle and obesity (43.8%) (Petrović et al., 2016; Haas et al., 2020; Ohlendorf et al., 2020). Different abnormal postures may be encountered in the dental office including excessive bending of the operator's head and the extent of neck, rotation, and tilting of the head, trunk inclination and rotation towards one side, increased curvature of the thoracic vertebral column and the lumbar curvature reduction, arms in an elevated position (more than 30 degrees) without enough support on the trunk or on the arm support may, and incorrect positioning of the lower limbs with thigh-leg angle of less than 90°.

Abnormal postures during working hours with excessive bending of the operator's head and the extent of neck, rotation, and tilting of the head account for a high biomechanical stress on cervical spine vertebrae that are not able to properly support the spine; cervical and upper thoracic spine muscles must, therefore, contract frequently to support the weight of the head in the forward posture.

Persistent, even low level contraction of cervical muscles may be involved in weakening of the spinal disks, eventual disk degeneration or herniation; in addition, muscle imbalance may also cause an abnormal shoulder posture. All these abnormal postures of the spine and shoulder and abnormal muscle contraction/ tension will generate a high amount of chronic persistent pain expressed as cervical spine and neck pain, tension neck syndrome, headaches accompanied by chronic pain in the neck, shoulders, as well as interscapular muscles, with significant impaired quality of life.

Furthermore, dentists are affected by various degrees of impingement syndrome particularly related to supraspinatus tendon involvement (Kalluri et al., 2018; Meisha et al., 2019); in fact, prolonged arm abduction which may result in chronic pain and trigger points in the upper trapezius muscle; the abnormal static posture of the arms in an elevated position (more than 30°) without enough support on the trunk or on the arm support may hamper the blood flow to the supraspinatus muscle and tendon (Harris et al., 2019).

- *Prevention of MSDs in dentistry*

The increased incidence of MSDs among dentists has led to multiple researches and especially in multidisciplinary collaboration. Ergonomics has made an essential contribution in highlighting these data as well as in the elaboration of preventive programs.

Known as the science of designing jobs, equipment and workplaces to fit workers, ergonomics also realizes the study of people at work and is commonly used in many fields of

medicine, particularly in dentistry in order to prevent the so-called work-related health issues. The main aim of ergonomics remains “to achieve the best mutual adjustment of man and his work, for the improvement of human efficiency and well-being”; a closer look can emphasize the role of ergonomics to avoid MSDs and soft tissue damage produced by acute or chronic exposure to problematic posture, force, repetitive motion, and vibration (Park’s, 2015).

Thus, different programs to improve professional performance and reduce professional impact was proposed. The design of the instruments has also improved, new rules were used in the activity of the dentist, preventive programs were introduced, while the technology and the instruments were reconfigured.

Besides, redesigned tools and instruments with a new ergonomic designed are usually promoted to ameliorate the frequency and prevent musculoskeletal complaints; modern equipment is able to improve posture and decrease neck/back pain as well as hand pathology in dentists.

All these implementations aimed not only to improve the dentist work-related health issues and quality of life but also address patient needs by reorienting his position in the dental chair (headrest, patient chair) and also the environment of the office regarding light, noise, color. Different authors have already suggested that MSDs can be reduced through a proper positioning of both dental practitioner and patient, but also by using regular rest breaks and exercises designed to counteract the particular risk factors for dentists (Haas et al., 2020; Meisha et al., 2019; Sultana et al., 2017).

Given my direct concerns in the field of ergonomics, I was concerned about achieving the most fertile connection in the theory-practice relationship and I paid attention to the ability of ergonomics to perfectly connect the musculoskeletal system with the content of the professional activity of the dentist. Thus, I focused on the analysis of risk factors generated by the professional activities, on the implementation of preventive measures and on the awareness of dental students for what professional risk means.

In this context we have organized and consolidated an interdisciplinary team consisting of trained dentists, rheumatologists, orthopedist and physiotherapists whose role in the diagnosis and treatment of occupational disease is consistent.

My scientific research was carried out in the field of spine and of the upper limb, especially of the distal segment (hand) in different settings of dental practice.

The results of our work in this direction were disseminated in various scientific meetings (in dentistry and also rheumatology), published in ISI and journals indexed in other international database (IDB) publications taking into account two subthemes as follows:

- *Cervical and lumbar spine pathology in dentists (item I.2.1.);*
- *Hand pathology (item I.2.2.).*

1.2.1. CERVICAL AND LUMBAR SPINE PATHOLOGY IN DENTISTS

The spine as a whole is a structure with a particular functionality acting as a support element for the head, trunk, limbs, with ample mobility in the context of a well-defined stability. The posture of resistance and at the same time of balance of the vertebral segment is the one that respects the three curves, the cervical and lumbar lordosis and the slightly kyphotic back. This neutral position must be approached frequently during both professional and extra-professional activity.

The mobility of the spine is considered to be wide (flexion more than 90°, extension about 25° as well as rotation and laterality). The engagement of the axial segment in the professional activity sometimes for long periods of time determines pressure phenomena at the level of the discs as well as muscular imbalances between the anterior, posterior, short intervertebral and long interregional groups.

The latest research in the field of vertebral biomechanics draws attention to the lower dorsal and lumbar segment which has been called core stability, an aspect that is achieved through the exclusive contribution of the flexor and extensor muscles of the area. By their contribution, the curvature and a reduced pressure on the spine are maintained, because the firmness of the abdominal muscles offers a positive pressure in the thoraco-abdominal cavity. Educating this segment by increasing the muscle tone mentioned leads to an improvement in the behavior of the spine so required by the professional act of dentistry. An awareness of the dentist on these issues and the introduction of muscle training in daily practice will produce positive effects with increasing professional performance and decreasing the incidence of spinal disorders.

The professional activity in dentistry particularly demands the vertebral axis, even if the activity is consumed mainly in a sitting or orthostatic position. The spine in both conditions works in loading which influences the intervertebral discs, the vertebral arches, the interapophyseal joints and of course the vertebral body.

The cervical spine but also the lumbar spine are the most exposed regions, the first because vicious positions of the head and of course the spine during routine practice. The lumbar region is also the subject of excessive pressures and stress because of both in the seated and orthostatic position, the column exerts the motor control of the entire axis.

PERSONAL RESEARCH

My personal research in this exciting field of ergonomics and work-related spine pathology comprises the following:

Nine articles published in IDB journals;

1. **Cristina Iordache**, Scutariu M, Ancuta Codrina, Preventia afectiunilor coloanei vertebrale la medicii dentisti, Rev Med Chir Soc Med Nat Iasi 2010 apr-jun, 114 (2): 571-76.
2. **Cristina Iordache**, Ancuța C, Chirieac R, Surlari Z, Influence of posture adopted by dentist on spine, Proceedings of the International Congress of the Romanian Dental Association for Education, 27 April-1 may, 2010.
3. **Cristina Iordache**, Ancuța C, Ancuța Eugen, Tanculescu O, Surlari Z, Posture and vertebral pathology issues in dental practice, Romanian Journal of Oral Rehabilitation (RJOR) 2012, 4 (1): 74-79.
4. **Cristina Iordache**, Fatu Ana Maria, Ignat Raluca, Pomârleanu Cristina, Chirieac Rodica, Codrina Ancuța, Musculoskeletal complains among dentists: focus on cervical spine involvement, Roumanian journal of Oral Rehabilitation, 2016, 8(4), 5-11.
5. Ancuța Codrina, **Cristina Iordache** *, Fatu Ana Maria, Aluculesei Cirprian, Forna Norina, Ergonomics and prevention of musculoskeletal work related pathology in dentistry: a pilot study, Roumanian journal of Oral Rehabilitation, 2016, 8(4), p 73-78.
6. **Cristina Iordache**, Fătu Maria Ana, Miftode Mădălina, Ancuța Codrina, Forna Norina, Musculoskeletal issues among dental medicine students: a cross-sectional study, Roumanian journal of Oral Rehabilitation, 2016, 8(3), p 65-71,
7. **Cristina Iordache**, Ana Maria Fatu, Antoanela Beldiman, Zinaida Surlari, Irina Bîrsan, Codrina Ancuta, Ergonomics and work related musculoskeletal conditions in dentistry, Romanian Journal of Oral Rehabilitation 10 (2), 2018, 105-112
8. **Cristina Iordache**, Magda Ecaterina Antohe*, Cristina Gena Dascalu, Rodica Chirieac, Codrina Ancuta, Ball Chair vs. Classic Office Chair in Dentistry: A Pilot Study, Journal of Dentistry and Oral Biology, 2020, 5 (1).
9. **Cristina Iordache**, Ana Maria Fătu*, Alice Murariu*, Zenaida Surlari, Ioana Cicu, Magda Ecaterina Antohe, Cristina Pomârleanu, Codrina Ancuța, The implications of ergonomics in classical and modern approaches in endodontic therapy, Romanian Journal of Oral Rehabilitation, 2020, 12 (1), 133-141.

Three book chapters published in the publishing house of our university (UMF Gr.T. Popa publishing house Iași), in collaboration with two distinguished professors of rheumatology in our university, prof. Codrina Irena Ancuța and prof. Rodica Marieta Chirieac; the chapters are:

- 1). “Aspecte ale patologiei musculoscheletale la medicul dentist”,
- 2).”Kinetoterapia – mijloc de prevenire a patologiei musculoscheletale la medicul dentist”,
- 3). “Incidenta și prevalența patologiei musculo-scheletale la medicii dentist și implicarea factorilor de risc profesionali”.

I have to emphasize the “**Musculoskeletal Pain Academy**” **project**, a multidisciplinary educational grant funded by the *International Association for the Study of Pain (IASP) Developing Countries Project: Initiative for Improving Pain Education 2011*; working as a member in an interdisciplinary team really helped me in my training as a researcher in the field, at the same time providing the optimal framework for the materialization of the concept of interdisciplinarity. The project took place under the auspices of the University of Medicine and Pharmacy "Grigore. T. Popa" Iași, within the “Gr.T.Popa” Center for Biomedical Research - European Center for Translational Research, Department of Pain Study. Essentially, we can consider this project as an initiative to increase the educational level in the field of pain, emerged in the organization and implementation of a web program dedicated to musculoskeletal pain.

The decision to address the field of musculoskeletal pain is based on the fact that pain and especially musculoskeletal pain remains an important issue of modern society, not only as a result of epidemiological indicators and pathophysiological and clinical aspects but also due to high socio-economic costs. The multifaceted etiology of different sub-types of musculoskeletal pain (joint, muscle, bone or generated by the suffering of abarticular soft tissue) affects the pathogenic mechanisms, clinical expression, methods of evaluation and monitoring and therapeutic options.

Therefore, we performed a series of cross-sectional, analytical and observational studies on the musculoskeletal risk factors in the field of dentistry. *We were interested in performing not only a descriptive assessment of MSD issues in relation to routine practice in dentistry, but also to assess the role of ergonomics in preventing the development and severity of musculoskeletal issues among dentists.*

Thus, the purposes of all the work undertaken in direction of musculoskeletal disorders were:

- to describe work-related cervical spine complains and to perform an electromyographic analysis of cervical muscles during specific working activities in dentists;
- to identify the risk factors and their consequences on the cervical spine in a cohort of dental practitioners who are currently involved in endodontic therapy;
- to investigate the prevalence of musculoskeletal complains, especially cervical spine involvement, among dentists;
- to systematically evaluate the frequency of self-reported musculoskeletal complains among students in dentistry, and to identify potential risk factors;
- to evaluate whether using a new-designed ball-chair is associated with better outcomes (concerning pain, fatigue, muscles’ activation in the lumbar spine) than the classic ergonomic chair among dentists.

I had the opportunity to publish together with my team preliminary results in journals indexed in international database. I will further present the main aspects and published results.

Paper 1 **The implications of ergonomics in classical and modern approaches in endodontic therapy**

By: **Cristina Iordache**, Ana Maria Fătu*, Alice Murariu*, Zenaida Surlari, Ioana Cicu, Magda Ecaterina Antohe, Cristina Pomîrleanu, Codrina Ancuța, **Romanian Journal of Oral Rehabilitation**, Vol. 12, No. 1, 2020 133-141.

Papers 2 Musculoskeletal issues among dental medicine students: a cross-sectional study,

By: **Cristina Iordache**, Fătu Maria Ana, Miftode Mădălina, Ancuța Codrina, Forna Norina,

Romanian journal of Oral Rehabilitation, 2016, 8 (3), p 65-71,

Papers 3 Ball Chair vs. Classic Office Chair in Dentistry: A Pilot Study,

By: **Cristina Iordache**, Magda Ecaterina Antohe*, Cristina Gena Dascalu, Rodica Chirieac, Codrina Ancuta, **Journal of Dentistry and Oral Biology**, 2020, 5 (1).

OBJECTIVES

The aims of our research on spine pathology developing in dentists related to their professional work were as follows:

- to identify the risk factors and their consequences on the cervical spine in a cohort of dental practitioners who are currently involved in endodontic therapy (**paper 1**);
- to systematically evaluate the frequency of self-reported musculoskeletal complains among students in dentistry, and to identify potential risk factors (**paper 2**);
- to evaluate whether the ball-chair is associated with better outcomes (concerning pain, fatigue, muscles' activation in the lumbar spine) than ergonomic chair among dentists. (**paper 3**).

METHODS

1st study: The implications of ergonomy in classical and modern approaches in endodontic therapy

We included 30 dentists who worked daily in private offices in Iasi and in the Iasi county area. They were classified as belonging to group A or B based on specific ergonomic criteria (the type of chair used by the dentists, 4/6 hands work, the use of magnification systems, the use of tooth isolation systems - the dental dam, the preparation of endodontic ducts using the rotary instrument): *Group A* included participants fitting in the ergonomic design; and *Group B* referred to the nonergonomic parameters meaning subjects working in the "classical" way, without any ergonomic facilities.

A standard questionnaire was applied to all participants and based on their answers we defined the two study groups; we recorded the following data:

1. *general parameters*: participant ID, age (years) and gender;
2. *anthropometric data*: height (cm), weight (kg);
3. *professional data* including:
 - number of working hours daily / number of working years meaning the professional experience;
 - usual working position (standing/ sitting)
 - type of chair used at work: with lumbar support/without lumbar support
 - team-work or individual work; No /4 handed dentistry /6 handed dentistry
 - different magnifying systems used at work: Yes/ No
 - rubber dam as a means of isolating the operator field: Yes / No
 - modern rotary tools during endodontic therapy: Yes/No /Occsionally
4. *clinical data*:
 - pain in the cervical region: Intensity (severity)/location/irradiation; pain character: acute /chronic.
 - type of onset: insidious/abrupt; at the beginning of the work day/at the end of the day.

- pain extent beyond working hours: Yes/No
- factors improving pain: rest/spine exercise; (gymnastics)/pain killers.
- concomitant complains: distal paresthesia in the upper limb; muscle spasm; decrease in muscle strength in the upper limb.

5. *paraclinical data:*

- radiological assessment of the cervical spine in order to prove the cervical spine pathology as the main etiology of the mechanical pain felt by the participants in our study.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

Statistical analysis was done in SPSS-19 software, with p settled <0.05 .

2nd study: Musculoskeletal issues among dental medicine students: a cross-sectional study

We performed a cross-sectional study on 100 consecutive students in dentistry (School of Dentistry, University of Medicine and Pharmacy „Grigore T. Popa” Iasi) during 2014 and 2015. Participants were classified in two equal groups according to their direct involvement in specific professional activities, as follows:

(i) group A, 50 students in their 1st and 2nd year of study, not yet engaged in working with patients and (ii) group B, 50 students in the 3rd, 4th, 5th and 6th year of study, directly engaged in professional working.

A questionnaire survey applied in all cases, designed into three parts:

- **first part** - *general health and demographics* (student ID, year of study, gender, weight, height, alcohol consumption, smoking habit);
- **second part** - dedicated to *risk factors for musculoskeletal work-related pathology* such as: working hours, type of activity, working position and chair type, type of dental instrument; and
- **third part** – *musculoskeletal complains* meaning pain (presence, location, intensity and severity) and muscle spasm

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

Statistical analysis was performed using the SPSS-19 program, both descriptive and analytic tests being applied.

3rd study - Chair vs. Classic Office Chair in Dentistry: A Pilot Study

We performed a pilot study on a sample of 50 dentists classified in two groups based on their work with either the classic ergonomic chair with an adjustable lumbar support (*group A, 30 cases*) or the novel gym-ball chair in routine dental practice (*group B, 20 cases*).

Group A comprised dentists who work exclusively on classic ergonomic dental units and group B enrolled dentists working on a ball type dental chair.

Both groups practiced general dentistry, comprising maneuvers of dental prostheses, from the classic approach to the modern, minimally invasive one, odontotherapy, endodontics and certain maneuvers of dento-alveolar surgery, in agreement with the existing competences for this type of training. Dentists with a history of vertebral pathology spine, with abdominal surgery as well as neurological diseases were excluded, in order to avoid the interference with the potential symptoms related to labor strains.

An Electromyography using a flat electrode was done in all dentists in both groups; paravertebral and abdominal muscles were tested twice, at the beginning and end of the workday as well. As objective methods we used electromyography with flat electrodes, whose route was

subsequently analyzed in corroboration with the specificities of each analyzed group, a valid method for the analysis of the muscular status investigated for both groups of dentists.

In addition, *a specific questionnaire* was applied in all cases, derived from the Cornell musculoskeletal discomfort questionnaire evaluating the sitting discomfort and working performance; we focused on two main items that reflect the level of comfort or discomfort (item 1) and low back pain on a visual analogue scale of 0 cm to 10 cm (item 2). The subjects' answers were evaluated using the contingency tables and the chi-squared test with the Fisher's correction, with a significance level of 0.05.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

The statistical calculations were made in SPSS 20.0.

RESULTS

1st study: The implications of ergonomy in classical and modern approaches in endodontic therapy

It is well-known that the professional process may result in significant musculoskeletal pathology (axial and upper limb) in dental practitioners through multiple mechanisms. Commonly, mechanical factors result from the specific biomechanical conditions/ stress related to several postures adopted by the physician during the working hours, such as static positions, repetitive movements with small amplitudes, the precision movements, are only some of the factors engaged by working in specific environments such as dental profession.

We performed a complex analysis of all the participants in the current study based on a standard questionnaire aiming to identify if specific ergonomic measures may positively influence the musculoskeletal morbidity in dental practitioners. Indeed, the number of participants presenting with cervical spine involvement related to their work was smaller in the ergonomic group A as compared to the number of doctors with cervical spine pathology in the nonergonomic group B.

General and anthropometric data

Epidemiological parameters are always essential when assessing the magnitude of the phenomenon investigated. Thus, in the present study we primarily focused on:

- *Group A* consisted of 15 participants (11 women, 4 men); 3 of them worked in rural offices;
- *Group B* included the same number participants - 15 (7 women, 8 men); 6 of them carried out their activity in rural areas.

We addressed our study to dental practitioners in their 3 to 6 decade as this is the most important age for professional activity of each dentist; furthermore, during this period, we also can talk about the negative consequences of the anthropometric data (height and weight), abnormal posture used during the working hours (sitting/standing), type of chair, the type of instruments, repetitive motions. A detailed analysis showed that participants in group A had a variable height between 1.55-1.80 cm, while for group B the values were between 1.60-1.79 cm. The individual characteristics of the subject (height, weight) are particularly expressed in the field of dental medicine.

Professional data

- *Working time* -It is generally accepted that several risk factors for the occurrence of the spinal pathology are related to specific activities related to dentistry; thus, the number of working years as well as the number of working hours performed daily are considered as fundamental in evaluating the consequences. The distribution by number of working years in our

participants largely varied between the 2 groups, from 10 to 40 years; moreover, in group A the average daily activity was 8 hours, while for group B was 7 hours.

- **Working posture**-The main sitting or standing working position is significant as it reflects the biomechanical loading of the spine (lumbar as well as cervical spine) and also the impact on the dentist's hand. In participants included in the group A, the sitting position was predominant because the use of magnification systems requires this type of posture; on the other hand, participants in group B performed their medical activity in a seated position in 41% of cases, in an orthostatic position in about one third (30%), while in another third (29%) an alternation between standing and seating was reported.
- **Type of chair**. We were also interested in the type of chair used, given the additional influence of an ergonomic or non-ergonomic chair on spine loading.

Dentists in group A used during the medical activity the following types of ergonomic chairs: 10 doctors used a chair with nonadjustable backrest; 2 doctors used adjustable backrest; 2 doctors used provided and with support for arms; 1 a doctor used a ball-type chair in alternation with a chair with non-adjustable lumbar support; no doctor used a stool chair (no backrest).

Dentists in group B had the following types of non-ergonomic chairs in the dental office: 11 doctors had a chair with nonadjustable lumbar support; 4 doctors had chairs provided with armrests; no doctor used a ball chair.

- **Type of work**. It is also acknowledged that ergonomic principles widely recommend the implementation of the working team (the so-called 4/6 handed dentistry) in routine practice, aiming to enhance the professional performance. In group A, 13 out of 15 dentists recognized the advantages of teamwork practicing 4-handed work; however, only 5 dentists out of 15 enrolled in group B did not tackle team work in practice.
- **Magnifying tools in routine practice - The practical use of diverse magnifying tools** (*magnifying* eyeglasses, microscope) was evaluated in all participants; only 3 doctors in group A used different magnification systems during their practice (2 subjects used the magnifying eyeglasses and only one the microscope during his endodontic work); in group B, only one dentist used in the daily practice the magnifying eyeglasses.
- **Rubber dam**. Another question derived from the questionnaire that had to be answered by the participants in both groups was the one regarding the use of the rubber dam as a means of isolating the operating field. In modern dental medicine, almost all therapeutic procedures are carried out after a previous isolation of the operative field. In addition to its protective effects (the mineral content helps enamel harden, regulates mouth acidity, represents a barrier against viruses and bacteria), saliva may distort the image of the dental surface, moistens, masks and infects the work area. Dental dam remains the most modern and efficient of the isolation modalities; it is largely used in endodontics, but it can also be used in other dental specialties, e.g. pedodontics, dental aesthetics as well as karyology. In group A, 5 out of 15 dental practitioners used current during endodontic treatments as a means of isolating the operating field, while in group B only one dentist occasionally used the dental dam.
- **Modern ergonomic tools**. Another item in the questionnaire applied to the participants in the current study was related to the use of modern rotary tools during the endodontic therapy.

The instrumentation of the root canal by the rotary means presents a number of advantages as opposed to the manual technique. In group A, 5 dentists used rotary instruments during endodontic treatment as a means of preparing root canals, while in group B only 2 dentists used rotary instruments.

Clinical parameters

The semiology of the locomotor system is mainly expressed by pain, muscle spasm, vicious postures, deformity, limited mobility and low tolerance for both statics and dynamics.

In our study, the clinical exam of the locomotor system was performed in collaboration with a trained rheumatologist.

It is already known that musculoskeletal disorders may be commonly found in dental practitioners given the biomechanical loading and stress as a result of prolonged static positions, incorrect postures, repetitive movements as well as isometric contraction of the hand and spine muscles. The reduced amplitude by which the movement is performed and the aforementioned elements contribute to joint wear, muscle ischemia, excessive traction on the capsulo-ligamentous apparatus.

Focusing on the cervical spine, we note that both orthostatic and seated position are related to significant biomechanical loading given different positions (flexion, rotation) adopted by the practitioner during the working hours. Furthermore, biomechanical stress (pressure, traction) may result in early damage of the vertebral disks in the cervical spine.

As the major symptom reported by dental practitioners directly related to prolonged stress is usually **pain**, we assessed in our study the pain and its characters (intensity, location, irradiation, its acute / chronic character, the time of onset, the time of onset) as well as the relationship with working posture.

Cervical pain was reported by 7 doctors in group A and 10 in group B.

- *The severity of pain was evaluated on a 0-10 VAS (Visual Analogue Scale)*, where “0” cm means the absence of pain and “10” the most severe pain reported by the patient in the last 7 days. Pain in group A was recorded in 7 patients, as follows: 0 = pain absent, 8 subjects; 2- 4 = mild pain, encountered in 3 subjects; 5-7 = moderate pain, encountered in 3 subjects; 8-10 = severe pain, occurring in 1 subject; in group B the cervical pain was found in 10 patients, as follows: 0 = pain absent for the cervical region, 5 subjects; 2-4 = mild pain, encountered in 4 subjects; 5-7 = moderate pain, encountered in 4 subjects; 8- 10 = severe pain, seen in 2 subjects.
- *The irradiation of the cervical pain* may be towards the upper limb, the occiput and to the dorsal and lumbosacral region, as well. In group A among the 7 participants presenting with cervical pain, 2 had occipital irradiation, in 2 subjects the irradiation was in the upper limb, while for the other 3 subjects there was no irradiation of pain. In group B, 3 doctors had occipital irradiation, 3 brachial irradiation, and 2 subjects presented with dorsal and lumbar irradiation.
- Three main causes of pain are commonly described, as follows: inflammatory pain (increasing at night or felt in the morning); mechanical pain (pain increasing with working activities and their duration or intensity); neurological pain (related to nerve involvement, frequently associated with the sensation of burning and tingling - paresthesia). In group A the following distribution of pain was recorded: mechanical pain in 3 subjects, neurological pain in 2 subjects, while in 2 doctors the pain was inflammatory. In group B, we noticed the following distribution of pain: 4 subjects had mechanical pain, 3 neurological type and in 3 subjects the pain was inflammatory.
- An important aspect related to *pain etiology is the time of occurrence*. The group analysis revealed the following: in group A, the pain suddenly started in a number of 4 subjects; the rest recorded a progressive evolution of pain; in group B, the sudden onset was recorded in 6 subjects, the manifestations of the others falling within the progressive character.
- In this framework that defines the characters of pain, we also noticed that in the 4 subjects from group A the pain was present during the activity in the patient from the beginning of the working day, and the rest of the subjects (3) felt the pain at the end of the day. In group B, in 6 subjects the pain was present during the entire activity from the first professional actions and 4 doctors felt the pain at the end of the working day.

- The *time of pain onset* also represented an important parameter. In both groups, the presence of pain is mentioned after a number of working years. Thus, the pain was described after 2-3 years of activity by 4 subjects, while the others reported pain after a longer period (5-7 years) in group A; also, 6 doctors described the onset of pain after 2-3 years and the others after 5-7 years in group B.
- Although musculoskeletal pain is commonly related to working activities, severe pain goes beyond the working schedule and is reported all day long, even by night, with significant impact on the quality of life. In group A the aspect was noticed in 4 doctors, while in group B 6 doctors presented with pain lasting after the end of the working day.

The questionnaire applied also included one question regarding the presence of *paresthesia, muscle spasm and decreased muscle strength*.

Thus, *paresthesia* was reported in the upper limbs in 4 subjects in group A and in 5 subjects in group B; *muscle spasm* was recorded on the posterior groups of the cervical spine and trapezius in 3 subjects from group A and 6 subjects in group B, respectively; finally, the decrease in *muscle strength* was demonstrated in the upper limb by 3 subjects in group A and 5 subjects in group B. When asked about the *relation between pain and the main position adopted during working hours*, a significant number of participants in group B have indicated a direct relationship between the working position and the occurrence of pain. The phenomenon was also reported by 2 subjects who used for a long period the magnifier tools.

We also looked for *abnormal static and dynamic postures of the cervical spine: hyperlordosis* was recorded in 2 subjects in group A and 4 subjects in group B. Cervical spine *mobility* is essential for both professional and daily activities; normal biomechanics means flexion (chin-to-chest index) = 0cm, extension (occiput-to-wall index) = 0 cm; laterality (chin-to-acromion index) = 0cm and rotation (tragus-to-acromion index) = 0 cm.

We demonstrated mainly decreased laterality and rotation in 6 dentists from group B and in only 2 from group A.

Radiological assessment

We performed also the radiological assessment of the cervical spine in order to prove the cervical spine pathology as the main etiology of the mechanical pain felt by the participants in our study. In group A, the spine X-rays confirmed abnormal posture and the deviations of the spine as well as mechanical lesions in 6 dentists, while in group B we demonstrated cervical spine lesions in 10 out of 15 participants.

2nd study: Musculoskeletal issues among dental medicine students: a cross-sectional study

The first part of the questionnaire included general data.

Thus, half of students enrolled in the group A were in the first year of study and half in the second, 35 were female and 15 male, aged between 19 and 21 years, with a height between 1.50 and 1.85 m. Students enrolled in group B were distributed as follows: 13 students in the third year, 12 students in the fourth year, 12 students in the fifth year, while the last 13 students in the sixth year; 30 were female and 20 male, age ranged from 22 to 28 years, and height between 1.53 and 1.80 cm.

The second part of the questionnaire applied referred to the **occupational risk factors** for developing musculoskeletal related complains; this part was filled only by participants in group B, specifically skilled to perform various maneuvers, either on simulator or patient. Students in their third year were involved in professional activities on a simulator basis: Oro-Dental Prevention, Anesthesiology in Dental Medicine, Cariology, Periodontology and Unidental Prosthesis. Conversely, students in the fourth, fifth and sixth year were systematically working on patients, several other disciplines being studied: Fixed Dentures, Partially removable dentures: Acrylic

dentures, Partially removable dentures: Skeletal dentures, Total Prosthesis, Endodontics, Dento-alveolar Surgery, Restorative Odontotherapy, Pedodontics (Table 38).

Table 38 Distributions of disciplines by year of study and student involvement in patient's care

3rd year	4th year	5th year	6th year
Oro-dental Prevention	Pedodontics	Periodontology	Restorative odontotherapy
Anesthesiology in dental medicine	Dental-alveolar surgery	Oral & maxillo-facial Surgery	Endodontics
Cariology II	Endodontics	Orthodontics and dental and facial surgery	Periodontology
SIMULATOR	Fixed dentures	Partially removable dentures:Skeletal dentures	Fixed Prosthesis. Ceramic restauration
Cariology I	Partially removable dentures: Acrylic dentures		Partially removable dentures
Periodontology	Total Prosthesis		Total Prosthesis
Unidental prothesis			Oral & maxillo-facial Surgery

- *The type of instrument used.* Distal upper limb, respectively hand has a particular significance in the context of dental medicine given the fundamental role of different types and patterns of prehension in the entire professional activity. Students in the third to sixth years are commonly using both ergonomic and non-ergonomic dental tools. Several characteristics usually help us to classify a dental tool as ergonomic or not, including the material used for the handle, the diameter of the handle, the handle shape, texture, weight, type of instrument (with one or two active ends), the absence or presence of fiber optic at dynamic tools level.
- *The working position.* Both sitting and standing postures among dentists are constantly related to particular strain on vertebral axis, particularly cervical and lumbar spine.

Ultimately, **the third part of the questionnaire refers to musculoskeletal complains** in enrolled students, respectively pain and muscle spasm.

- **Pain** was analyzed based on specific features such as: location (cervical, thoracic or lumbar spine; shoulder or hand); intensity (Visual Analog Scale, VAS) classified as mild, moderate, severe); worsening factors.

-*Pain location.* Students from group A does not perform any practical classes to patient. However, the questionnaire revealed two students with neck pain, two students with dorsal pain and seven with low back pain; one student declared painful shoulder, while two reported hand pain.

-*Pain intensity* measured on VAS was rated as mild (VAS under 4) by ten students, moderate during rest (VAS of 4 to 6) by four students; severe pain with a VAS greater than or equal to 7 was not claimed by any individual student

-*Worsening or improving factors.* Students were interviewed about factors modulating pain such as rest, relaxing techniques, analgesics use as well as triggering factors. Students included in group B presented both axial (cervical, thoracic, lumbar spine) and peripheral (shoulder, hand) pain. In the third year (13 students) three students had low back pain, one neck pain, no student accused dorsal back pain, and 5 subjects had pain in the joints of the hand. The intensity was classified as moderate by all those with axial and peripheral issues. In the fourth (12 students) and fifth year (12 students), cervical spine pain was reported by five cases, lumbar spine pain by eight students, while hand pain in eight students from the fourth year and seven from the fifth year. In addition, pain intensity was low for students featuring vertebral pain (five cases) and moderate for five of those with hand involvement. In the sixth year, nine students described cervical, lumbar,

dorsal, shoulder, hand pain, classified as moderate. Relaxation and short-term exercises were commonly associated with pain relief.

- **Muscle spasm** was as the second clinical parameter evaluated by the questionnaire, collected by history taken and physical examination (palpation): deltoid, trapezius, sternocleidomastoid, paravertebral dorsal, lumbar muscles and thenar eminence muscles. Painful muscle spasm was described for cervical muscle by two students and lumbar region by three additional students in group A, while thenar eminence painful muscle spasm was found in only one student. In group B, muscle spasm was identified as follows: one student in the third year on cervical spine and one student on lumbar spine; in the year fourth and five muscle spasm was reported by two students in the trapezius muscle and by four students in the thenar region; finally, students in the sixth year presented with muscle contraction mainly located in the paravertebral lumbar region (two cases) and hand muscles (three cases).

3rd study: Ball Chair vs. Classic Office Chair in Dentistry: A Pilot Study

Each dentist in group B was provided an accommodation training meaning a progressive escalation in working time on the gym-ball during one week, with an increase of 30 min per day as shown in **Table 39**.

Table 39 Gym-Ball accomodation training schedule

Day	Duration on Gym-Ball
1	30 minutes
2	60 minutes
3	90 minutes
4	120 minutes
5	150 minutes
6	180 minutes
7	210 minutes

An Electromyography (EMG) using a flat electrode was done in all dentists in both groups; paravertebral and abdominal muscles were tested twice, at the beginning and end of the workday as well, particularly the following muscles: m. multifidius (component surface), m. latissimus dorsi and m. rectus abdominis. (**Figure 7**) In our study, it was used Biopac MP45 (Biopac Systems Inc USA), EMG equipment, the single use electrodes, gel as a type of substrate conductive medium, and AcqKnowledge 4.0, software dedicated to the acquisition and processing of biomedical signals. One week training was performed before the correct EMG testing of the flexors and extensors muscles.

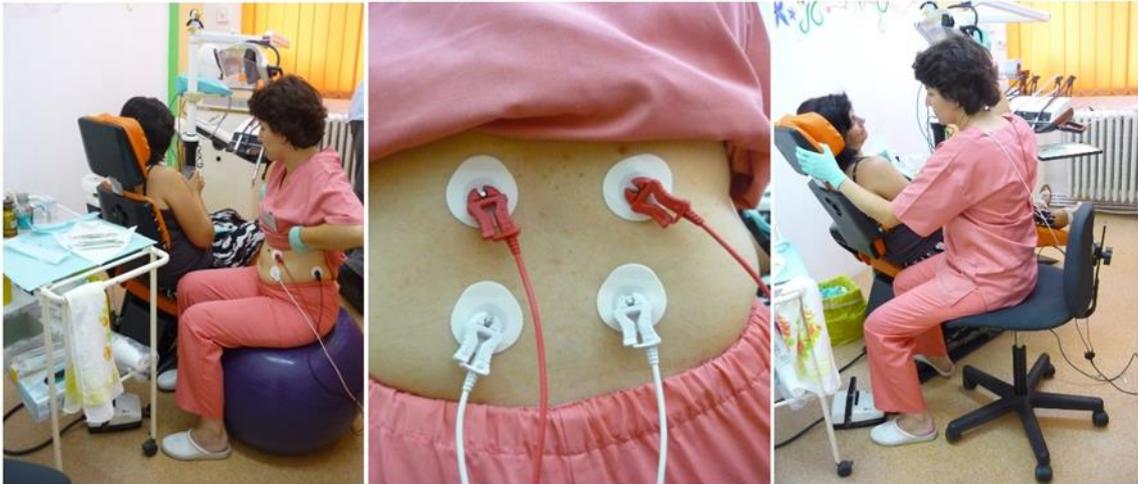


Figure 7 Electromyography in the abdominal and paravertebral muscles using flat electrodes at dentists working in a sitting positions on ball chair vs classic chair

There was no difference in demographics, comorbidities background, a common field of dental activities and work experience as summarized in **Table 40**.

Table 40 Demographic and anthropometric parameters

Demographic and anthropometric parameters		
	Group A (n=30)	Group B (n=20)
Age (years)	35 ± 2,3	35 ± 1,1
Gender (male:female)	3: 2	2: 3
Body mass index	65 ± 5,1	67 ± 2,3
Height	1.61 ± 10,1 cm	1.62 ± 10,5 cm

Firstly, we were interested in evaluating the overall impact of the classic ergonomic chair versus gym-ball chair utilized during working hours. 16 out of 30 dentists in group A considered that the ergonomic chair is comfortable, while 16 out of 20 sitting on a gym ball chair (group B) during routine practice responded favorable when asked about the comfort related to the new type of chair (p value =0.229, not significant) .

The second item of the questionnaire referred to vertebral pain elicited by prolonged fixed working postures and repetitive movements, expressing overloading as well as vertebral wear. 22 dentists from group A complained about mechanical vertebral pain progressively exacerbated at the end of the working hours; pain was moderate in 20 cases, with an intermittent pattern in the last one. Conversely, only 6 dentists among those using a gym-ball chair reported vertebral pain, classified as mild and sporadic (p value = 0.048, statistically significant) (**Figure 8**).

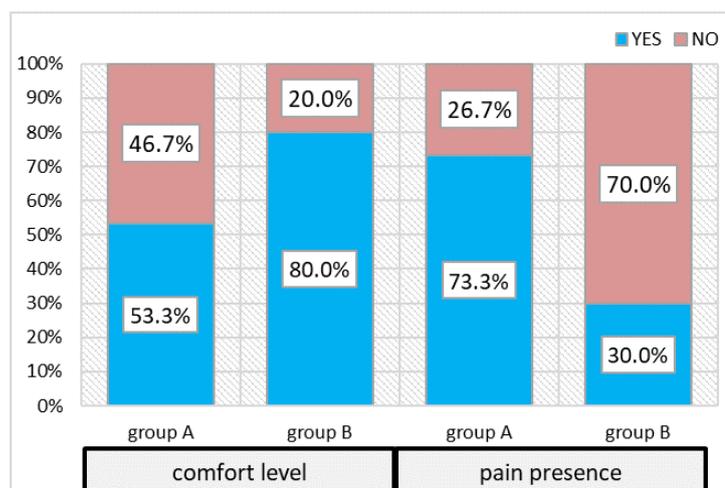


Figure 8 The comparative answers in group A vs group B regarding the two items

Secondly, muscle activation in the lumbar spine and their activity were assessed by the means of surface EMG registered during professional activity. As already mentioned, EMG with plain electrodes was systematically performed in all dentists, as such electrodes are less traumatic than the needle electrodes, permitting and getting information during activity. Several muscle parameters were typically detected including length, shape, amplitude and frequency of the electrical potentials.

DISCUSSIONS

1st study: The implications of ergonomy in classical and modern approaches in endodontic therapy

It is well-known that the professional process may result in significant musculoskeletal pathology (axial and upper limb) in dental practitioners through multiple mechanisms. (Sultana et al., 2017; Swathy et al., 2015). Commonly, mechanical factors result from the specific biomechanical conditions/ stress related to several postures adopted by the physician during the working hours, such as static positions, repetitive movements with small amplitudes, the precision movements, are only some of the factors engaged by working in specific environments such as dental profession.

We performed a complex analysis of all the participants in the current study based on a standard questionnaire aiming to identify if specific ergonomic measures may positively influence the musculoskeletal morbidity in dental practitioners. Indeed, the number of participants presenting with cervical spine involvement related to their work was smaller in the ergonomic group A as compared to the number of doctors with cervical spine pathology in the nonergonomic group B. We reported mainly chronic pain irrespective of the study group, but with a higher percentage in those participants performing their work in a non-ergonomic environment.

It is therefore obvious the role of ergonomics in protecting from different painful musculoskeletal conditions, particularly related to spine involvement.

Numerous studies have already shown that posture is very important for maintaining the normal functioning of the spine, particularly the neutral position (Barry et al., 2017; Bedi et al., 2015; Sultana et al., 2017). Furthermore, we have to mention the benefits of kinetic exercises in order to maintain the flexibility of the cervical spine and to achieve the neutral position during working activities. Such exercises for flexion-extension, laterality and rotation were proposed to all participants in both groups and performed on a regular basis daily with benefits for both decreasing pain, muscle tension as well as promoting the correct posture of the cervical spine (Mahboobeh et al., 2015; Ohlendorf et al., 2020; Sakzewski et al., 2015).

2nd study: Musculoskeletal issues among dental medicine students: a cross-sectional study

The first part of the questionnaire Groups were relatively homogeneous related to gender distribution: 15 male and 35 female in group A, 20 male and 30 female in group B. All participants in group A were aged between 19 and 21 years, and those in group B between 22 and 28 years. To remember, students in group A had no specific professional activities with patient participation, while group B enrolled students distributed among third to sixth year with some variability. Two main behavioral factors, namely alcohol and smoking have negative influences, triggering faster and enhancing symptoms of various diseases. We also referred to these parameters, in order to identify potential negative influences if excessive use in younger age.

The second part of the questionnaire The main endpoint of his second part of the survey was to identify risk factors for musculoskeletal complains in routine practice among dental professionals. To document, in their second year, students are studying ergonomics, focusing on its own relationship with the working environment, patient, dental instruments, and expand its knowledge on the exact meaning of a vicious position, muscle stiffness and repetitive motion as well.

In the third year, students already begin the work with patient; however, only a few hours per week are typically assigned for different disciplines including: Oro-dental Prevention, Cariology (second semester) and Anesthesiology.

Starting with the fourth year, students are practicing in the Department of Endodontics; the routine practice in such settings focus on repetitive movements with a reduced amplitude (range of motion), performed in a restricted area, and involve small tools (endodontic files). Additionally, students may confront with different vicious positions adopted during the working hours, maintained by prolonged isometric muscle contractures, which may result not only in local ischemia, but also in pain. Thus, ischemic phenomenon may account for painful homolateral disability of the hand, while controlateral hand may also become painful based on excessive muscles insertions traction.

Furthermore, different surgical techniques performed by a fourth year student promote a stronger and sustained musculoskeletal activity; thus, various stressing working postures and subsequent muscle spasm, are also accompanied by a force activity.

The fifth and sixth years are commonly characterized by significantly higher number of working hours, number of patients as well as number or performed maneuvers.

The third part of the questionnaire

- *Pain in group A.* Students aged between 19 and 21 years may feature vertebral pain mainly related to excessive physical effort, lack or insufficient knowledge about physiological behavior of the spine. It is widely recognized that the vertebral axis has the right attitude maintaining in any position a cervical and lumbar curvature and back straight in dorsal region. Routine daily activities such as anterior and lateral bending, lifting as well as wearing weights, must follow certain rules (the so called “spine protective recommendations”) in order to avoid muscle and vertebral disk stress.
- *Pain in group B.* Processing the data obtained from students enrolled in group B, we noted the occurrence and persistence of pain during working hours; mechanical pain progressively increase paralleling the working program as well as the complexity of therapeutic maneuvers used. Pain is, therefore, the negative consequence of professional work on the musculoskeletal system. Supplementary, the lack of experience of students (maneuvers and techniques), as well as the excessive physical and mental stress inherent at the beginning of the profession may equally contribute to both vertebral and hand pain. Correct posture together with implementation of the ergonomics principles are critical in order to prevent musculoskeletal injuries.

- *Muscle spasm.* Muscle spasm was commonly described among students in the third year. Even limited muscle spasm may induce pain and agonist-antagonist disequilibrium, with later consequences on joint function meaning reduced range of motion and subsequent disability.

3rd study: Ball Chair vs. Classic Office Chair in Dentistry: A Pilot Study

The EMG analysis clearly support muscle activity performed during routine profession; different phases of muscle involvement like muscle activation, the amplitude of contraction, frequency and Maximal Voluntary Contraction (MCV) are the subject of training, based on correctly identified exercises.

Several examples of paravertebral and abdominal muscle activation during work as well as differences detected by the EMG in both work settings (classic ergonomic chair, gym-ball chair) are presented below (**Figure 9-11**). From the performed electromyography, correlated with the results of the items analyzed in the questionnaire, the benefits of the ball type chair are clear as far as the status of the flexor and extensor muscle status is concerned. Equally, this status is correlated with the use of the ball type chair and the type of minimally invasive modern maneuvers performed by the dentists.

It is widely recognized that the whole spine, particularly cervical and lumbar regions are involved in professional activity of a dentist (Andersson et al., 1975; Johnson et al., 2016; Stokes et al., 2003). Whatever the posture adopted during working, ergonomic or non-ergonomic, different vertebral regions are overstretched as demonstrated by the physiological biomechanics rules of the spine; furthermore, spine biomechanics is extremely complex and only the neutral position (meaning lumbar and cervical lordosis, with a mild kyphotic upper back) is able to maintain the tolerance for exercise and a long-term normal functioning (Valachi et al., 2003; O'Sullivan et al., 2010; O'Keeffe et al., 2013).

Emerging data concerning vertebral biomechanics support the critical role of thoracolumbar junction as the core stability region for both static and dynamic posture. Several muscles are classically responsible for spine stability, including m. multifidus, m. spinalis, m. latissimus dorsi, right and transverse abdominal muscles, and diaphragm, as well (Gregory et al., 2006; Escamilla et al., 2010; Ainscough-Potts et al., 2006; Scott et al., 2015). Their training is realized only through a well targeted activity, while the active sitting posture on a gym-ball type chair is thought to promote such a specific training.

In addition, sitting on a relatively unstable surface (e.g. the convex ball-type surface) is usually recommended in order to maintain balance and a better sitting posture, based on significant participation of postural muscles in the core stability area (Escamilla et al., 2010; Brereton et al., 1998). Hence, this technique obviously helps to strengthen abdominal and back muscles, offering a better balance and posture. On the other hand, the upper belt muscles are also trained due to their specific involvement in routine dental practice.

Different studies involving the gym-ball in the field of fitness and spine rehab showed benefits related to low levels of muscle fatigue as well as increased productivity, promoting good physical health (Gregory et al., 2006; Schult et al., 2013). Moreover, this novel ball-type chair also significantly decreased the number of dentists declaring low back pain. Finally, positive outcomes among subjects enrolled in group B clearly focus on gym-ball utility, as follows a stronger abdominal and back musculature, recognized as spine stabilizers; a locally improved blood flow; a better balance between flexors and extensors of the spine meaning the agonist-antagonist torque, typically leading to a correct posture; strengthening of the scapular belt muscles; as well as a favorable approach to reduce overall stress.

A closer look to ball-chair in rehab and particular working settings, including the dental medicine, revealed conflicting data. Most of the studies showed comparable levels of discomfort and muscle activity when using a conventional office chair versus sitting on ball-chair (Schult et al., 2013; Elliott et al., 2016; Jackson et al., 2013). Moreover, no significant changes in the activity

of trunk muscle or spinal postures, with no positive outcomes were reported if sitting on an unstable surface. Electrophysiological studies such as EMG suggested no difference between the activation of muscles while sitting on a chair and on a ball; muscle activity in individuals performing a sitting work was also low (Brereton et al., 1998; Dankaerts et al., 2004, Reaz et al., 2006). Conversely, other studies reported effective m. multifidus activation when subjects were sitting on the ball (Scott et al., 2015). Although no additional benefit was demonstrated with the gymball chair among dental professionals, reduced activity of the rectus abdominis muscle and the external oblique muscle while sitting on the ball can favorably affect the functional recovery in different pathologies, including stroke. Furthermore, spasticity or rigidity may also benefit from specific rehabilitation using gym-balls as muscle tension may be reduced.

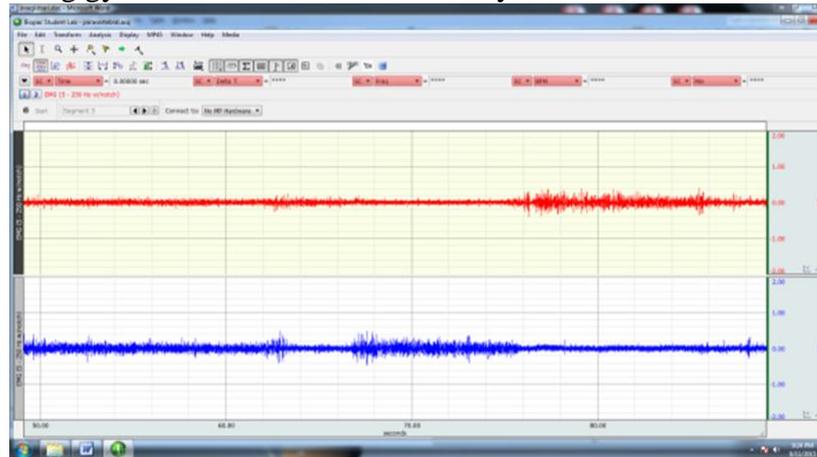


Figure 9 EMG showing paravertebral muscles activity (m. multifidus-right/left). Right paravertebral – red channel $A=0.23\text{mV}$; Left paravertebral – blue channel $A=0.48\text{mV}$

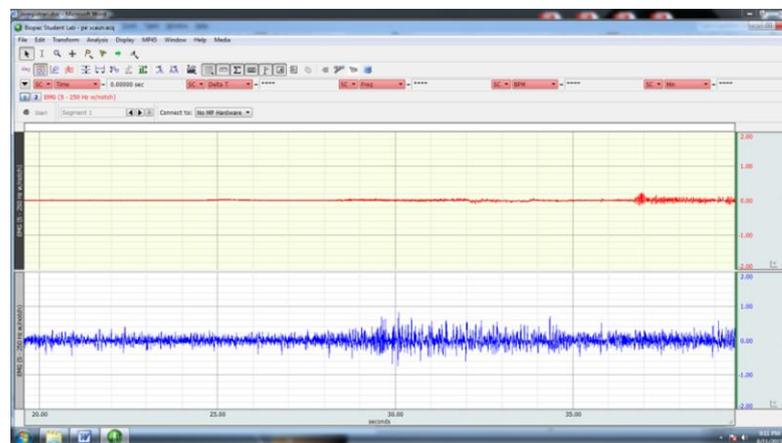


Figure 10 EMG for paravertebral muscles (m. multifidus) and lumbar muscles (m. latisimusdorsi) A1 paravertebral =0.30 mV; A2 lumbar =0.81 mV

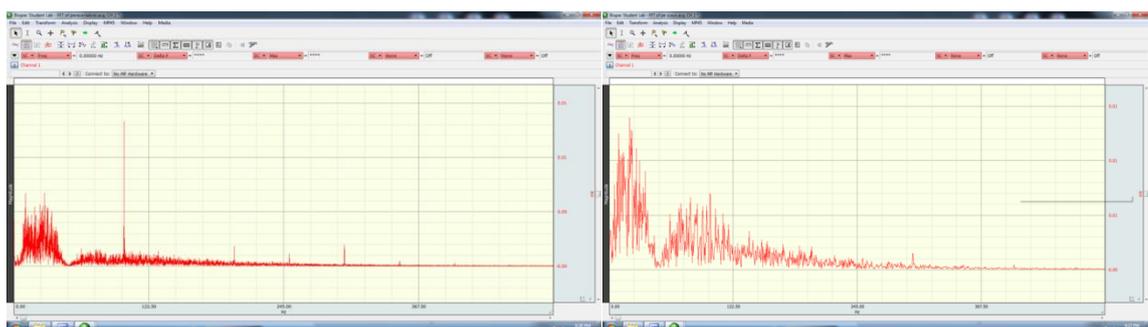


Figure 11 The frequency spectrum of the signal for less paravertebral muscles (a); The frequency spectrum from lumbar muscles (b)

CONCLUSIONS

- Professional activity of a dental practitioner is widely recognized not only for the excessive biomechanical stress of the spine and the peripheral joints, but also for the high percentage of axial and peripheral musculoskeletal disorders (**paper 1**);
- Given the special conditions of the cervical spine during daily practice in dentistry (e.g. prolonged static positions, vicious positions, prolonged isometric contraction, attention, precision of the professional procedures), the burden of musculoskeletal imbalances as well as impaired quality of life remains significant (**paper 1**);
- Moreover, the endodontic field of the professional activity also generates different pathological conditions at this level. As a consequence, chronic pain, paresthesias, decreased muscle strength developed on a background of X-ray modifications including the malalignment of the cervical spine and degenerative disco-vertebral processes are commonly reported among dental practitioners, especially in those performing their daily activities in a non-ergonomic environment (**paper 1**);
- Musculoskeletal pathology, particularly vertebral issues, are commonly reported among dental professionals, due to specific mechanical settings related to work (**paper 2**);
- Since different ergonomic postures adopted by the student/dentist are classically associated with less vertebral (lumbar spine) sufferance, increased knowledge about ergonomic techniques, positions and movements is required, with continuing care for inward and auto-training (**paper 2**);
- Conversely, non-ergonomic postures usually result in significant more vertebral complains, particularly chronic severe pain requiring therapeutic intervention (**paper 2**);
- A comparative study between students in their first years of study, without direct involvement in true professional activity, and students in the last years of study, deeply engaged in specific professional activities, is able to identify musculoskeletal consequences such as pain and muscle spasm and to emphasize work-related pathology (**paper 2**);
- Ergonomic principles must be applied in routine dental practice and the student educated about the prevention of musculoskeletal pathology (**paper 2**);
- Spine is critically involved in normal orthostatic and sitting postures, and is intensively engaged in routine professional activity among dentists. A suitable working posture is always required in order to reduce muscle fatigue and discomfort, even if that means a frequent change of posture (**paper 3**);
- The correct vertebral posture is the neutral position, preserving precise curves in different settings. Latest research highlighted the efficacy of a gym-ball type ergonomic chair to detriment of classic ergonomic office chair despite the lumbar and arm support in dentistry (**paper 3**);
- Electrophysiological studies using the detection EMG with surface electrodes revealed the role of spinal extensors and flexors (the so-called agonist-antagonist torque), showing certain benefits of ball chair (**paper 3**);
- In order to prevent and to diminish the muscles fatigue, very common among dental practitioners, the best solution is to alternate the work sitting on ball-chair type with the work sitting on classic ergonomic chair (**paper 3**).

- **Hand pathology (item I.2.2.)**

Another direction of my research has analyzed the dentist's hand, related to specific work conditions comprising precision, force and often addressing vicious positions.

It is widely accepted that the professional activity of the dental practitioner is fundamentally a manual activity which requires all segments of the upper limb (especially hand) (Kumar et al 2020; Lietz et al. 2018). Therefore, during professional activities, a major interdependence is achieved between the practitioner's hand, the instrument used and the tissue to which it is addressed, hard components but also soft structures.

The characteristics of this interrelation depend on the physical qualities and abilities of the practitioner, type of instrument (diameter, texture, shape, weight) but also on the patient's anomalies (morphological), comorbidities, etc.

The professional activity in dentistry is also burdened by physical and mechanical conditions (force, precision, vibrations). All the elements listed above are, in fact, risk factors for the occurrence, in a remarkable frequency, of musculoskeletal pathology. In order of frequency, work-related musculoskeletal disorders are located at the level of the cervical spine, lumbar spine, joints of the hand, shoulder and elbow (Bakar et al., 2019; Kalluri et al., 2018; Saliba et al., 2016).

Conditions such as osteoarthritis of the small joints of the hand, carpal tunnel syndrome (Alhusain et al., 2019; Haas et al., 2020), bursitis, tendonitis and tenosynovitis (Haas et al., 2020; Landim et al., 2016), flexor and extensor tendonitis (Kennedy et al., 2016), as well as de Quervain's disease (Liu et al., 2020) are already well known in the literature.

According to Rice et al, there is an increased risk for the dentist, that directly proportional to the number of working hours to present pathological phenomena such as those described that have an unfavorable impact on health, professional performance by affecting digital-digital and digital-palmar grips, on the neutral position of the wrist, the force, the precision.

Therefore, musculoskeletal pathology directly related to professional performance is not limited only to the distal extremity - hand, but is also expressed to the other articular and non-articular segments of the upper limb including shoulder, elbow, arm and forearm.

Several predisposing factors for hand and wrist injuries during professional activity of a dentist are already known, as follows: forceful work, excessive working without allowing rest, repetitive flexion and extension motions of the wrist and fingers as well as other movements in which the wrist is deviated from neutral posture into an abnormal or awkward position, and extended use of vibratory instruments and mechanical stresses to digital nerves from sustained grasps to sharp edges on instrument handles (Haas et al., 2020).

In the trinomial hand - instrument - tissue, the role of the instrument has only recently attracted attention and ergonomic tests and studies have already proposed improvements in its design. The design of dental instruments is currently considered as an important factor in inducing negative effects on the musculoskeletal system. Besides, it is important to recognize that different characteristics of a dental instrument may induce ergonomic issues; the most important are the size and shape of the instrument, diameter of the handle, surface configuration where the instrument contacts the fingers, weight of the instrument, balance and alignment of the instrument, maneuverability of the instrument in space, how well the moving parts can be manipulated and maintenance of the cutting edge (Deolia et al., 2018; Hass et al., 2020; Sachdeva et al., 2020).

In this context, the practitioner must take measures, apply ergonomic principles in the direction of selection, grip, maintenance and use of instruments and devices (Hass et al., 2020). As a consequence, a greater variety of handle *sizes, shapes, materials and textures* able to improve the pinching effect and distribute forces over the pads of the fingers are already on market (Gomolka, 2000).

It is now recognized that handling instruments with inappropriate characteristics could, potentially, affect work productivity and result in work-related musculoskeletal problems; it seems that small diameters of the handles (1/4 inch or less) require higher hand forces to hold and

operate them, while instruments with large diameters handle allow the operator to grip the instruments with the pads of the fingers and consequently distribute the strain through a larger group of muscles (Sachdeva et al., 2020). Because grasping a very small object need enhanced precision and this can be achieved by shortening of the flexor muscles, potentially leading to waste their contractile ability. In addition, a flexed posture of the wrist further shortens the flexors of the fingers and is able to worsen the condition. Therefore, we understand why dentists are required to correctly select the handle *sizes* that are appropriate for their hand size and, also, their professional activity. (Sachdeva et al., 2020).

Looking for different other characteristics of the dental instrument, we better understand the role of ergonomic design. Thus, the shape of the instrument handle is also important: opposed to a hexagonal handle, a round one with hard edges is able to decrease the muscle stress as well as digital nerve compression. On the other hand, a smooth, round-handled instrument regularly entails more pinching force to keep the handle from spinning in the hand. Furthermore, small diameter, hexagonal shaped instrument handles produce a mechanical stress that may cause digital nerve compression. And finally, handles with shallow, circumferential grooves allow secure grasp due to a better friction with the fingers (Marsh, 2019).

Taking into account all of these, several preventive measures applying ergonomic and organisational measures have been proposed engaging the balance between activity and recovery with relaxing periods, avoiding overload and recognition of differences (Kalluri, 2018).

PERSONAL RESEARCH

My personal research in ergonomics and work-related spine pathology topics comprised

5 articles published in local as well as international IBD journals:

1. **Cristina Iordache**, Ana Maria Fătu, Rodica Chirieac, Codrina Ancuța, Work-related hand pathology among dentists: A pilot study, International Journal of Biology and Engineering, 10, 2016, p.225-228.
2. **Cristina Iordache**, Fătu Maria Ana, Miftode Mădălina, Ancuța Codrina, Forna Norina, Musculoskeletal issues among dental medicine students: a cross-sectional study, Romanian journal of Oral Rehabilitation, 2016, 8 (3), p 65-71.
3. **Cristina Iordache**, Ana Maria Fatu, Antoanela Beldiman, Zinaida Surlari, Irina Bîrsan, Codrina Ancuta, Ergonomics and work related musculoskeletal conditions in dentistry, Romanian Journal of Oral Rehabilitation 10 (2), 2018, 105-112.
4. **Cristina Iordache**, Ana Maria Fătu, Surlari Zenovia, Toma Vasilica*, Bursuc Ana Maria, Ancuța Codrina, Ergonomic measures and kinetotherapy in the prevention of musculoskeletal disorders in dentistry: focus on hand pathology, Roumanian Journal of Medical and Dental Education, 7 (2), 2018, 34-41.
5. **Cristina Iordache**, Doriană Agop Forna, Norina Consuela Forna, The carpal tunnel syndrome at dental physician, Romanian Journal of Medical and Dental Education, 3, (2), 2014.

Several abstracts (8) were accepted as oral and e-poster presentations in national and international manifestations.

We will further present several of our results published in ISI and IBD journals

Paper 1 Ergonomics and prevention of musculoskeletal Work related pathology in dentistry: a pilot study,

By: Ancuța Codrina, **Cristina Iordache***, Fatu Ana Maria, Aluculesei Cirprian, Forna Norina, **Romanian journal of Oral Rehabilitation**, 2016, 8 (4), p 73-78

Paper 2 Ergonomic measures and kinetotherapy in the prevention of musculoskeletal disorders in dentistry: focus on hand pathology,

By: **Cristina Iordache**, Ana Maria Fătu, Surlari Zenovia, Toma Vasilica*, Bursuc Ana Maria, Ancuța Codrina,

Romanian Journal of Medical and Dental Education, 7 (2), 2018, 34-41.

OBJECTIVES

The main aims of my research in hand pathology related to dentistry were:

- **(Paper 1) Ergonomics and prevention of musculoskeletal Work related pathology in dentistry: a pilot study**
 - (i) *to evaluate occupational-hand pathology in dentists and potential trigger factors and to highlight the role of physical therapy in preventing and management of different musculoskeletal issues in dentistry settings.*
- **(Paper 2) Ergonomic measures and kinetotherapy in the prevention of musculoskeletal disorders in dentistry: focus on hand pathology)**
 - (i) *to identify the pathology that occurs in the dentist's hand in relation to different professional risk factors, particularly the trapezio-metacarpal osteoarthritis - a painful and highly disabling entity related to subluxation or dislocation complications, and*
 - (ii) *to highlight the role of kinetotherapy for the prevention as well as therapy of the dentist's hand.*

METHODS

1st study: Ergonomics and prevention of musculoskeletal Work related pathology in dentistry: a pilot study

We performed a prospective 12-months study on 30 dentists (20 women), aged between 30 and 60 years, working in private practice, aiming to assess professional hand involvement. Enrolled dentists were classified in two equal groups, according to their participation in a kinetic program: group A, dentists performing an individual kinetic program on a daily basis, and group B, dentists without being involved in a physical therapy program. All subjects were followed up for 12 months.

A specific questionnaire derived from the Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) was applied in all cases, *evaluating different musculoskeletal items* such as *pain* (meaning location, intensity, potential irradiation, mechanical or inflammatory rhythm), *paresthesias, muscle spasm and amyotrophy, but also joint mobility* (wrist, metacarpophalangeal joints). Several other parameters were also included in our analysis, comprising grip force, types of dental tools used in routine practice (ergonomic or non-ergonomic), a complex imagistic (ultrasonography, X-ray) assessment of the hand, as well as the daily kinetic program.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

2nd study: Ergonomic measures and kinetotherapy in the prevention of musculoskeletal disorders in dentistry: focus on hand pathology

We enrolled twenty experienced dentists selected according to several inclusion criteria: a daily program of minimum 6 working hours, more than 15 years of professional experience, performing all techniques and procedures commonly encountered in a dental office.

All dentists were evaluated according to a standard questionnaire based on the following items: the presence of mechanical or inflammatory pain; the site, intensity and irradiation of pain; assessment of joint mobility of the first as well as 2 to 5 metacarpophalangeal joints; grip evaluation; types of instruments used during different professional manoeuvres

(ergonomic/nonergonomic handle); radiological and ultrasound examination of the hand; the presence or absence of routine kinetic exercises scheduled during working hours.

Dentists were classified in two main groups: group A (10) performing an individual kinetotherapy program and group B (10) without the kinetic program.

The study protocol has the approval of the Ethics Committee and all subjects have signed the informed consent before enrolment in the study.

RESULTS

1st study: Ergonomics and prevention of musculoskeletal - Work related pathology in dentistry: a pilot study

Demographics (gender, age), *anthropology* (weight, height) and *professional parameters* (years of employment and experience, number of working hours per day) were typically recorded in all cases, emphasizing the role of overlapping risk factors for workrelated musculoskeletal pathology.

Pain. Documented as a key musculoskeletal complain, generating significant physical and psychosocial discomfort, impaired working productivity and modified quality of life, pain was recorded in all subjects according to a specific protocol including location (wrist, metacarpophalangeal, proximal and distal interphalangeal joints), irradiation (forearm, arm), intensity (mild +, moderate++, severe+++), rhythm (mechanical, meaning pain increased with work; inflammatory, meaning pain at night). 6 dentists reported pain at wrist level, 8 in their metacarpophalangeal had no pain; 11 cases presented with forearm irradiating pain, while 4 with arm pain. The majority (13) of dentists described mild pain, 5 moderate and only 3 of them severe pain.

Paresthesias. Another essential and very disabling symptom, commonly related to nerve involvement and predominantly with distal expression, paresthesias were reported only in 3 cases. Although, paresthesias may account for either median, cubital or cervical spine nerve roots involvement, all 3 cases had a typical median nerve involvement.

Muscle spasm. Muscle spasm is commonly responsible for excessive pain and impaired working capacity; we evaluated the muscles of the hand, forearm and arm and revealed 8 dentists with brachial biceps spasm as well as hand flexors contractures.

Amyotrophies. Amyotrophy expressing a dual morphological and functional damage of the muscle accompanied by decreased muscle force with significantly impaired specific dental duties and activities was demonstrated particularly in the thenar region. In fact all 3 subjects with thenar amyotrophies presented also with paresthesia reflecting the median nerve pathology.

Range of motion (ROM). Clinical exam paid also particular attention to hand biomechanics and specific ROM of wrist, metacarpophalangeal and interphalangeal joints, as a functional ROM is always required for suitable dental activities in routine care. To remember, wrist mobility typically account for 60-70° of flexion/ 80-90° of extension and laterality, while fingers for 90°of flexion/ zero degrees extension (**Figure 12**).

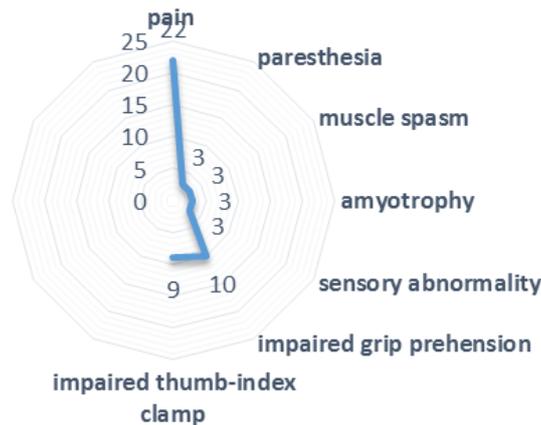


Figure 12 Musculoskeletal complains among studied dentists

Grip was tested, particularly for the thumb-index clamp, while sensitivity was also evaluated following typical signs of nerve damage in the thenar and hypothenar eminence. 5 dentists had a sensory disturbance, mainly in the median nerve territory

Hand X-ray revealed different stages of degenerative joint involvement, as follows: trapezio-metacarpal osteoarthritis in 9 dentists, with advanced modifications, even subluxation in 4 of them; osteoarthritis of the wrist in another 8 dentists with cuboidsaphoid osteoarthritis in 4 subjects; proximal interphalangeal joint osteoarthritis (Bouchard's nodules) were registered in 8 dental professionals, while distal interphalangeal osteoarthritis (Heberden's nodules) in 5 subjects. Just to remember, all subjects diagnosed with degenerative joint pathology recognizing as trigger professional routine activity in dentistry presented with typical radiological lesions such as subchondral bone sclerosis, narrowing joint space, and osteophytes.

Ergonomic analysis A specific ergonomic analysis meant to support the role of specific risk factors for work-related musculoskeletal and, particularly, hand pathology, was performed in all cases. We were mainly interested in evaluating 3 main features:

- (i) the working posture (orthostatic, sitting and mixed positions) with repetitive tasks and specifying the type of ergonomic chair (with lumbar support, with armrests);
- (ii) ergonomic evaluation of the biomechanical hand function and posture during work (correct position of the little finger below the thumb, with a flexion-extension range of motion of the wrist under 10 degrees);
- (iii) types of dental instruments used (ergonomic or non-ergonomic).

Finally, we point on the following data:

- working posture during routine practice in our dentists was typically a sitting one for 7 cases, predominantly standing in 9 cases, while the remaining cases preferred a mixed posture meaning half of time seated, half standing;
- about one third (28%) of dentists worked on ergonomic chairs with both lumbar support and armrests, while the majority (72%) only with lumbar support;
- up to 35% dentists do not know the correct/ protective range of motion for flexionextension wrist amplitude during working;
- 75% of dentists do not work with ergonomic handle tools.

The second objective of our study was to evaluate the role of an individual kinetic program aiming to either prevent or manage work-related hand pathology. As already mentioned subjects were classified in two main groups according to their involvement in a specific physical training and followedup for 12 months. Based on a complex biomechanical analysis of hand during specific activities in dentistry we formulated and applied a kinetic program inspired from the

general physical therapy targeting the relaxation of all segments of the hand, mobility-training using the normal range of motion, muscle stretching and toning. A specific kinetic program was designed for each individual case; in addition to classic exercises (forearm pronation/supination, flexion/extension of the wrist and fingers), dentists have also used various rigid, elastic or plastics devices.

The kinetic exercises were performed by dentists included in group A at least 30 minutes daily, 5 days weekly during a 12 months interval of follow-up, except holydays. All subjects were available for a final visit at the end of training period.

At the end of the study, significant more subjects in group A (performing physical therapy) as compared to group B (without physical therapy) displayed no musculoskeletal complains and discomfort, improved working performance and quality of life.

Work-related hand pathology is widely confirmed among dentists, specifically connected to different professional factors such as working postures and movements, number of working hours, cumulative time and experience, as well as type of devices and tools handled. Moreover, dentistry performed according to ergonomic settings is essential in order to reduce the burden of musculoskeletal features and to improve related disability and working performance.

Firstly, the current study focus on various musculoskeletal complains defining handpathology related to precise dental activities; although heterogeneous from pathobiological and clinical picture, dentist's hand represents more than a concept in dentistry. Furthermore, musculoskeletal comfort questionnaire is a self-administered survey adapted for hand involvement and is able to consolidate and homogenize the information on various musculoskeletal problems. Besides, a complex imagistic assessment based on both hand X-rays and ultrasound if the hand performed in all dentists enrolled in the study highlighted the specific substrate responsible for musculoskeletal complains. In the majority of cases, the exact etiology of work-related hand pathology was the degenerative damage in at least one joint – trapezio-metacarpal (10), proximal interphalangeal (9), medio-carpal (9), distal interphalangeal (7). Flexor tendons sufferance may also account for clinical signs and symptoms, although with a lower frequency.

Secondly, our study bring into attention a detailed ergonomic analysis of working settings (positions, devices, tools, chairs), hand biomechanics, working performance, stressing the significance of working in an ergonomic environment.

And **thirdly**, we were interested in evaluating a specific kinetic program adapted to each individual based on its own work-related hand complains, with a long-term (12 months) followed-up. Beneficial aspects of physical therapy performed on a regular basis were directed towards an improvement of hand involvement during professional routine practice, with subsequent upgrade of disability and quality of life.

2nd study: *Ergonomic measures and kinetotherapy in the prevention of musculoskeletal disorders in dentistry: focus on hand pathology*

General data. 10 women and 10 men aged between 45 and 65 years old, with an experience of 17 to 35 working years, and 6 to 9 daily working hours were finally analysed.

Clinical data for dentists in group A

- *Pain*, the cardinal symptom of the musculoskeletal disorders, was routinely investigated in all individuals; as mentioned before we were interested in evaluating several pain characteristics such as location (carpal, metacarpal, metacarpophalangeal level), irradiation (forearm), intensity (“+” assigned to low intensity, “++” to moderate intensity, “+++” to severe pain), rhythm (present during professional activity meaning mechanical pain and / or exacerbating by night meaning inflammatory pain). All 10 dentists in group A reported pain in first carpal-metacarpal joint of the working hand, radiating to the radial part of the forearm in 4 cases; 6 dentists described mild pain,

3 moderate pain, while in only one presented with severe pain. Furthermore, 2 dentists had an inflammatory pain, while the others demonstrated only mechanical pain.

- In 4 dentists we described *deformity of the metacarpophalangeal region*; both moderate (subluxation) and severe deformation (dislocation) were reported.

- *Amyotrophic thenar region* related to articular dysfunction strengthens the clinical picture and disability in 7 dentists.

- *Thumb mobility*. We assessed wrist as well as thumb mobility; limitation of flexion and adduction with hypermobility on extension, abduction and opposition of the thumb was found in dentists diagnosed with either dislocation or subluxation of the trapeziometacarpal joint. Moreover, pain and limitation in the mobility of the carpalmetacarpal joint of the thumb related to different degrees of damage of the articular structures with or without secondary subluxation was also found in 5 dentists with significant impaired work quality.

- *Grip-force modulation* in multi-finger prehension during wrist flexion and extension as well as tip-to-tip prehension were tested in all dentists and we demonstrated impaired prehension in 5 individuals.

- *Pain and paresthesia in the median nerve* distribution of the hand that are typically provoked by activities involving repetitive hand use was demonstrated in 3 cases.

Clinical data for dentists in group B

-*Pain* in the carpal-metacarpal joint of the thumb was also reported by all 10 subjects classified in group B, with the same irradiation to the radial part of the forearm in 5 cases. Pain was mild in 5 subjects, moderate in 4 and severe in only one dentist. However, nocturnal exacerbation of the hand pain was registered for 2 subjects.

-*Pain and paresthesia in the median nerve* distribution of the hand that are typically provoked by activities involving repetitive hand use was demonstrated in 4 cases, while a decrease in muscle strength of the thumb stated by 5 dentists.

-The same *deformity of the carpalmetacarpal region of the thumb* was noticed in 5 of dentists from group B, some of them presenting with moderate subluxation, while the others with dislocation. -*Amyotrophic thenar region* resulting in significant disability and impaired working performance was seen in 7 out of 10 dentists in group B.

-*Thumb mobility* was also evaluated and a hypermobility was found in 4 cases, while limited mobility for all tested movements was reported in another 3 cases.

-Finally, we assessed the *grip prehension* as well as the tip-to-tip prehension, especially for the thumb, index and medius, and we found impaired tests in 4 subjects.

Imaging studies for group A

We performed a complex imaging assessment of the hand and wrist including plain X-rays and ultrasonography. We highlighted the following changes: (i) trapezio-metacarpal osteoarthritis in 5 dentists, with severe damage and dislocation in 4 cases and a moderate subluxation in one dentist; (ii) radio-carpal osteoarthritis in 3 subjects; (iii) cuboid-scaphoid osteoarthritis in 2 subjects; and (iv) metacarpo-phalangean osteoarthritis another 2 subjects (**Figure 13 a,b**).



Figure 13 Comparative hand and wrist X-ray: (a) mild bilateral thumb subluxation, narrowing of the PIP and DIP joint space; (b) bilateral thumb subluxation, narrowing of the PIP and DIP joint space

Ergonomic assessment

We were interesting in evaluating the compliance with the ergonomic rules regarding the correct position of the hand during professional activity (5th finger located inferior to the thumb, magnitude of wrist flexion–extension less than 10 degrees), the type of instruments used (ergonomic/non-ergonomic handles) and the presence of rest moments with or without relaxation hand and finger exercises as well.

The ergonomic analysis showed that up to 38% of dentists do not know and apply the rules regarding the amplitude of the wrist flexion-extension. In addition, 85% of the dentists surveyed showed that they do not use instruments with an ergonomic handle. Moreover, a rest interval was not correctly defined for 75% of the interviewed subjects.

Kinetic program applied in dentists from group A

Based on the analysis of the work of the dentist's hand, we focused on an exercise program inspired by the general kinesiotherapy that aimed at relaxing all the sub-segments of the hand, driving the movement on the entire motion each joint, muscle stretching, flexor-extensor rebalancing and toning of different muscles.

The *exercise program* was proposed to each dentist in the group A. For significant improvement, besides analytical exercises, some synthetic exercises aided by different devices can also be practiced.

The kinetic program was performed for 7 months for all dentists in group A. At the end of follow-up subjects were asked to retake the initial questionnaire.

Final results showed thumb pain in 6 dentists, with irradiation along the radial edge of the forearm in only 2 cases; pain was mild in 4 cases, moderate in 2 of them, while severe pain was not registered. Furthermore, inflammatory pain was found only in one subject. Median nerve related paraesthesia was reported in one person. Only 2 dentists had limited mobility of the thumb after the regular kinetic exercises.

Moreover, deformation of the metacarpophalangeal region was demonstrated in one dentist; amyotrophy of the hand originally recorded in 7 subjects was subsequently encountered in only 3 of them. The grip prehension was reduced in 2 dentists in the final evaluation.

For dentists belonging to the group B without any kinetic exercise, the final retake of the questionnaire showed persistence of pain in the thumb (10 cases) with radiation to the radial edge of the arm (7 cases). Pain was mild in 3 cases, moderate in 4 of them, while severe pain was described in 3 doctors. Additionally, nocturnal pain was found in 3 subjects and paresthesias in the

medial nerve area in 5 cases. Deformity of the metacarpo-phalangeal region was found in 6 subjects.

DISCUSSIONS

1st study: *Ergonomics and prevention of musculoskeletal Work related pathology in dentistry: a pilot study*

Work-related hand pathology is widely confirmed among dentists, specifically connected to different professional factors such as working postures and movements, number of working hours, cumulative time and experience, as well as type of devices and tools handled. Moreover, dentistry performed according to ergonomic settings is essential in order to reduce the burden of musculoskeletal features and to improve related disability and working performance.

Firstly, the current study focus on various musculoskeletal complains defining hand pathology related to precise dental activities; although heterogeneous from pathobiological and clinical picture, dentist's hand represents more than a concept in dentistry. Furthermore, musculoskeletal comfort questionnaire is a self-administered survey adapted for hand involvement and is able to consolidate and homogenize the information on various musculoskeletal problems.

Besides, a complex imagistic assessment based on both hand X-rays and ultrasound if the hand performed in all dentists enrolled in the study highlighted the specific substrate responsible for musculoskeletal complains.

In the majority of cases, the exact etiology of work-related hand pathology was the degenerative damage in at least one joint – trapezio-metacarpal (10), proximal interphalangeal (9), medio-carpal (9), distal interphalangeal (7). Flexor tendons sufferance may also account for clinical signs and symptoms, although with a lower frequency.

Secondly, our study bring into attention a detailed ergonomic analysis of working settings (positions, devices, tools, chairs), hand biomechanics, working performance, stressing the significance of working in an ergonomic environment.

And *thirdly*, we were interested in evaluating a specific kinetic program adapted to each individual based on its own work-related hand complains, with a long-term (12 months) followed-up. Beneficial aspects of physical therapy performed on a regular basis were directed towards an improvement of hand involvement during professional routine practice, with subsequent upgrade of disability and quality of life.

2nd study: *Ergonomic measures and kinetotherapy in the prevention of musculoskeletal disorders in dentistry: focus on hand pathology*

The comprehensive work accomplished during dental care is mainly related to integrity the osteo-articular system of the hand. The complex structure of the wrist meaning joints together with the muscular system is responsible to different types of movements mandatory for the specific professional activity in dentistry.

Unlike the other four fingers, the thumb is able to perform more extensive and varied actions. Moreover, among the two main functions of the hand, pressing can be done without the participation of the thumb, while its role is totally required for fulfilling the function of prehension.

Although the thumb role in prehension is widely acknowledged, the other segments of the hand are also important for the bi-digital or tri-digital finger system involved in prehension (thumb and another one or two fingers); poly-digital prehension by joining the other four fingers or poly-digito-palmar prehension are also commonly used during routine dental care.

Based on these two main functions of the hand, the doctor can make a correct and stable grip of the instruments – a basic step to perform specific dental procedures with better precision and skills, enhancing work efficiency.

Every dentist should be aware of the importance of implementing ergonomic principles in daily practice in order to prevent musculoskeletal issues due to the nature of their work.

Physical exercises performed on a regular basis during a complex kinetic program specifically designed for the dentist hand as in our research improved outcomes namely improved muscle force and mobility of the thumb in the majority of cases included in group A, and also the grip prehension.

A closer look to group B including dentists without controlled physical exercised demonstrated pain persistence - mild pain in 3 doctors, moderate in 4 and severe in the other 3 dentists. Furthermore, hand deformity and median nerve involvement were also reported at final evaluation

CONCLUSIONS

- Work-related hand pathology accounts for significant morbidity and physical discomfort among dental professionals. With a multifaceted pathobiology ranging from inflammatory to degenerative damage of both soft tissue, nerve and joints (wrist and fingers), musculoskeletal issues are typically linked to professional triggers during routine practice in dentistry. **(Paper 1)**
- Working posture (sitting, standing, mixed positions), repetitive movements, dental tools (design, size, handles, material) and chairs (lumbar support, armrest) as well, should promote ergonomic principles in order to minimize work-related musculoskeletal complains and to optimize professional activities. **(Paper 1)**
- An adequate kinetic sequence based on relaxation, stretching, toning and mobilization performed on short periods (10 minutes) during working time should be implemented in daily professional program, as specific exercised lead to improvement of musculoskeletal symptoms, restoration of functional ability, and advance working performance. **(Paper 1)**
- Ergonomics, the science that studies the relationship between the individual and his environment, aims to improve professional performance by proposing rules and principles to be applied in the dental office focussing on dental office design, instruments, tasks and postures. **(Paper 2)**
- Furthermore, awareness regarding the role and importance of implementing dentistry ergonomic principles is mandatory in order to advance work efficiency the in the dental office.
- Individualized kinetic programs aiming to reduce pain, restore joint mobility, tone muscle groups and coordination are successful in refining work-related hand pathology in dentists. **(Paper 2)**

DIRECTION 3**ERGONOMIC AND AESTHETIC APPROACHES IN DENTISTRY****STATE OF THE ART**

According to Patzer, the face, especially the mouth, teeth and smile, seems to remain the most significant part of the body because of its meaning in promoting physical attractiveness: “the hierarchy of importance for facial components appears to be mouth, eyes, facial structure, hair, and nose”.

In addition to other medical specialties, dentistry is able to shape the aesthetics of the lower face, especially on the arches. Looking from the aesthetical point of view, the expectations of our patients are increasing as well as our methods and techniques to resolve their requirements; furthermore, from the point of view of the specialist these requirements are becoming easier to meet due to technological developments and the development of the dental materials industry. Obviously, technological improvements developed in response to the growing demand of the patients for esthetics; on the other hand, the demand of dentists for materials with similar optical characteristics to those of the natural teeth is also increasing (Goldstein, 2018).

However, sometimes the aesthetic requirements are unrealistic and difficult to fulfill, and we can talk about real life challenges and opportunities to offer up-to-date and personalized treatment plans. Different techniques and methods such as whitening techniques, dental veneers, ceramic crowns, orthodontic treatments or implants are currently used to restore facial appearance of patients and to achieve patient satisfactions and expectations.

Esthetic dentistry becomes a very actual interdisciplinary domain based on various approaches of dental status comprising restorative dentistry, prosthetics, orthodontics, implantology, surgery (Blatz et al., 2019; Cernica et al., 2013; Hutu, 2017). It aims to substitute injured as well as malformed tooth structures with artificial materials with biological, functional and physical properties very similar to natural teeth.

Ergonomic aspects play a particularly important role in modern dentistry, supported by related research in order to optimize both the clinical process and the technological line approached. Modern dentistry not only mean the existence of modern techniques and devices meant to increase the quality of the medical act but also the use of revolutionary restoration materials, intended to restore the shape and function of the affected dental structures but also to the concomitant protection of the remaining tissues (Coachman, 2016).

Aesthetics, strength, biocompatibility and retention are the most important qualities that restoration materials must meet to be biologically accepted, to function properly and not to interfere with the development of physiological processes (Lăzarescu, 2017).

Advanced research carried out in this specific field tries to respond as well as possible to these challenges, developing new biomaterials with increased clinical performances. Thus, the explosion of new materials and technologies in the last decades advanced a personalized management taking into account all the benefits and weaknesses of different materials and technologies, in order to adapt them to specific clinical settings (Blatz et al., 2019).

Talking about restorative materials we can use direct restorative materials which can be placed directly in the prepared tooth cavity during a single appointment. Ancient restorative materials are classically based on bone and ivory, while modern ones comprise waxes, gums, alum, honey, ground mastic, powdered pearl, white Corelle, lead, tin, gold, amalgam, darcet,

gutta-percha, silicate cement, acrylic resins, composite resins and glass ionomer cement (Bayne et al., 2019).

Practical, dental biomaterials are applied in an aggressive and hostile oral microenvironment characterized by a specific pH, salivary flow and instable mechanical loading. (Faaz Zohaib, 2018).

It is widely recognized that aesthetic rehabilitation represents an important clinical goal of the *prosthetic therapy*. Obviously, patients ask for a therapeutic approach usually based on aesthetic reasons. Furthermore, the dental providers (physician and dental technician) are taking into account different clinical settings and scenarios when suggesting a suitable design; it is important to understand how to create a gnathological preparation of the abutment teeth, how to maintain and how to rehabilitate the occlusion by means of biocompatible dental materials.

Aesthetic restorations in reduced partial edentation include metal-composite restorations, polystyrene restorations, fiber-reinforced resin restorations, metal-ceramic restorations, all-ceramic restorations (Lăzărescu, 2013; Goldstein et al., 2018).

Ceramic masses used in dental medicine have revolutionized a few decades dental prothetics. Dental ceramics are the most natural appearing replacement material for missing tooth substance available in a range of shades and translucencies to achieve life like results. Ceramics were the last to move into the high-technology phase of development. There is a widerange of ceramic materials and systems on the market that areavailable for use in dentistry (Goldstein, 2018).

Dental ceramics are divided into different groups according to several parameters as follows: (i) their chemical composition (feldspar, leucite, alumina, glass alumina, and glass ceramics), (ii) type of application (tooth reconstruction, ceramic-covering metals, veneers, inlays, crowns, and anterior bridges), (iii) the manufacturing procedure, and (iv) the structure of the material (cast metal, burnished metal foil, glass ceramics, CAD/CAM ceramic, and sintered ceramic core) (Ahrberg et al., 2016; Lazarescu, 2013).

The *metal-ceramic or all-ceramic crowns* stand out due to their high biocompatibility, color stability, high abrasion resistance, and clinical efficacy (Blatz et al., 2019; Goldstein et al 2018).

A ***metal ceramic crown*** is typically a composite entity consisting of two main components: the *metal substructure*, and the *porcelain veneer*. Mechanical and physical qualities of alloys were improved, especially surface qualities for obtaining physicochemical links performance in combination with aesthetic materials; also the chemical composition and heat treatment improved stability, so optimal biocompatibility. The inability to transmit light remains one of the main disadvantages of a metal ceramic restoration, with a negative influence on the aesthetic outcome of the restoration because it may appear dark (Sharkey, 2010); furthermore, allergic reactions to metal elements such as nickel in the metal alloy may also develop in some patients (Goldstein, 2018).

The general trend in dentistry is to replace materials that are aesthetically distasteful, although meeting functional requirements. Thus, the metal alloys used in dental treatments, from amalgam alloy to metal prosthetic restorations, even from gold alloys, are losing ground to the new generations of composites or integral ceramics (Goldstein, 2018).

Today, ***all-ceramic restorations*** are the most aesthetically restorations available in dentistry; their use result not only in life-like appearance of the tooth, but also in high levels of patient aesthetic satisfaction. One alternative to the metal ceramic rehabilitation with similar resistance to the metal but higher aesthetic and biocompatible parameters is zirconia. (Hutu, 2017)

The main purpose of oral rehabilitation is to restore the aesthetic appearance to the dental level in accordance with the surrounding tissues and correlated with the facial appearance. It is necessary to evaluate all these aspects by a dual smile and face analysis, objectively and with the help of previously established marks, in order to obtain the best aesthetic results.

Digital Smile Design (DSD) is an example of planning aesthetic restorations based on dentosomatofacial analysis parameters related to the aesthetic requirements of prosthetic configuration. We talk about a modern technique for complex and complete dental rehabilitation management, which allows planning of the main details for the doctor and for the patient, necessary for the correct perception of the proposed prosthetic treatment. The program offers the possibility of a digital design of the patient's smile as well as a temporary representation of the smile for the patient (Goldstein et al 2018; Omar et al., 2018).

Digital Smile Design is a concept, starting with the fulfillment of a virtual project of the future prosthetic restoration in the aesthetic area, using as accessories a computer, a software and digital patient photos.

Last years allowed a significant advance in both in research activity and in clinical practice in dentistry; several computer software programs for Digital Smile Design are already on market, using multi-conceptual tools that can strengthen diagnostic vision, improve communication, and enhance treatment predictability; such software is able to realize a vigilant analysis of the facial and dental characteristics of the patient; in addition, complex clinical, photographic and diagnostic management are suggested (Coachman et al., 2016; Coachman et al., 2017; Daher et al., 2018; Jafri et al., 2020).

Fixed prosthesis is also based on both classic biomaterials (e.g. restorations with metal support) as well as modern, non-metallic materials associated with modern CAD-CAM (Computer Aided Design – Computer Aided Manufacturing) technologies (restorations on non-metallic support, zirconia type) and minimally invasive preparations. CAD-CAM systems design the future zirconium skeleton, its virtual design contributing to the final characteristics of such a skeleton represented by precision, accuracy and ideal adaptation to organic substructures (Ahrberg et al., 2016; Abdulla et al., 2020; Cervino et al., 2019).

Aesthetic trajectories are in full accordance with the aspects of functionality that are found both in dental rehabilitation by direct methods and in rehabilitation based on prosthetic techniques and technologies that involve the realization in a dental laboratory.

The third research direction within the habilitation thesis brings together two main points emerged as:

1.3.1. Ergonomic-aesthetic implications in prosthetic rehabilitation;

1.3.2. Ergonomic-aesthetic implications in restorative dentistry.

1.3.1. Ergonomic-aesthetic implications in prosthetic rehabilitation

Ergonomics does not only mean optimal times and prevention of musculoskeletal imbalances, but also the identification and implementation in the clinical algorithm of contemporary equipment based on complex dentofacial analyzes, which are the basis for optimal clinical and aesthetic results.

Dental prosthetics can be compared to an equation in which the unknowns are represented by the patient's clinical picture, his general condition, the chosen clinical algorithm, the

corresponding technological line and, last, but not least, the biomechanical and biological behavior of the biomaterials involved.

The studies developed in the field of dental prosthetics are divided into two major categories - fixed and mobilizable prostheses. The criteria used for this splitting are related to several factors including patient background, age, the amplitude of the edentation, and the type of prosthesis.

Several abstracts were presented in various national and international conferences; moreover, I have published two articles in ISI journals and six in IDB journals.

Publication on this topic included:

1. Diana Cerghizan, Tatiana Branasco, Isabela Brujbui, Vasilica Toma, **Cristina Iordache**, Restoration the Dento - somato-facial Aesthetic Balance, a Target of Dental Therapy, Regardless the Patient's Age, *Revista de Chimie*, 68, 10, 2017, 2358-2362.
2. **Cristina Iordache**, Ana Maria Fatu, Bogdan Vascu, Magda Antohe, Possibilities and limits in the rehabilitation of the parameters of the dento-somato-facial aesthetic balance through metal-ceramic therapy, *Romanian Journal of Oral Rehabilitation*, 13 (1), 2021,311-321.
3. K. Erar, G. Gurau, V. Stefanescu, G.Carp, L.L. Pavel, D. Bosinceanu, L.L. Hurjui, A. Murariu, S. Berbece, **Cristina Iordache**, M. Balos, I. Fulga, D. Fratila, A. Beznea, Improvement of Acrylic Resins Structure in Removable Prosthesis Base Polymerization *Materiale Plastice*, 57 (4), 2020, 353-359.
4. **Cristina Iordache**, Andrei Alexandru Iliescu, Kamel Earar, Gabi Topor, Edlibi Al Hage Walid, Aesthetic requirements in protective therapy of lesions coronary odontations without loss of substance, *Romanian Journal of Oral Rehabilitation* 11 (2), 2019 251-258.
5. Elena Luca, **Cristina Iordache***, Oana Țănculescu, Zenaïda Surlari, Dragoș Virvescu, Laura Checheriță, Arina Ciocan-Pendefunda, Maria-Antonela Beldiman, Aspect of aesthetic rehabilitation using Dental Smile Design, *Romanian Journal of Oral Rehabilitation*, 11 (2), 2019,119-123.
6. Magda Ecaterina Antohe, **Cristina Iordache***, Gabriel Drug, The Smile Aesthetics and its Implications in Social Prosthetic Rehabilitations, *Biomedical Open Access Journal For Medical and Clinical Research* 1(7), 2017, 1863-1866.
7. Antonela Beldiman, Anca Vițalariu, Monica Tatarciuc, Odette Luca, **Cristina Iordache***, E. Luca, Technological aspects on aesthetic rehabilitation with fixed prosthesis on zirconia framework, *Romanian Journal of Medical and Dental Education*, 8 (1), 2019, 60-64.
8. Zenovia Surlari, **Cristina Iordache**, Dan Nicolae Bosinceanu, Elena Raluca Baci, Oana Țănculescu, Dana Gabriela Bosinceanu, Dragoș Virvescu, Gabriela Ifteni, Zirconia – dental material for future - a overview, *Romanian Journal of Medical and Dental Education* 7 (2), 2018, 68-74.
9. Oana Țănculescu, Cristina Ifteni, Gabriela Ifteni, **Cristina Iordache**, Corina Cristescu, Adrian Doloca, Computer applications for the evaluation of the dento-somato-facial aesthetic balance, *Romanian Journal of Oral Rehabilitation* 4 (1) 2012, 91-96.

I will further present the main aspects and published results:

Paper 1 Possibilities and limits in the rehabilitation of the parameters of the dento-somato-facial aesthetic balance through metal-ceramic therapy,

By: **Cristina Iordache**, Ana Maria Fatu, Bogdan Vascu, Magda Antohe

Romanian Journal of Oral Rehabilitation, 13 (1), 2021,311-321.

Paper 2 Improvement of Acrylic Resins Structure in Removable Prosthesis Base Polymerization

By: K. Erar, G. Gurau, V. Stefanescu, G.Carp, L.L. Pavel, D. Bosinceanu, L.L. Hurjui, A. Murariu, S. Berbece, **Cristina Iordache**, M. Balos, I. Fulga, D. Fratila, A. Beznea,

Materiale Plastice, 57 (4), 2020, 353-359

Paper 3: Computer applications for the evaluation of te dento-somato-facial aesthetic balance,

By: Oana Țănculescu, Cristina Ifteni, Gabriela Ifteni, **Cristina Iordache**, Corina Cristescu, Adrian Doloca,

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1st study Possibilities and limits in the rehabilitation of the parameters of the dento-somato-facial aesthetic balance through metal-ceramic therapy

The evolution of restorative techniques has made the means of dental treatment of dento-somato-facial aesthetic imbalances more and more accessible and at the same time more and more competitive, more able to reproduce the illusion of persistence of natural dental arches (Hutu, 2017; Lăzărescu, 2013).

Currently, dento-somato-facial aesthetic treatments have as main goal to improve the health of the human body but also maintain an important role in increasing the self-confidence of subjects as a result of the aggressive campaign to promote a typical image of what man means successful in the 21st century: young, strong, healthy, with a wide smile that reveals two dental arches with perfectly aligned teeth, as white as pearls (Goldstein, 2018).

Regardless of the evolution of materials and technologies for making prostheses, the metal-ceramic variant remains one of the most frequently used because it has multiple advantages both from an aesthetic point of view and from a mechanical, biological and economic point of view. Aesthetically, porcelain is currently the only dental restorative material capable of maintaining its texture, surface condition and color for long periods of time without affecting its natural appearance. However, due to their fragility, the ceramic materials alone have certain limitations, which makes the mixed technology, metal-ceramic to still have the supremacy in the field. The limits imposed on this therapeutic means by the presence of the metal skeleton were somewhat overcome by the development of new techniques meant to mask this presence: the use of marginal porcelain, the use of opalescent ceramic masses, etc. (Golstein, 2018).

Aesthetic considerations have gradually influenced over time in various forms dental management so that they have reached the point where suboptimal aesthetic aspects are no longer accepted in the therapeutic outcome. Current standards dictate the avoidance of procedures that aim at an aesthetic compromise as well as the choice of those procedures that ensure an aesthetic benefit wherever possible. The latter involves respecting the integrity of the dento-gingival junction and any dental restoration must be in harmony with the adjacent periodontium. Predictable therapeutic success involves not only a complete and accurate diagnosis but also the development of an appropriate therapeutic plan (Lăzărescu, 2013).

Modern dentistry now has a variety of methods to restore balance somatosensory aesthetic dental facial development the recording techniques et and materials in recent decades is absolutely spectacular. The patient today has higher expectations has exigency that are to be fulfilled and which involve applying a set of complex techniques to be satisfied (Hutu, 2017).

Thus, the development for example of ceramic restorations in the front area, which succeeded to restore the excellent condition of the illusion of naturalness may be compromised by the factors that alter composite and dental facial such as an exaggerate exposure of the gum, malpositions of neighboring teeth or antagonists and improper coronary dimensions (Goldstein, 2018).

The aim of the study is to analyze the opportunity of rehabilitation of metalo-ceramics and limits the possibilities to quantify the rehabilitated disturbances of balance the parameters of the facial aesthetic dental somatosensory setting in the treatment necessary in the studied group.

MATERIAL AND METHOD

A sample of 75 patients, 45 women and 30 men have been evaluated, ages between 24 and 69, who came at the clinical basis for Education of the Faculty of Dentistry Iasi, respectively in private practice. Distribution of the patients from the point of view of age groups was the following (**Figure 14**).

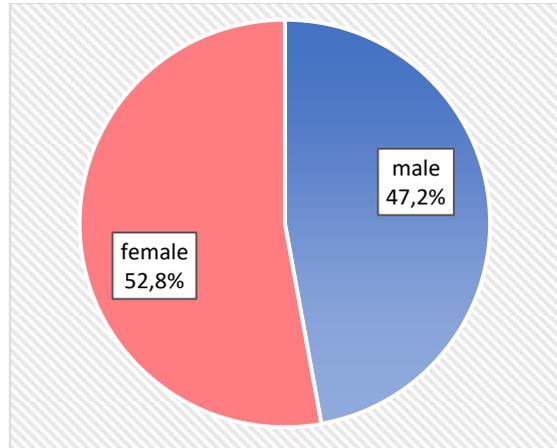


Figure 14 Study group structure

RESULTS

The dental pathology with which these patients presented was varied and was distributed as follows: teeth with intrinsically caused discolorations (6 %), devital teeth, teeth with incorrect endodontic treatments, traumas suffered during the period of dental buds;teeth with coronary fractures (12 %);teeth with extensive coronary dental lesions (58 %);teeth with covering crowns that no longer corresponded to the exigencies imposed by a correct prosthetic treatment (lack of marginal and axial adaptation, color change) (24 %) (**Figure 15**).

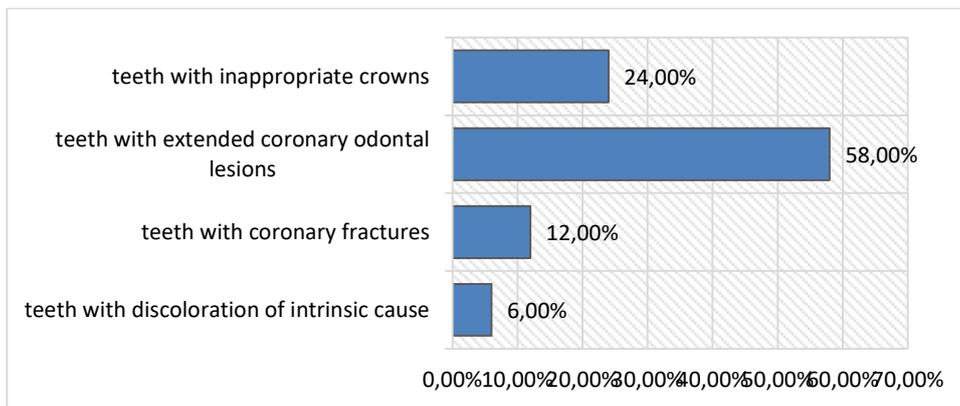


Figure 15 Dental pathology analysed

Dental conditions were accompanied in 86 % of cases by impaired marginal periodontitis by *chronic gingivitis* (75 % of cases), *gingival recession* (16 % of cases) and *superficial chronic marginal periodontitis* (9 % of cases) (**Figure 16**).

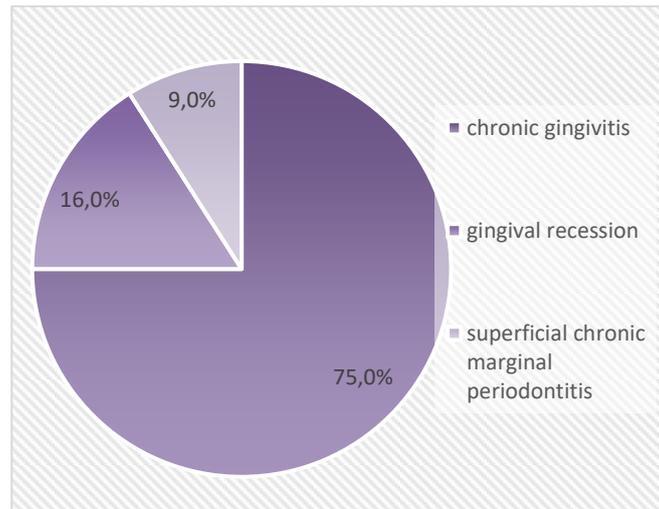


Figure 16 Dental conditions of the study group

The prosthetic restorations anchored in the metal-ceramic register were distributed as follows: restoration of metal-ceramic joints 16%, individual multi-tooth metal-ceramic restorations 21% metal-ceramic bridges 48%, metal-ceramic casting bridges: 15% (**Figure 17**).

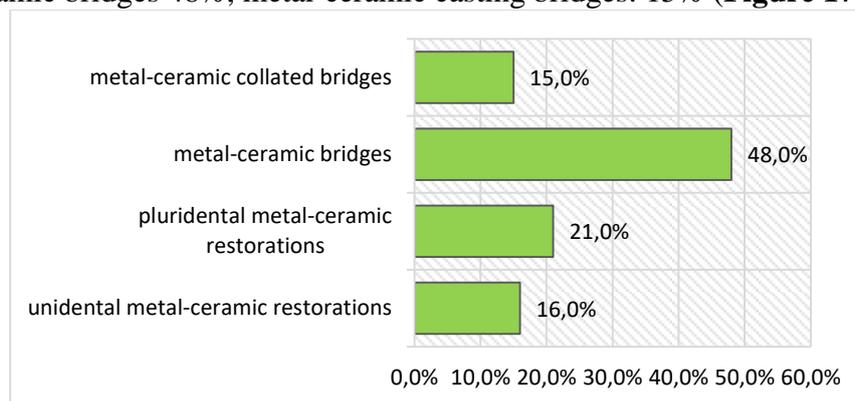


Figure 17 The prosthetic restorations of the study group

The restoration of the dento-somato-facial aesthetic balance by means of unidentary metal-ceramic prostheses must consider the restoration of the main parameters of this balance: shape, contour, structure, texture, proportions and dimensions as well as color, with precautions related to the particular conditions imposed by the location of this type of reconstruction: the anterior area of the arch, exposure to illumination and direct view, exposure of the package area most often, the vicinity of natural teeth, the importance of anterior mandibular and especially maxillary arch teeth facial and dental composition .

The contour of the dental units is the first morphological detail that is noticed by the human eye, before any other information related to the color, structure or shape itself is recorded. The possible aesthetic imbalances registered at the level of a tooth from the region of the anterior mandibular arch and especially the maxilla become immediately observable and generate very strong visual tensions. As a result, the requirements related to the restoration of shape and contour at this level are even higher.

An important parameter that influenced the clinical finality was the position of the central maxillary incisors in relation to the upper lip (**Figure 18**).



Figure 18 The position of the central maxillary incisors in relation to the upper lip

Within our study 37% of patients aged between 21 and 50 showed a more than 2mm exposure under which normally it is around 3 mm to young people and around 1 mm to elderly (due to abrasion phenomena on the one hand and to the modifying of the muscle tone of the lips on the other side) (**Figure 19**).



Figure 19 Distance at the edge of the upper lip maxillary central incisors, insufficient

In these cases it is necessary to establish measures to lengthen the crowns of the maxillary central incisors by: prosthetic restorations, orthodontic extrusion (**Figure 19**). The choice of the optimal method of treatment will depend on the proportion existing in the patient's face, the length of the crown of the maxillary incisors and the type of occlusion. In 10% of cases there was an exaggerated exposure of the surface of the maxillary incisors (**Figure 20**).



Figure 20 Aspects of exaggerated exposure of the surface of the maxillary incisors

DISCUSSION

It should be emphasized that the gingival crest will be established as to restore the correct proportion at the dental level ensure optimal gingival exposure when smiling and to restore the symmetry of the dental arch.

If the existing level of gum generated teeth of an inadequate length reported to the optimum margins levels of maxillary incisors then it must be moved to the apex by interventions of periodontal surgery addressed only to the gum or both gum and alveolar bone through interventions of orthodontic intrusion or by orthodontic intrusion and subsequent prosthetic restorations.

Although the technology for carrying out these restorations has evolved considerably, as well as the materials that can be used for this purpose, the multitude of problems imposed by: the location of a single-tooth restoration or a bridge in an area of maximum visibility of the arch, natural teeth and, direct exposure to light involves a careful clinical evaluation and paraclinical for knowledge are of all the details prosthetic field associated with a rigorous management led dental tissues, periodontal, so as to ensure the necessary conditions for success approach therapeutic.

As in the case of dental arches, restoring the aesthetic balance of dental units involves restoring the balance between the fundamental parameters of dento-somato-facial aesthetic harmony: shape, contour, proportions and dimensions, color, structure and texture that we will present below.

From the point of view of shapes there must be a full harmony between the shape of the teeth restored by fixed metal-ceramic prostheses, the shape of the facial frame and the dento-alveolar arches. There are also studies that suggest that correlations can be made between tooth shape, age, sex and personality: in the young patient, the central incisors have a well-defined morphology, unaffected by abrasion, women have lateral incisors with rounded contours, suggesting grace and femininity, and patients with authentic personalities have canines with well-expressed cusps.

Restoring the contours of the odonto-periodontal units is another approach in order to restore the dento-somato-facial aesthetic balance. The contour of each tooth will respect the contour of the natural teeth and the emergency profile of the brittle teeth, which implies a sufficient and correct preparation of the organic substructures.

Restoring the harmony of this parameter will also lead to the correct restoration of the contour of the dental arches, with an impact on the entire facial composition.

Restoring proportions and dimensions is an essential principle for the aesthetic rebalancing of dental units. Each restored tooth must respect the dimensions of the natural teeth, in full harmony with the remaining teeth.

The central incisors must dominate the dental composition and be relatively symmetrical, this tooth representing the point of maximum attraction at the level of the maxillary dental arch.

Starret et al showed that the ratio between the width and length of the incisors and the canines, respectively, is in both cases around 77-85%. The central incisor and the canine have close coronary lengths, 1-1.5 mm longer than the lateral incisor.

Any alteration of the normal dimensions of the teeth of the maxillary frontal group, which are the most exposed to direct vision, must be corrected, possibly by interventions on the gingival festoon, so as to obtain the expected aesthetic result. Temporary prosthesis becomes absolutely indispensable in these cases.

CONCLUSIONS

1. Dento-somato-facial aesthetics is a field that has known in the last two decades an unprecedented evolution on the one hand as a result of advances in the field of restorative materials and on the other hand due to the evolution and development of various therapeutic methods, both conceptually and practically. To the same extent, the models intensely promoted by the media have led to the imposition of extremely high aesthetic standards that have led to a change in patient expectations related to different procedures.
2. The discrepancies between the success rate estimated by specialists and the aesthetic success rate appreciated by patients can be attributed to the fact that most of the time their perception is different, each patient being unique and having different aesthetic

requirements that must be investigated, understood and interpreted in terms of implementation possibilities from the beginning.

3. A rigorous clinical and paraclinical evaluation is necessary in order to be able to investigate absolutely all the parameters that govern the dento-somato-facial aesthetic balance. Requires meticulous restoration of all details related to shape, contour, proportions and dimensions, texture and surface condition, color, with an average success rate of about 87%.

2nd study Improvement of Acrylic Resins Structure in Removable Prosthesis Base Polymerization

Acrylic resins have dominated the technology of dental prostheses for several decades, being the bases of mobile prostheses, artificial teeth, veneers, and even single-tooth prostheses (Jacket crowns, inlays), immobilization rails, etc. Depending on how the materials are presented, there are several systems: one-component systems, two-component systems; three-component systems. Most materials come in a biocomponent form. Three-component systems are rare, and one-component systems have emerged with the possibility of choosing when to initiate light polymerization. The dosage makes sense only in multicomponent systems. The temperature can initiate polymerization reaction in the following ways: high temperature, direct activation of the monomer (used in industry), the average temperature indirectly by the decomposition - placing an initiator (used in the dental laboratory); at low temperatures, the use of a co-initiator greatly favors the decomposition of the initiator. The temperature required for MMA polymerization in the dental laboratory is between 60-100°C. The temperature causes the polymerization reaction to accelerate, so in the warmer areas of the material there will be more reaction chains than in cold areas. This can cause variations in the average molecular weight of the polymer and the proportion of residual monomer. Excessive temperature rise can cause the monomer to boil and bubbles are formed in the polymer mass. This happens especially in thick parts of the material where the heat cannot be removed enough and quickly (Acosta-Torres et al., 2008; Ausavice, 2003).

At a temperature of about 125°C, the polymer is thermoplastic. Between 125° and 200°C the polymer decomposes by depolymerization; at 450°C, 90% of PMMA is depolymerized. It can occur during the finishing and polishing of the material, due to the release of frictional heat produced by the rotary instrument. Increased speed, worn milling cutters, excessive pressure on the instrument, non-stop work or neutralization of a cooling system are the main factors of heat increase. The thermal conductivity of polymers is generally low; the heat cannot dissipate quickly in the mass of the material and thus the increase of the local temperature is high. This way, the degree of polymerization of the polymer is altered and a free monomer can appear, which will remain in the material. This aspect takes place especially in PMMA degradation, when the monomer releases molecule by molecule from the material. All these lead to inferior mechanical, physical and physiognomic properties and a lower biological tolerance. The thermal regime of the thermo-polymerization must be observed (Avon et al., 2007; Aykent et al., 2010).

The novelty aspects of this study reside in the interrelation aspects brought about by the structural modification of acrylates through the chemical bonding of copolymers, respectively of antiseptic substances with controlled release and the final chemical-biological behavior of the material resulted following the polymerization.

The temperature of the polymerization paste is an additional factor that can influence polymerization. Clinically, a high internal conversion rate results in increased resistance to wear, fatigue, and chemical stability. The pressure regime is a factor that influences polymerization, but without initiating it. In the laboratory, certain phases are performed without the need for a pressure

regime, such as: the performance of temporary prosthetic works, individual spoons, occlusion patterns. The vacuum is used not so much for polymerization as for its precursor. The gaseous inclusions in the material are thus forced to come to the surface due to the pressure gradient. The material will be more homogeneous and, therefore, will result in a protein piece with better characteristics. The use of vacuum in polymerization would make the sub-polymerized layer disappear from the surface due to the lack of inhibitory influence of oxygen in the air, because only a pressure gradient is required. Pressure polymerization (at the rate of several atmospheres) makes the material better condensed. Another variant of pressure polymerization is the injection of the paste into a mold, representing a thermobaropolymerization by injection (Azzarri et al., 2003; Barbarosa et al., 2008).

MATERIALS AND METHODS

A number of 6 test tubes were analyzed in a first stage by means of the SEM technique, under the form of thin rectangular plates of 40 mm in longitudinal dimension and approximately 20 mm in width, with a thickness that varied from 1.8 to 2.5. The mixing ratio between polymer and monomer is specific for each type of product; some acrylates are prepared in the proportion of two parts powder and one part liquid, and others are prepared by mixing three parts powder with one part liquid. Acrylates with a mixing ratio of 3:1 are superior because they have a lower monomer content, are more resistant and have minimal shrinkage. Test tubes were made of flexible acrylate of the Flexite and polyamide type, which were injected according to the technological line destined to this type of material. The Poliapress injecting machine was used. Flexite cartridges were used, which were injected in the mold that contained the specific dimensions of the analyzed test tubes. 10 cm in length, 0.5 cm in thickness and 2 cm in width (**Figure 21**).



Figure 21 Poliapress injecting machine.

The test tubes of classical acrylate were made by mixing the acrylate with the monomer, the final material being inserted in the mold and later subjected to the polymerization process.

We created a number of 5 test tubes in which we used various proportions of a type of copolymer elaborated at “P. Poni” Institute of Macromolecular Chemistry from Iasi. AM 88 – maleate copolymer of Na, methyl methacrylate in proportion, to which groups of Eugenol linked.

The biological analysis was carried out by appreciating the degree of adherence of candidiasis yeast, bacteria frequently met at the level of the oral cavity with elder patients. The AFNOR artificial saliva was used, according to the French standards, to which improvements were made, being inoculated with strains of *Candida albicans* yeast isolated from a case of prosthetic stomatitis (103 yeasts/mm²). The test tubes obtained were introduced in 5 containers, incubated at 36, for 72 h. Later, they were introduced in dental plaque revelator, rinsed with pure

water, dried, and then recycled. To the basic components of the AFNOR saliva - NaCl 0.70 g/L, KCl 1.20 g/L, Na₂HPO₄ 0.26 g/L, NaHCO₃ 1.50 g/L, KSCN 0.33 g/L, Urea 1.35 g/L – glucose was added, 5 g/L and casein peptone.

Candida albicans has negative effects on the acrylate it adheres to due to its filament structure, contributing significantly to the degradation of the acrylic material, which is why the individualization of the non-adherence possibilities is extremely important. The test samples elaborated at the same size were subject to the traction forces on the Hekert test machine within the Polytechnical Institute of Iasi, the Department of Material Resistance.

RESULTS

The SEM analysis reveals structural continuity; at the level of the test tubes whose copolymer proportion was below 1/3 of the powder quantity, there appear aspects of discontinuity with implications at the resistance level in case of test tubes in which a reduction of the monomer was attempted in view of obtaining a higher degree of biocompatibility. Equally, a reduced quantity of Eugenol fails to influence the continuous structure of the acrylate. Polymerization by injection confers a dense structure to the injectable acrylate analyzed, with a net structural superiority compared to the classical acrylate (**Figure 22**). The absence of the monomer confers a net biocompatibility to injectable structures, but allows the adherence of candida yeasts.

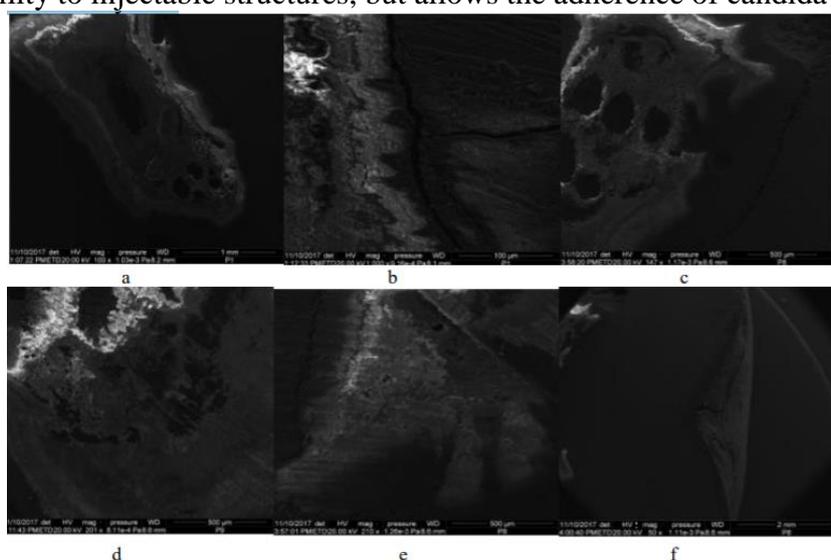


Figure 22 SEM analysis of six sample: a. acrylate +AM88 4g, b. acrylate +2 mg AM88, c. acrylate+5 mg AM 88 + eugenol, d. acrylate and quantitatively diluted liquid, e. classic acrylic sample, f. flexible sample

The techniques for achieving the powder and liquid ratio are weight dosing, weighing of powder and liquid. The monomer must be in the proportion indicated by the package leaflet that accompanies the product. For the homogeneity of the chemical composition and for color uniformity, it is recommended to mix it with a glass rod, after which the container is covered with a glass plate, to prevent vaporization of the monomer.

In the first phase, the mixture forms a friable paste; in the second phase, a sticky, flaky and sticky paste is formed, which flows; in the third phase, the paste is non-sticky, it comes off easily from the walls of the container. In this state of plastic paste, the substance is introduced into the mold.

Upon contact between the monomer and the polymer particles, the outer layers dissolve progressively (the monomer has an active role and the polymer has a passive role): having free valences. The polymerization initiator (benzoyl peroxide) known as the catalyst, produces the release of the double bond of the monomer, followed by activation. As the monomer continues its action of dissolving the polymer particles, the paste becomes more and more viscous, non-sticky, taking on the appearance of dough.

Negative results from the perspective of *Candida* adherence were also noticed in case of test tubes which contained the AM88 copolymer and the eugenol formations introduced at a structural level. These significantly negative results are based on the antibacterial effect of the copolymer, boosted by the eugenol addition (**Figure 23**). The chemical structure of the AM88 copolymer in the presence of sodium carboxylate, which confers a polyelectrolyte nature, influences the antimicrobial action.



Figure 23 Aspects of the *Candida Albicans* adhesion to the specimens

The duration of these phases is variable, being influenced by the temperature of the environment and of the container; the physicochemical properties of the product (enlargement of the polymer particles) and the presence of plasticizers that facilitate the penetration of the monomer inside the particles.

Following the examination of the tensile strength of the traction test samples one can notice the fragile strength of the classical acrylate at a Force of 1550 N, the breaking of samples which had in their structure a quantity of copolymer AM88 in excess of 4mg, respectively 5mg and eugenol, which gave in at a force of 1400N, respectively 1200 N and the high tensile strength of test samples made of flexible acrylate.

The presence of the AM 88 copolymer, respectively of Eugenol, the substance that binds chemically to the copolymer providing a controlled release, offers the acrylic structure obvious antiseptic qualities; however, the biomechanical resistance is reduced as the quantity of copolymer increases.

If the proportion between monomer and polymer, indicated by the leaflet, is not observed, a series of inconveniences appear: the excess of monomer that determines the increase of the coefficient of contraction of the acrylic mass at the level of ready-polymerized prostheses; the appearance of pores, both in the thickness of the plate and the saddles, as well as on the surface, with negative effects for the mechanical resistance, the maintenance of hygiene and the chromatic appearance; the excess of polymer that determines the reduction of plasticity, the non-uniformity of the chromatic aspect of the prosthesis; low mechanical strength. In self-curing RAs, the polymer powder contains the initiator and the liquid (monomer) contains the accelerator and inhibitor.

DISCUSSIONS

Self-curing acrylic resins have wide applications in the manufacture of gnathoprosthetic devices: making temporary fixed AGPs, making teaching models from RA, modeling with RA. The handling time depends on temperature, mixing intensity and powder/liquid ratio; acrylate fingerprint-model of root canals to make DCRs, making the individual spoon of acrylic resins. The disadvantages are related to the increased percentage of residual monomers, chromatic instability, reduced stiffness. The disadvantages of self-curing resins have led to the use of light curing, thermo-polymerization or other hybrid processes (Barbosa et al., 2007; Bidanda et al., 2008). Thermo-polymerization is a polymerization reaction that requires an external caloric intake for initiation. The required temperature depends primarily on the temperature of decomposition of the initiator into free radicals. The heat required for the thermo-polymerization process is obtained by introducing the model-resin-sink assembly in a water bath brought to the desired temperature (maximum 100° C) with the help of a heat source. The lack of water temperature control leads to the obtaining of an acrylate with poor mechanical properties (Tyas et al., 2004).

Thermo-polymerization can be used only in indirect techniques, especially for final prosthetic parts and less often for temporary or intermediate stages: obtaining physiognomic components on crowns and mixed bridge bodies, plating a metal skeleton with RA, in the crowns and mixed bridges, making inlays in the DRC by indirect technique; making temporary crowns and bridges; some techniques for making individual ligatures or occlusion patterns; making mobile and movable prostheses, making artificial teeth; making temporary fixed prostheses; repair of fractured prostheses, although, in these cases, selfcuring acrylates are preferred, avoiding a new heat treatment-safe source of deformations; Photopolymerization is the polymerization initiated by the external contribution of electromagnetic radiation, by irradiation with UV or visible radiation. The photopolymerizable resins for making the bases of the adjunct prostheses are materials based on UDMA and acrylic copolymers, inorganic microfine silica fillers and photo initiation system. They are delivered in the form of foils of a plastic consistency, being foldable. The use of argon laser systems for light curing leads to improved mechanical properties (Ohlmann et al., 2008).

Polymerization of the base of the prosthesis is made of acrylic resin, by introducing it in the form of a paste in patterns. Polymerization consists in the formation of a very large molecule, resulting from the gradual addition of identical monomer molecules, resulting in an increase in molecular weight. According to Skinner, the acrylic resins used for the bases of prostheses must have the following biological and physicochemical properties: be tolerated by the tissues with which they come into contact; be stable in all conditions of use; be insoluble, tasteless and chemically neutral in all foods and enzymes in saliva; not to be distorted, dilated or contracted at the temperature of the oral cavity or under occlusal pressure, be resistant to abrasion and brushing for maintenance; be easy to polish to present surfaces without porosities; be with aesthetic chromatic aspect; be with a stable chromatic appearance; easy to handle; be easy to repair in case of fracture. Acrylic resin comes into liquid and powder form. The liquid is the monomer represented by methyl methacrylate. It has the following physicochemical properties: it is transparent, boils at 100°C, is volatile, flammable, insoluble in water, with specific odor, is a strong organic solvent, it can polymerize spontaneously under the influence of light and heat, which requires be preserved in brown vials, in which 1% hydroquinone or pyrogallol are added with an inhibitory role in polymerization. It has a density of 0.945 g cm³ at a temperature of 200°C and a molecular weight of 100. The powder or polymer is the polymerized form of methyl methacrylate. It is composed of specific particles, obtained by dispersing the centrifuged monomer in a neutral liquid (water at high temperature); inert substances (talc) are added to the base substance to prevent physical or chemical bonding of the particles. The well-matched products have various shades of pink, being accompanied by keys for choosing the color, in correlation with the color shade of the patient's gingival mucosa. There is also a colorless powder indicated

for patients who show intolerance to the dye incorporated in the acrylate. Superacryl acrylic resin (Spofa) is produced in six shades of pink, each marked with a letter: A; B; C; D; E; F. The colorless superacryl is marked with the number 0 (zero). Each kit is accompanied by instructions for use regarding the proportion of the mixture, the preparation technique, the polymerization rules, etc. Thermo-polymerization of acrylic resin - polymerization is a physicochemical reaction in which the monomer binds to the polymer and forms the molecular chain from which a solid body results (Ohlmann et al., 2008; Rammelsberg et al., 2005).

In the oral cavity, the sources of moisture contamination are diverse. The most important is saliva. Another source of contamination is the suction fluid and blood from the marginal periodontium. Moisture is harmful for several reasons. Most monomers and polymers are hydrophobic, so no contaminated areas can appear on contaminated surfaces. Polymerization is a process that takes place over time; it continues slowly due to the chemical mechanism, hardening the material in areas not exposed to light radiation. Self-curing is a polymerization reaction that takes place without the material requiring an external energy input for its initiation. It is sometimes also called chemical polymerization (chemo-polymerization), which is somewhat inappropriate, because obtaining polymers is generally a chemical reaction. The initiation systems in this case consist of two compounds, which leads to the need for biocomponent systems. Factors influencing the polymerization time are temperature-time increases with decreasing ambient temperature; powder particle size; type of polymerization increases with particle size; the volume of acrylic paste subjected to polymerization has no significant influence on time. pH has a value between 4 and 5, being minimal after the second day of polymerization. It grows slowly and reaches the value of 5 only after 2 months. In self-polluting prosthetic RAs, mixing the powder with the liquid is followed by a gradual increase in viscosity, to the saturation stage, similar to what happens in thermo-polymerizable RAs. This increase in viscosity is due to physical and chemical changes in the mixture. The great advantage of thermo-polymerizable RAs over self-polymerizable ones is the stronger diffusion of the monomer and the crosslinking agent in the thickness of PMMA beads. Thermopolymerizable RAs have a lower residual monomer content, superior hardness, rigidity, and strength. However, the solubility and absorption of water are similar, regardless of the type of polymerization.

The SR Ivocap acrylic resin is much more impact resistant (5845.2N / m) than the others. The technique of thermobaropolymerization with injection compensation leads to the formation of polymers with superior impact resistance. The pressure regime is a factor that influences the polymerization, without an initiation.

The injectable acrylic polymer, which contains polycarbonate nylon, has a higher bending and lower modulus of elasticity (Vanzeveren et al., 2003).

These changes increase the impact resistance are accompanied by an increase in transverse deformation. For SR Ivocap, low values of elasticity were obtained. Regarding the hardness of the obtained materials, it was found that the polymerization technique has an important influence on it and that with the increase of the pressure, materials with higher hardness are obtained.

CONCLUSIONS

The polymerization regime performed correctly fails to influence the resistance of the biomaterials used, the latter being influenced by the structure of the acrylates, which was optimized through the chemical bonding of the AM88 copolymer, respectively of the eugenol.

The optimum chemical – biological results are due to the addition in the meta-methyl powder of 2 mg of AM 88 copolymer, which modifies the surface state of the material and decisively influences the adherence of candida filaments. With the increase of the copolymer

quantity and the addition of antiseptic substance with controlled release, the antiseptic effect increases but the aspects of structural discontinuity revealed by the SEM analysis are correlated with a low tensile strength. The polymerization pressure regime does not increase the bending strength.

The product made by the technique of thermo-polymerization with injection compensation has the highest values of breaking strength. Breaking strength is an essential element in evaluating the quality and duration of use of the prosthesis.

3rd study: Computer applications for the evaluation of the dento-somato-facial aesthetic balance

Today, as a consequence of the evolution and development of numerous technics and aesthetic materials, dentistry is considered, more than ever, an art. As in most art forms, the final results of the dental technics have to be also very pleasant. However, unlike other art forms, the aesthetics cannot be only the contribution of the artist. The concept of the dental aesthetics is subject of numerous variations which has to do with the personal interpretation and individual perception. Although the final result is controlled by the dental practitioner, the patient has to directly contribute to the decision making process.

DSF (Dento-Stomato-Facial) Aesthetic Software is an application that focuses on aesthetic evaluation based on the following inter-related directions: body aesthetics, dental-facial aesthetics, dento-gingival aesthetics, dental-dental aesthetic and dental aesthetics.

This paper proposes a new approach of the dento-somato-facial aesthetics by focusing on the following interconnected elements: body aesthetics, dental-facial aesthetics, dentogingival aesthetics, dental-dental aesthetic and dental aesthetics. At the same time, the paper presents a novel computer application for the assessment of the dento-somato-facial balance. The original contribution of this software is the approach of the aesthetics disequilibrium from the somatic point of view as well as facial and dental point of view, unlike other software that focus only on the facial and dental aspect.

The reason of this enhanced approach resides in a profound knowledge of the stomatognathic disequilibrium, each component, including the somatic one, playing an important part in achieving the desired harmony on the whole.

MATERIAL AND METHODS

Computers demonstrate their utility in all the clinic-technological phases of the therapeutic algorithm and also in the dental training of the future practitioners. DSF aesthetic soft is an application that employs different image processing technics and modern data base systems and development platform for a better identification and usage of the dento-facial and somatic aesthetic evaluation criteria (**Figure 24**). This application runs on Windows XP, Windows Vista and Windows 7 and for generation reports Microsoft Office (2003, 2007 or 2010) is required. The goal is to process different images and to make measurements, angle calculations, planes drawings which are all specific to aesthetic balance assessment. The application uses Microsoft Access Database.



Figure 24 DSF Aesthetic Soft splash screen

RESULTS

The software is based on the following modules:

1. Patient management Like most of the dental software designed for dental practices, DSF Aesthetic Soft contains a patient management module. It can create, edit, delete, load and save patient data. Patient data are saved in data based which can be used in other platforms or can be imported in other dental applications.

The database is structured on several tables, containing specific data. For patient management, the patient table is used containing information like first name, last name, birth date, address, phone, email, ID etc. Already existing patient data can be loaded and the evaluation process can be continued or restarted by adding new measurements or re-measuring some parameters. New patients can also be created. Already existing patient data can be loaded and the evaluation of the patient can continue by adding new measurements or modifying existing ones. Also patient data can only be visualised. Using the application new patients can be added (**Figure 25**).

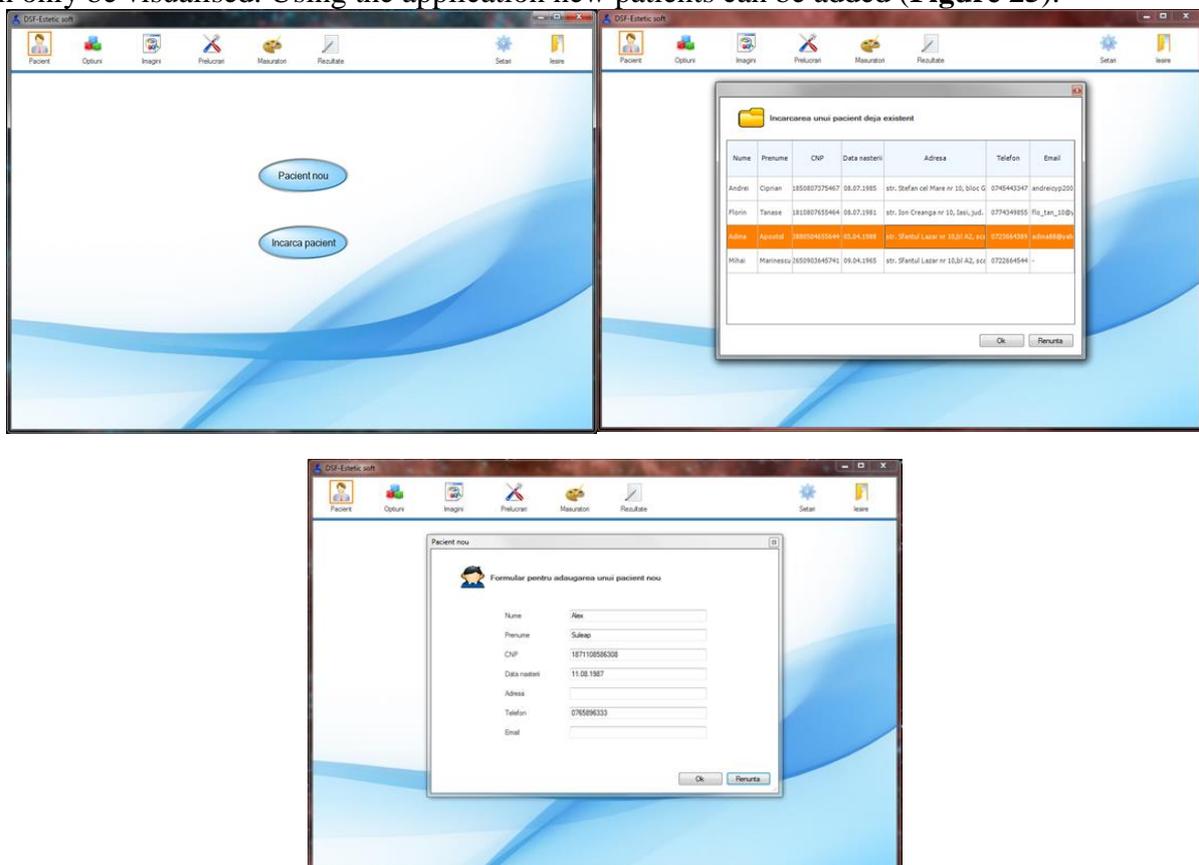


Figure 25 (a) Patient module function; (b) Loading patient data; (c) Adding new patient

2. Application options This software focuses on the esthetical evaluation on 3 levels: somatic balance, facial balance and dento-facial balance (**Figure 26**).

a. Somatic balance This type of evaluation requires 2 pictures: one from front and one from the side. The pictures include the whole body because measurements of different segments of the skeleton are desired (from the shoulder, waist, elbows, iliac crest, knee etc.)

b. Facial balance For this evaluation 2 pictures are required: picture from the front with closed mouth, one from the side also with the closed mouth. The pictures must include only the head of the patient, because the points of the interest are trichion, ophrion, nasion, menton, etc.

c. Dental - facial balance For this type of evaluation six pictures are required: front picture with smile, front picture with a wide smile, front picture with evident dental arches, side pictures with smile, side picture with wide smile, side picture with dental arches.

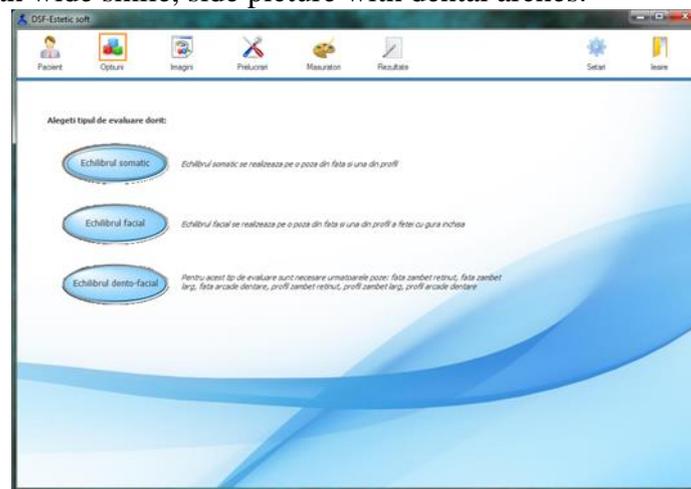


Figure 26 Evaluation types

3. Images selection Patients images should be grouped in folders as follows: in the application folder one subfolder for each patient should be created. Inside this folder, 3 different folders should be created, one for each evaluation type (somatic, facial, dento-facial). Other images could be created like whole body front picture. The best images can be selected having as criteria the image quality and the visibility of the important elements which are at the base of the evaluation (**Figure 27**).

The used images and their purpose are stored in the data base. The table pictures contain information like: the folder where the picture file is located, picture file name and usage of the picture (if it is a front whole body picture or a picture of the dental arches). The user has to select the source folder which contains the desired images and then select the images that will be used for the evaluations.

4. Standard image processing As in the case of image processing applications standard image processing is required also in this software. One of the most important features is image rotation which is needed for setting the subject in vertical position. The picture can be rotated with an angle between -10 to 10 degrees. This is an important step for standardising the image which will ensure more precise measurements. The "zoom" feature is useful for visually amplifying some elements contained in the picture.

Other functions like brightness contrast have the role of enhancing the quality of the picture which will help the measurement process. The most important role of these image processing functions is to create high quality image of the subject. However a picture that not contains the necessary information cannot be greatly improved by the image processing technics. This is way the image acquisition is very important in the first place. Proper lighting and a good resolution are recommended. If the acquired image is of poor quality, then retaking that picture might be the best option, instead of processing it.

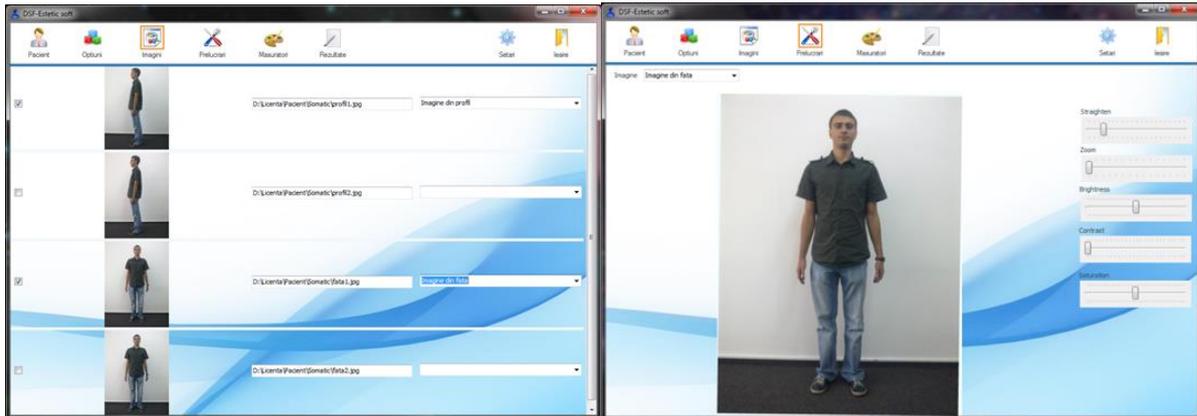


Figure 27 Image selection. Image processing

5. Measurements This is the most important step for the evaluation process. At this stage the user has already selected a patient and the type of the desired evaluation, has important the necessary images and performed the necessary image processing. If at this point the images have not the necessary quality for starting the images process, then all the above steps have to be repeated. In this module the user will define certain guide points on the body which will help in measuring distances, ratios, angles etc.

Every guide point is saved in the data base, in the table points using the xy coordinates which will define the point location in 2-dimensional space. These points define different elements like left shoulder, right knee etc. These points that the user has to define are grouped in several section based on the desired evaluation type. However, for each picture some reference points have to be defined. These points are not used in the actual computation but are essential for the evaluation. Some of these points define the marker line.

The marker line is the line for which the real size is known. This is necessary for calculating the ratio between the image dimensions and the real world dimensions. The marker line could be any element not necessary related to the subject body. It could be also an object visible in the image.

In the image below we used the forearm which is parallel to the image plane. In the above example we used somatic evaluation, based on the front image. The symmetry based on the median line is analysed. This means the reference is the median plane. For this the user has to select one point and then draw the vertical line that runs through it. Next all the points from the displayed list have to be defined: left shoulder, right shoulder, left elbow etc. If one point is skipped some evaluation will not be possible. In the example bellow the display points have to be defined for evaluating the segments: vertex, menton, shoulder etc. For each point a horizontal line is drawn dividing the subject's body into several sections. For defining a point, reference image can also be used. Other examples for defining points for facial evaluation front and side images are showed below (**Figures 28, 29**).

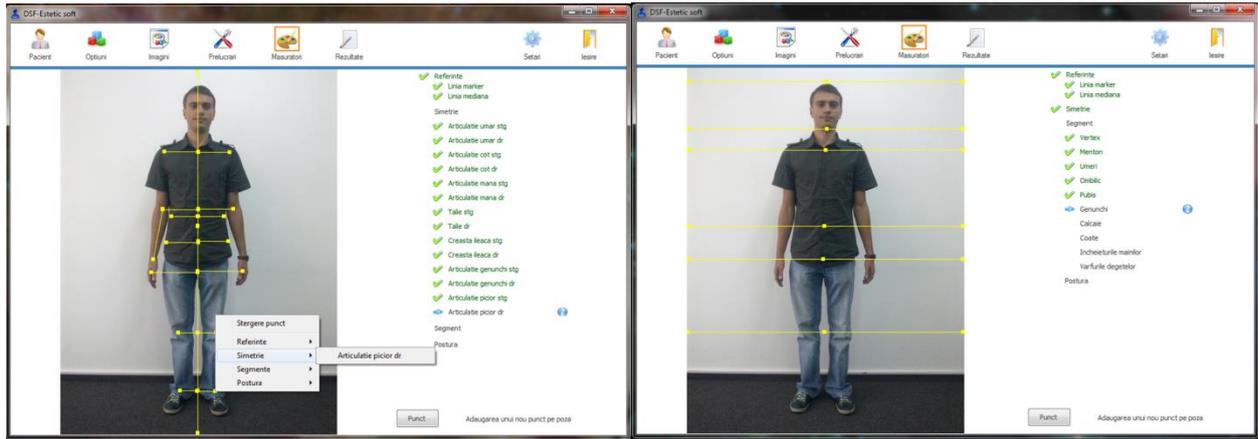


Figure 28 (a) Defining points. (b) Defining segments

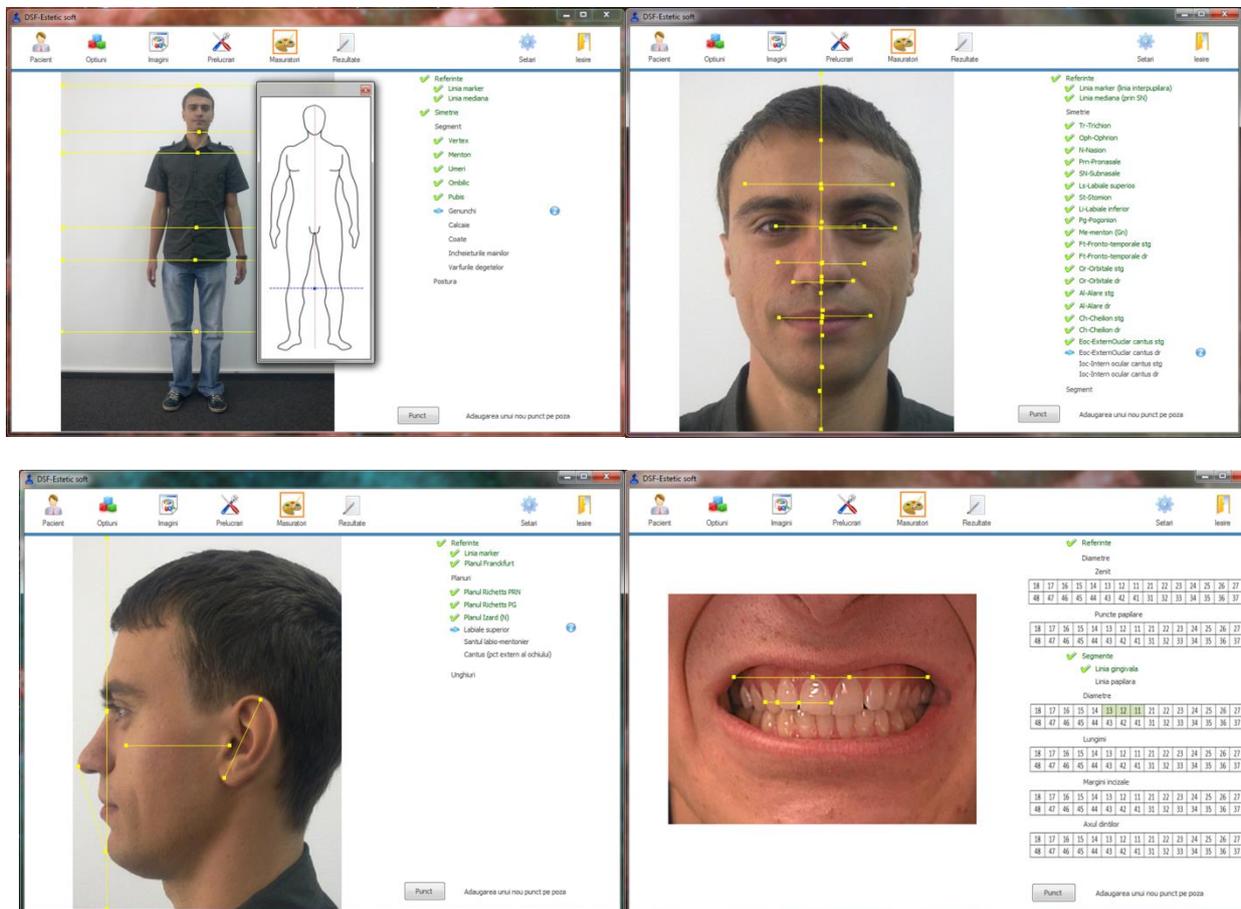


Figure 29 (a) Reference image. (b) Reference points front image. (c) Reference points side image. (d) Reference points dental image

A necessary stage in diagnosis is the analyses of cephalogram. The specialist can draw the necessary planes and angles in order to establish the type of the dental facial imbalance (Figure 30).

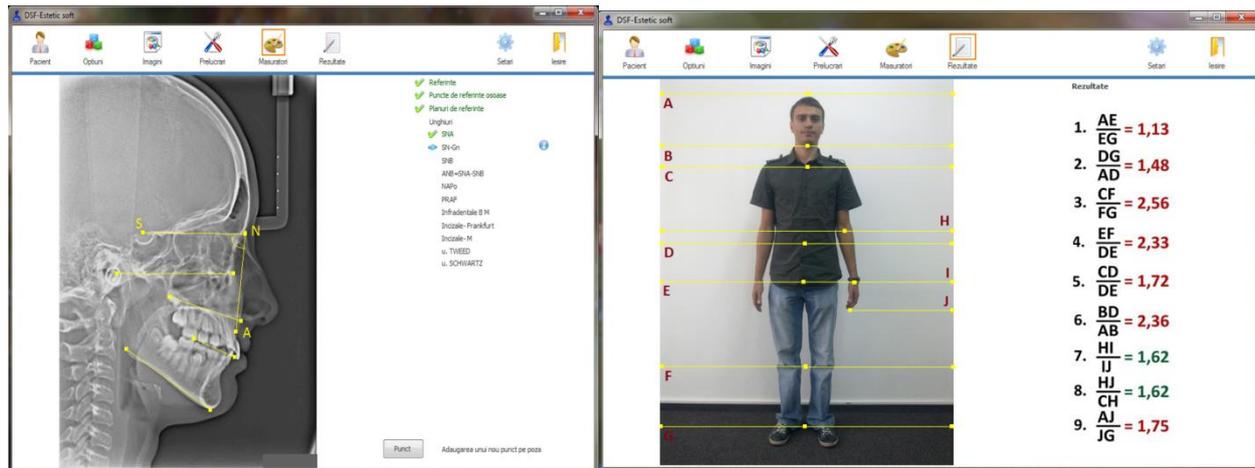


Figure 30 (a) X-ray measurements. (b) Full body ratio calculation

6. Reporting Once the points, segments and planes of interest, the software automatically performs the data processing. This consists of comparison between similar sections, distance calculation between different points and reference planes, ratio calculation and comparisons with references values.

In the images above, symmetries based on the median line are evaluated for the full body as well as for face and dental arches. Similarities and ratios between the segments are also evaluated.

On user request, the software will display all the resulting values or only those who lie outside the normal range. The final reports can be shown over imposed on the patient's image pointing out the deviating segments or on a standard image from the own library. These standard images can also be accessed through the help menu.

Even though the software reveals the abnormal geometrical relations, guiding the specialist towards diagnosis, the final interpretation belongs to the medical expert who will establish the final diagnosis. This is achieved by correlating data from the computer application with information obtained through clinical and paraclinical evaluation which are obligatory in a complex and complete approach of the case.

It is more and more obvious that to be a high standard medical specialist requires not only good training in theoretical al practical aspects of a specific medical area but much more. "No doubt, Pius Servien used to say, you have to be born for science and for art as well". It requires besides of vast medical culture, the knowledge of ethical and moral principles in general, and also sound intellectual qualities. Beyond that the specialist has to nurture his or her aesthetic sensibility good taste and artistic refinement. How the medical specialist could otherwise perceive and understand the abnormal situations, the disease which affects the beauty and harmony of a healthy human body? Without all these qualities the personality of a specialist appears cold and sterile, transforming him / her into a repository of scientific knowledge.

DISCUSSION

In the context of the technical and informational revolution that characterizes our century, dentistry offers a wide field of applicability for a whole series of discoveries and researches carried out in other fields, with which it apparently has nothing to do: the aeronautical and space industry, the construction industry. machines, automation and robotics, informatics, statistics, architecture, biomaterials, etc.

The computer demonstrates its utility in all clinical and technological phases of the therapeutic algorithm and, in addition, in the training phase of students and future dentists. In the particular case of dental practice, in order to streamline healthcare, numerous software programs have been created that aim to create a database containing the records of all patients, personal data

and the work performed. Also, together with the patient, different appointments of the subsequent sessions can be made on the computer, as well as the sequence of the maneuvers to be performed and the individual patient's file.

There are a number of computer programs designed to establish an interactive relationship between doctor and patient; such programs allow the patient to participate in choosing the type and appearance of prosthetic reconstructions, and, moreover, these applications offer several solutions for the same case, the patient having the option to choose the most convenient from his point of view. Computer technologies are clinical realities of modern dentistry. Although difficult to access on a large scale, primarily due to high costs, they are undoubtedly the future tools of high-performance medical practice.

The application employs different images processing technics and the modern .net development platform. The application contributes to a better identification and use of the dento-facial and somatic aesthetic evaluation criteria. The software can display all the determined measurements or only those which diverge from the normal ones. The final reports can be presented either superimposed on the patient picture showing the deviated segments or on a standard image from the software library which can be also access at any time though the help function.

Although the application can reveal the deviated values from the normal ones, thus pointing towards a diagnostic, the final interpretation however belongs to the dentist. The practitioner will establish the final diagnostic by correlating the data obtained from the computer application with that from clinical and paraclinical evaluation which is necessary for a complete and complex approach of the case

CONCLUSIONS

1. This paper proposes the approach of the dento-somato-aesthetics based on the following the interrelated directions: body aesthetics, facial aesthetics, dento-facial aesthetics, dento-gingival aesthetics, dento-dental aesthetics and dental aesthetics.
2. We present a computer application for evaluating dento-somato-facial balance. The original contribution of this application is the software concept that proposes the approach of aesthetic imbalances not only from dental and facial point of view, but also from somatic point of view.
3. The motivation of this concept resides in a profound knowledge of the stomathognat system imbalances. Each component, including the somatic one plays a very important role in the overall harmony.
4. The main characteristic of this paper is the interdisciplinary way of thinking by correlating anthropometric and orthopaedic data, different dental specialities and computer processing, resulting in a software with immediate clinical and educational applicability.

1.3.2. Ergonomic-aesthetic implications in restorative dentistry

Dental aesthetics designates the goals of dental treatment interventions across all specialty areas, from preventive and restorative dentistry to prosthodontics, orthodontics, periodontics, as well as oral and maxillofacial surgery

The increasing request for esthetics in dentistry has fashioned a wide range of ceramic, composite and porcelain restorative materials accessible for dental restorations. The variety of restorative options available for clinicians has reformed outstandingly over the last 30 years. The challenge is to choose optimal materials based on durability, cost, fluoride-releasing properties, aesthetics, chairside time and ease of use. Furthermore, developments in restorative material formulations as well as adhesive technology have expanded the treatment possibilities for the

clinician and technician and provided simpler, more conservative, and more economical solutions to many restorative and esthetic challenges.

Therefore, dental rehabilitation remains a complex process in a systemic context in interrelation with the biomaterials used, with their degree of adhesion according to the type of dental lesion.

Within this sub-direction, aesthetics and ergonomics represent very important therapeutic principles, whose practical implementation is also dependent on a series of variables that influence the chosen therapeutic solution. Thus, the location of dental lesions is correlated with their topography and with the aesthetic standard-functional standard binomial.

The research carried out brought together the following publications:

Paper 1 Methods for the assessment of esthetic posterior restauration,

By: Cristina-Angela Ghiorghe, **Cristina Iordache***, Claudiu Topoliceanu, Pancu Galina, Antonia Moldovan, Sorin Andrian

Romanian Journal of Oral Rehabilitation, 10 (4), 2018, 130-135.

Paper 2 Composite Resins – Multifunctional Restorative Material and Practical Approaches in Dental Field,

By: Alice Murariu, Ciprian Dinu, Doriana Agop Forna, Victoria Stefanescu*, Gabi Topor, Norina Consuela Forna, Silvia Fotea, Gabriela Gurau, **Cristina Iordache**

Revista de Materiale Plastice, 57 (2), 2020, 276-284.

Paper 3 Mechanical Properties of Bis-GMA/HEMA Resin Composite with Addition of Silicon Dioxide Nanoparticles

By: Gabi Topor, Kamel Earar*, Ion Ciuca, Sorin Berbece, Victorita Stefanescu, Adrian Beznea, Camelia Grigore, Marius Maris*, Silvia Fotea, Cristian Onisor, Ramona Firea, **Cristina Iordache**, Gabriela Gurau

Revista de Materiale Plastice, 58 (1), 2021, 257-264.

1st study: Methods for the assessment of esthetic posterior restauration

Due to the longevity associated with a low cost, the indications of the composite resins are extremely various, the range including dental caries, dyschromia, exposed dentin demineralisation, diastema, dental fractures, abrasion, attrition, surface erosions and development defects.

Last years, dental practitioners focused on the use of the esthetic materials for posterior direct coronal restorations. The producers improved the range of composite materials to supply both excellent adhesion to the dental tissues and esthetic reconstruction of the affected dental tissues (Sadawsky, 2006). The longevity of posterior esthetic composite restorations is ensured by collaboration between patient and dental practitioner that will motivate and monitor the appliance of the oral hygiene measures, will assess the composite restorations and will use at certain time intervals the minimal invasive repair techniques, finishing, polishing, and refurbishment. This collaboration will increase both the longevity of posterior esthetic composite restorations and satisfaction and life quality of the patients (Calley, 2009).

Regarding the decision of repair or replacement of the posterior esthetic restorations, the use of proper assessment criteria is of major importance considering that the use of improper criteria can lead to failed decisions regarding the repair/replacement or even at overtreatment.

Academy of Operative Dentistry promoted the idea of minimal invasive interventions and the prolonging of the restorations longevity by monitoring at regular time intervals and the focus mostly on repair interventions and less on replacement (Lynch et al., 2014).

In 2007 new criteria for the restorations assessment were published in Journal of Adhesive Dentistry and Clinical Oral Investigation. These criteria were approved by FDI Scientific Committee in 2007 as „standard criteria”. The clinical assessment of the composite restorations may be useful to evaluate the quality of the restorations applied by dental practitioners in private practice (Geissberger, 2010).

The aim of study was to assess, based on FDI criteria, a group of esthetic posterior direct restorations and to establish the proper refurbishment or repair methods.

MATERIALS AND METHODS

59 composite resins posterior restorations, from 15 patients, were assessed based on FDI criteria. The evaluation was done on esthetic, functional and biologic properties. Data were statistically analyzed using Microsoft Excel 2007.

RESULTS

In **figure 31** is seen at the tooth level 1.4 a disto-occlusal esthetic restoration, with changes of morphology, color, rusty to the surface. It also presents a marginal secondary caries.



Figure 31 Clinical aspect of composite resins restauration 1.3, 1.4

Our results regarding the esthetic criteria found high number of esthetic acceptable criteria for surface luster (3.7), surface staining (3.4), color stability and translucency (3.8), and anatomic form (4.5). For a low number of restorations with unsatisfactory or unacceptable criteria, it was indicated replacement (**Figure 32**).

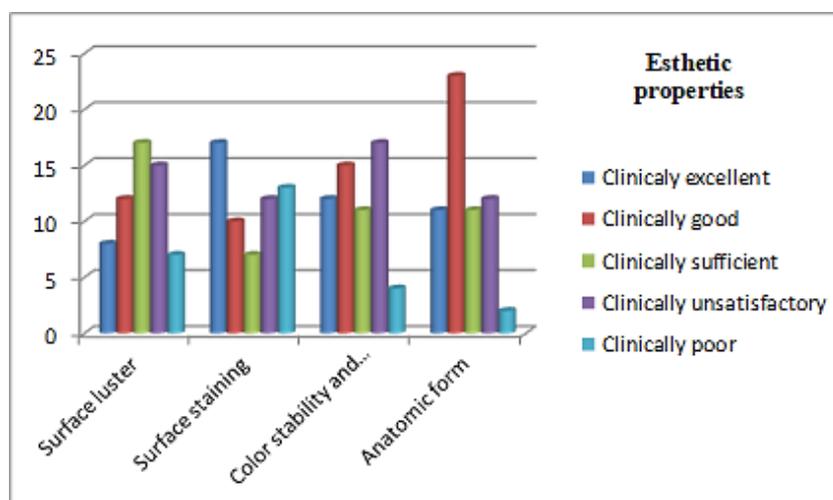


Figure 32 Esthetic properties

In **figure 33** are presented data regarding functional FDI criteria for the assessed composite restorations. The graph shows that most of the investigated posterior composite restorations received excellent FDI functional criteria.

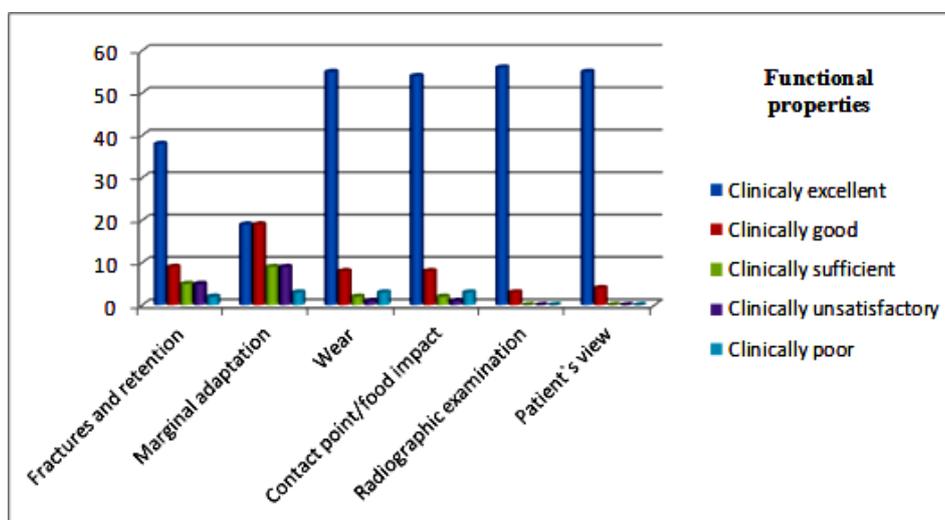


Figure 33 Functional properties

Also most of the assessed posterior composite restorations are associated to excellent biologic FDI criteria (**Figure 34**).

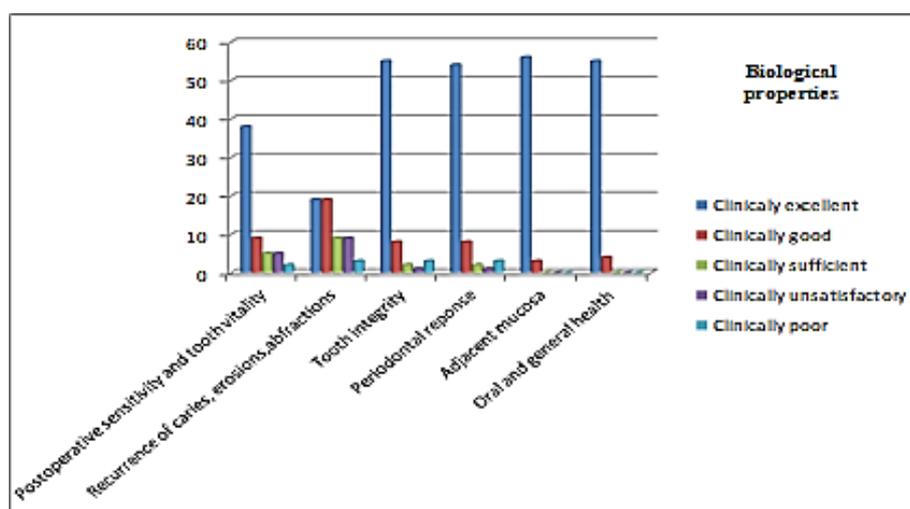


Figure 34 Biologic properties

Regarding the final global score, when the three FDI criteria (esthetic, functional, biologic) are added in a final value, the most severe score will give the final score. When a parameter is considered as clinically unacceptable, the reason must be recorded and a decision of repair or replacement must be taken.

The localised defects with satisfactory clinical access can be repaired as follows: spaces sealing, new material adding in marginal minor fractures, partial surface removal and covering, refurbishment of the restorations areas that changed colour (Geissberger, 2010). The repair is a minimal invasive strategy, with or without preparations in material/hard dental tissues, consisting of the addition of material after the defect was explored.

Refurbishment is defined as a minimal invasive intervention consisting of recontouring, repolishing or sealing, without the addition of a new material layer.

The investigated clinical cases stressed the need for early clinical and radiographic assessment of the posterior esthetic direct restorations. Using FDI criteria the dental practitioners will prolong the functional durability of those restorations.

DISCUSSIONS

Marquillier T. et al (2018) compared studies based on USPHS and FDI assessment criteria and concluded that FDI criteria are more relevant and standardised, related to clinical judgement of dental practitioner and patient opinion (Marquillier et al., 2018).

The data accuracy obtained by using FDI criteria was highlighted by studies performed in last decade. FDI criteria facilitate the practitioner's ability to assess the quality of the posterior esthetic direct restorations (Coelho-de-Souza et al., 2010; Da Rosa Rodolpho et al., 2011).

Kim et al. (2017) found that FDI criteria can be applied on photographic images of the old esthetic direct restorations. This can help the practitioner in the comparative assessment of composite restorations for long time intervals (Kim et al., 2017).

FDI criteria can be successfully applied to assess flow composite restorations 36 months after baseline as well as in the case of the indirect coronal restorations (Kitasako et al., 2016; Munteanu et al., 2016).

As the composite resins are the choice material for the posterior teeth restorations, meta-analysis determined a yearly failure rate of 1%-3% (Lynch et al., 2014; Heintze et al., 2015; Manhart et al., 2004).

Most of the clinical studies comparing various brands of composite resins were performed on time intervals of maximum 5 years. These studies found that the failure is due to factors related to patient rather than composite resins properties (Demarco et al., 2012). Despite the recording as general variables, these factors are rarely investigated.

The cariogenic risk was included as statistical variables only in researches conducted by Opdam NJ et al.(2007, 2010) and van de Sande et al. (2013) (Opdam et al., 2007; Opdam et al., 2010; van de Sande et al., 2013). The presence or absence of glassionomer liners was investigated for the assessed direct restorations in two studies (Andersson-Wenckert et al., 2004; Da Rosa Rodolpho et al., 2007). Opdam N.J. et al.(2007), Pallesen U. et al.(2013) and Ghiorghe C.A. et al. (2017) included the presence of glassionomer liner as influencing factor on longevity of the posterior composite restorations (Opdam et al., 2007; Da Rosa Rodolpho et al., 2007; Ghiorghe et al., 2017).

Demarco F.F. et al. (2012) consider the cariogenic risk as a major factor that influences the longevity and failure rate (Demarco et al., 2012). This aspect is confirmed by meta-analysis performed by Opdam et al. (2014) that found 2-3 times increase of the yearly failure rate for patients with high cariogenic risk comparing with low cariogenic risk patients (Opdam et al., 2014). The cariogenic risk is related to the 2, 8 times increase of failure rate of the posterior composite direct restorations and bruxism is the factor that increase 4,4 times the failure rate of the posterior direct composite restorations (van de Sande et al., 2013).

The improper use by patients of bleaching agents or antibacterial mouthwashes, with acid pH, can damage the surface status of the composite direct restorations (Munteanu et al., 2014; Ghiorghe et al., 2013).

Astvaldottir et al. (2015) found the secondary marginal caries as the most frequent failure factor, associated or not with direct restoration fracture (Ástvaldsdóttir et al., 2015). Chauhan R. et al. (2015) performed a meta-analysis regarding the longevity of the esthetic posterior direct restorations (Chauhan et al., 2015). The most frequent failure factors were secondary marginal caries and restorations fractures. Most fractures were produced in the first 3 years after baseline, while over 75% of the secondary marginal caries came into sight after 3 years. The esthetic posterior restorations at last 4 years old had 7% failure rate, with secondary marginal caries as the most frequent failure factor.

The longevity of the esthetic posterior direct restorations can be affected by low quality of adhesion conducting to postoperative hypersensitivity or marginal closure failures, especially to gingival wall of class II Black cavities (Ghiorghe et al., 2017).

CONCLUSIONS

1. The introduction of new restorative techniques and new restoration materials requires proper therapeutic decisions adjusted for each clinical case.
2. The knowledge of materials and techniques is requested to perform long-term direct restorations with high success rate.
3. The clinical assessment of the composite restorations may be useful to evaluate the quality of the restorations applied by dental practitioners in private practice.
4. Dental practitioners can decide minimal invasive interventions versus replacement, thus prolonging the functional, anatomical, and esthetic durability of the esthetic posterior direct restorations.

2nd study: Composite Resins – Multifunctional Restorative Material and Practical Approaches in Dental Field

In daily practice, composite resins offer special benefits. They allow clinicians to follow a predictable, conservative and safe chair protocol to improve patients' smiles and restore worn or decayed dental structures. Combined with the best adhesive protocols, these procedures can be used successfully to achieve beautiful results (Jackson et al., 2000; Robertson et al., 2002; Myshko, 2004). Composite laboratory resins respond very well as a restorative multifunctional material without a limitation in terms of aesthetics without strain on the financial point of view. This materials are available to clinicians and do not require much effort on the part of either the technician or the dentist. Thus, photopolymerizable composite resins can be a very good indication where the technical conditions of the clinic or the material condition of the patient exclude the use of porcelain. The evolution in time of composite resins is the following:

In 1871, Thomas Fletcher introduced a new material for fillings, called *cement silicate*. Its use in dentistry continued for a long time, although the aesthetics obtained were not ideal. It represented the elective material until the development of composite resins.

Composite resin technology was first introduced in 1958 with the development of a high molecular weight monomer called bisphenol Aglycidyl methacrylate or Bis-GMA. Along with the development of acid etching in 1955, these two discoveries represented the breakthrough for the composite resin technologies currently in use (Davis, 2003, Tery et al., 2009).

The first composite resins were composed of a base and a catalyst and were chemically polymerized. This made the procedure somewhat difficult, but their use was still simpler than in the case of silicate cements, and the aesthetics were superior. With the introduction of light-curable composite resins in the 1970s, dentistry became more predictable, proving longer working time and better physical properties. These composite resins were more stable in color and contained smaller particles than their predecessor self-curing resins (Ferracane, 2011).

In the late 1970s, microfill resins with medium submicron particle size were introduced, which led to increase polishability and wear. The following decade saw a decrease in particle size and an increase in filler load, which significantly improved light-curable composite resins for universal use in the front and side regions. Today, after 50 years of material science and laboratory development, as well as clinical trials in human subjects, composite resins have been revalidated as a universal restorative material. Numerous various composite resin systems are currently

available. To determine which material will work best in a given clinical situation, clinicians need to know the composite resin infrastructure, which contains three phases: the organic phase (matrix); dispersed phase (filling); and the interface phase (coupling agent). In essence, composite resins consist of a continuous polymeric or resin matrix, in which the inorganic filler is dispersed. The addition of fillers to dental composite resins significantly strengthens their physical properties by increasing the strength and strengthening the matrix, reducing the coefficient of termic expansion. There are many fillers for composite resins. These materials include quartz, alumina, zinc, zirconium, to name a few. Fillers may vary in size, depending on the manufacturing process (Mucci et al., 2009; Terry, 2009).

Many manufacturers are trying to increase the amount of filler in resins, in order to improve such mechanical and physical properties, such as would be the resistance to compression and to bending, modulus of elasticity, coefficient of termo expansion, the absorption of water and resistance to wear . They were developed in more systems of classification on the basis of size particles, the distribution and the amount incorporated. The classifications are more commonly referred to as a hybrid, microhybrid, composites with micro filler and the newest with nano - filler. The disclosures of these classifications may vary from one system to the other. The hybrid and microhybrid materials have, in general, a content of the filler of about 75% by weight. The particles of the filler may vary in size from 1-3 microns, and include particles of dioxide of silicon, which have usually a size of 0.04 microns. Hybrid materials show strength superior to the tensile, shrinkage reduced of the polymerization the coefficient decreased by expansion heat, resistance improved in abrasion and a more good resistance to fracturing. The disadvantage of hybrid materials is their weak polishability and the need for maintenance of gloss over time. In order to have a strong adhesion between the matrix and the filler, a coupling agent is used. The modification of the filler component remains the most significant development in the evolution of composite resins. The use of the photopolymerizable composite resins was first felt in the in dental surgeries. Here this kind of materials together with the lamps them light spectrum have deeply changed operative dentistry. Before them there were no initial restorations that used the heat as an item of polymerization of the acrylic resin and for the crowns that were to be fixed into their seats. With low elasticity and relative dimensional instability, they caused fractures in the cement under the action of caries, cracks or restoration edges (Ferracane, 2011; Craig`s, 2012)

In 1940, acrylic autopolymerizable (type I) could be placed towards the prepared cavity of the tooth. The polymer and monomer were combined and inserted into the prepared cavity of the tooth where they polymerized. The difficulties that arose when using this material were: color instability; the fact that they get darker when exposed to light (these difficulties made the material not be used in longterm recovery); very short working period for processing (1.5 minutes); poor compressive strength (10,000 psi); low abrasion resistance; low elasticity coefficient (2.4 GPa); increased level of water absorption; polymerization expansion of 7% of the volume; increased coefficient of thermal expansion. Last deficiency, which is actually the most important, it is that it can create problems in marginal adapting. The second type of resin was made by Bown in the early 60s. His studies inserted into the resin contents an organic compound related to a proportion of inorganic filler as an agent to adhere to the resin matrix - a mixture between bisphenol and glycidylmetacrilat (BISGMA). In the early 1970s, the use of ultraviolet light began to activate a photosensitive element. This element was replaced by a component that reacts to light in the visible spectrum ($\lambda = 400$ nm). The initial chemical resins and those in the light spectrum is also be used in the current way. The photopolymerization system has the following advantages: can be controlled throughout preparation; the finishing of the restoration can be taken away; the control throughout polymerized is assured.

However, the autopolymerizable resins have also the advantage that they can be placed in the oral cavity inaccessible to light (Ferracane, 2011; Craig, 2012). From the point of view of mechanical and physical qualities the composite resins are superior by: resistance to compression;

low coefficient of thermal expansion, low water absorption; increased surface hardness (Romănu, 2003; Weimann et al., 2005; Behr et al., 2005).

Today, research provides the clinician with three major categories of composite resins: microfilled, macrofilled, hybrid. Composite microfilm resins appeared in 1980 from the need of a material with a high degree of finisability, color stability and a clinic durability. The filler particles (load) have a diameter of 0.4 μm , a load that represents approximately 35 - 50% of the weight of the composite resin, in contrast to macrofilled which have 70-80% filler. It is used more when the prevailing aesthetics such as the restoration of cavities of classes III, IV and rebuilding the lower cavity and cavities class V and prosthetic for vestibular veneers or situations in which the polishing surface is desired (Subir et al., 2003; Kim et al., 2004; Meric et al., 2005).

The composite resins macro type describes a type of composite resins with inorganic filler consisting of particles of sizes larger than 1-5 μm in diameter, which is 70-80% of the weight of the material. Due to the large particle size this material cannot be polished in the same way as microfilled. The advantage is a significant increase in hardness and wear resistance. It has indicated and the user cavities of class I, II, IV and for the restoration of the incisal edge of jaw incisors. Lately, there are used rarely, due to the poor aesthetic qualities. Hybrid type composite resins appeared to meet the need to combine both qualities (gloss and strength).

Thus, many factories started to produce a hybrid with a quantity increased to 70-80% with both types of microparticles (0.4 μ) and macroparticles (1-3 μm). The indication for use is the same as for macrofille. Today, many manufacturers are trying to increase the amount of filling resin for them, to thus improve mechanical properties and physical properties, such as compressive strength and flexural strength, elastic modulus, thermal expansion coefficient, water absorption and resistance to wear (Dyer et al., 2004; Van Heumana et al., 2008).

Microstructure is in particles of dioxide of silicon submicroscopic having dimensions of approximately 0.04 μm . Taking into account the difficulty wetting these particles lower, the concentration of the filler is usually, 35% from weight. The amount of more reduced particles allows a great polishability, and the ability to maintain the gloss in time. These types of materials are significantly weaker than hybrids and show a higher absorption of water, the lack of radioopacity and less resistance reduced to fracture.

They are better used in combination with a hybrid material on the oral surface, for a better resistance in the areas with low stress, too. They are very suitable for restorations of class 3rd and 5th, and also for facets, directly (Woo et al., 2008).

MATERIALS AND METHODS

The purpose of this study is to analyze the biomechanical behavior of four types of composite resins, two of them used in direct restorations and the other two for prosthetic restorations created in the lab.

The deformations, hardness and elasticity were analyzed under the same conditions, namely at 200 Mpa, as these are very important parameters for the biomechanical behavior of the analyzed biomaterials, the specificity elements being correlated with the biomaterial structure, polymerization time and polymerization modality.

In the category of composites used for direct crown restoration, the materials under analysis were represented by Gradia anterior (GC), a hybrid composite material designed for esthetic restorations, prevalent in the anterior area and by Gradia posterior (GC), a hybrid resin composite with micro-filling for posterior crown restorations.

From the category of lab composites we selected Gradia Plus(GC), a photopolymerizable microceramic composite, whose internal structure consists in improved bonds between the organic-inorganic filling and the resin matrix and the Solidex composite (Shofu), a micro-hybrid photo composite with a filling of over 53% of ceramic particles. 4 test samples were created using the analyzed materials, with the same dimensions (250x25x5 mm), being subject to traction forces

on the universal testing machine (Textenser). *Polymerization of cabinet composites* (Gradia anterior, Gradia posterior) was made with a Woodpecker LED.B Photopolymerization lamp, Voltage: 110-240V, AC, 50-60Hz, wavelength: 420- 480nm and luminous power: 1000-max 1200 mW/cm² and the working time was 20s. *The polymerization of laboratory composites* was achieved at 90s with the means of the polymerization oven (Laborlux 3), with following characteristics 310-500nm, 300W.

The operation regime of the Textenser universal trial machine for variable forces was determined through the 27 (FATIGUE) switch in ON position (when it is in OFF position, the machine only executes trials at unique traction). Lamp 28, located under switch 27, is lit when the switch is moved to ON.

The cycle counter 29 needs to be set so that the indication of the cycle limit number (30.a) exceeds the indication of the performed cycles number (30.b), which is usually brought to zero by pressing the black button near the lower window (performed cycle counter). During the trials, in the lower counter the number of performed cycles is summed up and the upper counter shows the number of cycles to be performed. The strain limits (movement of the mobile beam) were chosen with an accuracy of 0.1 mm with the device 24, (marked with STRAIN LIMIT): low value (LOW) and high value (HIGH) were chosen by rotating the selectors. As a synthesis of the biomechanical behavior outcome related to the used resins versus the resins used in the lab of dental technique using indirect means, a relatively wide range of higher value parameters stands out with regard to resistance for the lab composites compared to those used in direct restorations.

RESULTS

Regarding the stress resistance, the superiority of Gradia Plus lab composite stands out, followed by Solidex, with a much lower stress resistance for the composites used in the direct restorations, a better resistance being displayed by the Gradia composite for the posterior area and the Gradia composite for the anterior area. A deformation risk was recorded for the composites used for direct restorations, a higher risk in case of Gradia composite used for esthetic restorations, followed by gradia posterior, whose higher hardness recommends it in the areas of greater masticatory forces (**Figure 35**).

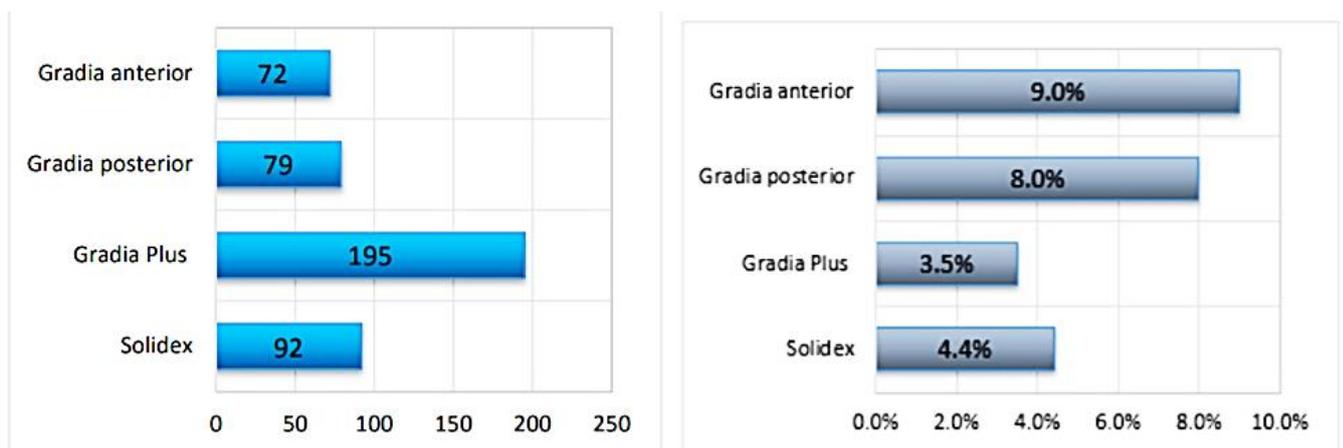


Figure 35 Aspect of resistance risk and stress resistance at analysed materials

Very good deformation resistance was obtained for lab composites, the first place being taken by Gradia Plus, which through the chemical bonds established between the organic-inorganic filling and the resin matrix reached a hardness of 9.9350, the following position in terms of hardness being taken by Solidex, and for the lab composites higher values were recorded, 598 for Gradia plus and 512 for Solidex, while for the direct restoration composites, the elasticity

module reached was 398 for Gradia posterior and 368 for Gradia anterior, a property that influences their selection in relation to the particularity of the clinical case (**Figure 36**).

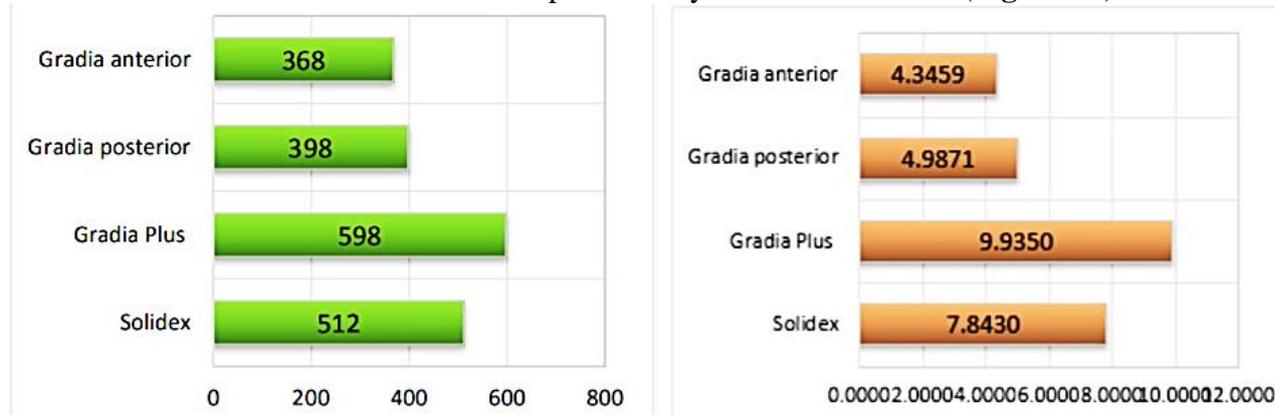


Figure 36 Aspect of hardness and elasticity moduls at biomaterial analyzed

In order to try and to give strength and polishability both in a single composite, manufacturers have introduced resin composite hybrid with smaller particles, the size of the average of the particles at about 0.02 μm to 1 μm .⁹ This allows the clinician to deploy a single restoring material, with all the properties of mechanical and physical improvement of the prior resins. The major disadvantage of these types of composites is in need of maintain the gloss. The gloss is satisfactory at first, but tends to be lost over time (**Table 41**).

Table 41 Comparision between the clinical problems raised by the composite resins used in the clinic and those used in the laboratory

CLINICAL	LABORATORY
Contraction during polymerization leads to open contacts. The risk of porosity leads to gaps in the material.	The laboratory ensures dimensional stability and eliminates any porosity.
The variable rate of wear leads to restrictions on the application in the posterior area of the oral cavity.	The surfaces have a hardness with a wear rate compatible with that of the substance of the natural tooth.
The micro-sites created around the edges of the recovery lead to problems such as soft deposits, secondary caries and adverse pulp response.	Significant reduction of micro-places.
Polymerization can cause stress.	Minimal reactions only if bonding is used.
Load particles can generate rough surfaces (not when using microfilament resins).	The homogeneity of the microphilic structure does not allow to obtain such an effect.
Difficulties in creating morphology with the free hand.	Any required design will be manufactured in the laboratory and returned ready for fixing.
The change in color during polymerization causes difficulties in choosing the shade.	The laboratory has materials that ensure color stability. Subsequent modifications can be made if another shade is obtained. They can be easily re-polished in the oral cavity and can be repaired just as easily with composite resins used in the clinic.

Following the methods of using them to initiate the polymerization on laboratory state (high physical factors that intervene), is obtained a material with inherent outstanding.

DISCUSSION

Compared with the acrylates these composite resins are much more resistant to wear during a good color stabilization assured by the acrylate. It is also worth noting the high degree of polishing that can be used clinically. These materials can be repolished after their period of alteration and used again with the same glow which is a very important technical detail for clinicians and patient. Another important aspect is the one that most clinicians seem to accept, namely that these glossy surfaces are accepted by the gingival tissues with a minimal inflammatory response. Composite resins have a wear rate very close to that of natural teeth. This aspect of the problem puts them in a favorable light in terms of clinical use. Many researchers made are aimed to calculating the resistance of their composite photo polymerizable in time (Hikita et al., 2007; Mangani et al., 2007). The study also stopped comparatively on the different types of light - curable composite resins. Thus, a study conducted by David James, following for a period of 3 years a composite resin for laboratory use, was followed by another study carried out by Mitchen on several composite resins for clinical use over a period of more than 5 years. A clinical study conducted by Bishop over a period of over 4 years showed that using laboratory composite resins, 91 clinically satisfactory inlays were obtained from 92 follow-up inlays. The only unsatisfactory inlay was the first one made, which leads to the idea that it could be an error due to lack of experience. Another study, conducted this time by the University of Alabama, reveals its strength in time of the crowns of the shell/coating made of this material. The results demonstrate an average annual wear of 7 μm / year. This value approaches the laboratory composite resins abrasion to that of the structure of the natural tooth. It worth remember the fact that the rate of abrasion decreased during the study, that can make us to believe that time for use of this material in the oral cavity may be extended. Comparison of a number of other materials and laboratory resins makes us realize the clinical importance of them (Van Meerbeek B et al., 2003; De Munck et al., 2005; Nicola et al., 2009).

The composite resin is one of the most versatile dental materials and when it is used correctly, with peculiar attention, can provide restorations comparable with the ceramics. The appropriate usage often requires a further training further to get a level of master skill. When used in appropriate situations, these materials have to last many years, the strength and maintenance of gloss being a significant gain. The ability to be minimally invasive and to preserve the structure of the tooth is another significant benefit. Composites are used in a regular manner to restore cavities, closing spaces, lengthening teeth, covering dark teeth or colored and for bonding tooth fractures (Ryge 1980; Behr et al., 2003; Raj et al., 2007).

Selecting the type of material suitable for certain clinical situations, such as mentioned above, it is a matter open to debate. Hybrid and microfilled composites are often used in combination to achieve a restorative result that provides optimal physical and mechanical properties. The hybrid material provides strength and opacity, and the microfill provides the ultimate shine and shine durability. This incremental layering technique with composite resins leads to an optimal polymerization depth, with the reduction of shrinkage effects or stress forces during the polymerization. In addition, the polychromatic effect can be observed when layering different restorative components with various refractory indices, different shades and opacities. By using anatomical layering by successfully overlapping the dentin, enamel and incisal composite, a more realistic color can be obtained, similar to the surface and optical characteristics that mimic nature.

The use of resins is important when patients present with diastema. The diastema may be due to small congenital teeth, or it may be a situation where there is simply a larger space between the teeth. The use of composite resins in this type of situation is minimally invasive and usually reversible. In general, no dental structure should be removed, and the procedure is done in a single session. When the space is small, the material for this type of clinical situation can be either a microfill composite or a nanocomposite, both of which are easy to handle and provide an excellent final result. When a patient presents with the fracture of the ceramic facets on an extended bridge,

the composite resin can be used to repair the defect. This type of procedure is not always predictable, but when performed correctly and with proper occlusion control, a successful outcome can be achieved. When performing a defect repair with metal exposure, many composite materials are required. The use of opaquer, pigments, hybrid substances or nanofillers in the final layer can provide a beautiful result by masking the underlying metal structure. Manufacturers are constantly striving to improve the physical properties and ease of use of these materials. New nanomaterials are welcome supplements to the already refined range of composite resins available for clinical use (Ohlmann et al., 2006; Ohlmann et al., 2008).

Laboratory composite resins offer two distinct advantages that can reduce the risk of periodontal reactions. Second, the edge of the work should be extended subgingivally where the dental structure is deficient. Coronary restorations of this type appear to be associated with excellent tolerance on the part of the gingival tissues.

Depending on the qualities of the composite resins produced, each manufacturer gives certain indications that he considers valid.

Taking into account both the multitude of producers and the variety of types of composite resins, it is very difficult to give general indications of this type of biomaterials. However, some of the basic indications of these materials could be: inlays, onlays; shell crowns; bridges; vestibular facets; restorations following endodontic treatments.

CONCLUSIONS

Composite resins offer a conservative and cost - effective solution for many clinical situations; the use of laboratory composite resins appears as a natural necessity in joint prostheses. This conclusion is based on the increase in the level of aesthetic demand from patients from all walks of life; light- curable composite resins are a very good solution in the case of aesthetic restorations, where for various reasons, the use of porcelain is not indicated.

3rd study: *Mechanical Properties of Bis-GMA/HEMA Resin Composite with Addition of Silicon Dioxide Nanoparticles*

Since ancient times, man has made a case study regarding the choice of materials for operative dentistry. Through trial and error along centuries of testing, researchers have never stopped developing new materials and techniques in order to prevent tooth structure loss, tooth wear or dental trauma. Currently the range of materials existing in this crucial area for society is larger than ever, and this trend seems to be in perpetual consolidation. An important role in the properties of biomaterials for the adhesion of biological cells is played by the composition of the material used and its charge (Thian et al., 2018; Lahann et al., 2003), as well as by the affinity for water and surface roughness (Chen et al., 2016). These biomaterials are subjected to physical and biological study, and the level of interaction with the human body is analyzed (Lungu et al., 2010).

The basic requirements of biomaterials are mechanical characteristics, biocompatibility and resistance to corrosion in body fluids and tissues (Lăzărescu, 2013). Biocompatibility is the ability of the substance to interact with fluids and tissues of the body without causing undesirable harm to the body, such as toxicity and irritant effects, inflammatory and allergic reactions. In the production of novel biomaterials for dentistry applications, biocompatibility and biodegradability are considered main characteristics (Lăzărescu, 2013).

The objective of this work was to observe the effect of 4 nanoparticle dimensions on the Bis-GMA/ HEMA resins, which from the knowledge acquired by the authors in this study field, it represents a novelty. Based on the obtained composites, several mechanical properties were analyzed.

MATERIALS AND METHODS

Materials: For the composite materials, Bisphenol A diglycidyl methacrylate (Bis-GMA) was used as main monomer and hydroxyethylmethacrylate (HEMA) was the co-monomer. As initiator and co-initiator, camphorquinone and dimethyl aminoethyl methacrylate were added to the mixture. The SiO₂ nanoparticles with 30, 50, 100 and 150 nm dimension were used as composite fillers. All substances were purchased also from Sigma-Aldrich.

Mixtures of 60 % Bis-GMA with 30 % HEMA were prepared under mechanical stirring. A concentration of 9 wt.% SiO₂ was added to the pure monomers and the monomer mixtures.

The composites of Bis-GMA/HEMA were produced by the following process: the monomers were mixed with camphorquinone and dimethyl aminoethyl methacrylate, both of which amounted to 1 wt%. In order to ensure a homogeneous viscous solution, high power mechanical stirring was used. After 60 minutes, the SiO₂ nanoparticles were carefully added and continuously stirred for 24 hours. The composition of the obtained samples is presented in **Table 42**.

Table 42 Sample concentrations

Bis-GMA [%]	HEMA [%]	SiO ₂ nanoparticles	
		Conc.[wt.%]	Size [nm]
60	40	0	0
		10	30
			50
			100
			150

Light curing of the resin was initiated through a 30 min irradiation with UV/Vis light by a 375 W mercury vapor lamp (L 6/58, Famed-1) in ISO standardized Teflon molds.

The obtained Bis-GMA/HEMA – SiO₂ biomaterials were tested for flexural strength (Fs), flexural modulus (Ey), work of fracture (EWF) and compressive strength (Cs) by using an Instron universal test machine (China-Made, Universal Testing Machine). Sample measurements (l=25 mm, w=2mm, h=2 mm) and test specifications were performed according to ISO 10477 and ISO 4049 standards.

The flexure strength was measured by charging in 4-point bending. The load applicator is not a single point source, it consists in two points divided by a well -prescribed width. The advantage of the 4-point technique is that it focuses the stress across a larger beam area, thus indicating that the beam can collapse in this region. To analyze the compression strength of the obtained composites, an axial force was applied to a cylindrical specimen at a constant strain rate, setting up tensile and shear stresses that cause failure inside the sample (Suttiponparnit et al., 2011).

Mechanical properties were calculated by applying the following formulas:

Flexural strength (Fs):	$F_s = \frac{3 \cdot F \cdot l}{2 \cdot b \cdot h^2}$	(1)
Flexural modulus (Ey):	$E_y = \frac{l^3 \cdot F_1}{4 \cdot f \cdot b \cdot h^3}$	(2)
Work of fracture (EWF):	$EWF = \frac{A}{b \cdot h}$	(3)

where:

- F – the applied load at highest point (N);
- l – span length;
- b – test specimen width;
- h – test specimen thickness;
- F1 – load at a suitable point in the straight line portion of the trace (N);

- f – test specimen deflection (mm);
- A - the load applied to deflect and fracture the specimen (J) (Franco, 2015).

RESULTS

Any dental restorative or prosthetic content, as well as natural teeth, must have adequate functional integrity to resist in the oral cavity for a long period of time, ideally throughout the patient's entire life. Therefore, the study of mechanical properties is extremely important. One of the key threats of dental reconstruction is the formation and propagation of cracks and the potential failure of dental implants obtained from composite resins. The addition of nanoparticles to the resin to improve the mechanical strength of the composite is one of the methods of interest. It is well established that Bis-GMA / HEMA polymers achieve a high crosslinking between monomers, one of the reasons is the fact that HEMA molecules are much smaller (Luo et al., 2016), creating a good mobility of the Bis-GMA molecules to move in the nanocomposites. In addition to the neat sample, the addition of nanoparticles will only increase mechanical stability. However, even in the nanoscale, there are still notable variations, with the majority being related to their size. Decreasing the particle diameter will lead to an increase in the active surface area, as depicted in **Figure 37**.

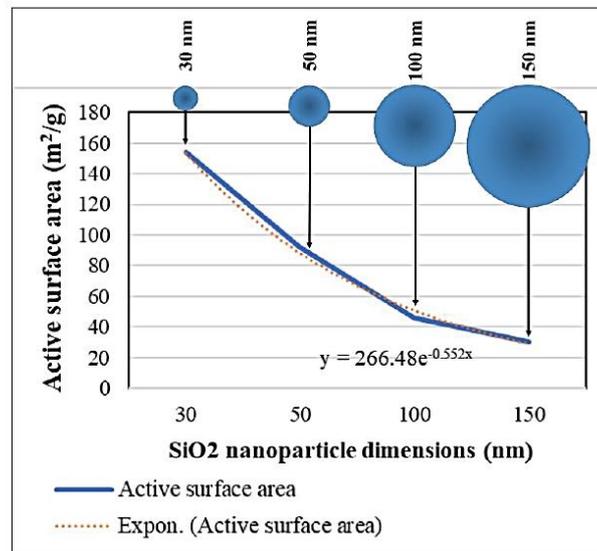


Figure 37 Graphical and schematic representation of correlation between nanoparticle size and active surface area

The active surface area was calculated based on SiO₂ bulk density of 2.64 g·cm⁻³ and simple geometry equations. Of course, these values are theoretical and are extracted from the ideal shape of a nanoparticle, the sphere. A higher surface area of nanoparticles is understood as a larger number of connections with the polymer chains, which therefore will likely increase the mechanical properties of composite resins.

It is very important to take into account that nanoparticles can lead towards agglomeration under a certain nanometric size due to an enhanced collision energy between particles at the mixing step, which can cause significant defects in the matrix resin structure that can only be detected with a microscope.

Following the study of the mechanical strength of the samples obtained, it was observed that the addition of SiO₂ nanoparticles significantly improved the flexural strength (Fs) of the resin composites compared to the Bis-GMA / HEMA blend, as it can be observed in **Figure 38**.

By decreasing the SiO₂ nanoparticles dimension it was observant that the flexural strength is improved. Addition nanoparticles with a size of 150 nm show a decrease in mechanical properties due to the overcrowding of the fillings which brings a disadvantage in the resin matrix.

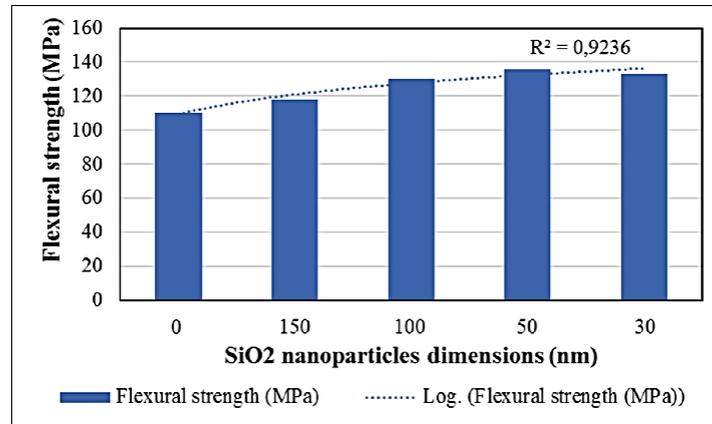


Figure 38 Flexural strength

All the composites showed stronger flexural properties with the addition of SiO₂ nanoparticles than the neat resin (**Figure 38 and 39**). The flexural strength (Fs) and flexural modulus (Ey) of the composites was stronger when the SiO₂ nanoparticles dimension was 50 and 100 nm, reaching a peak value for the material with 50 nm SiO₂ nanoparticle.

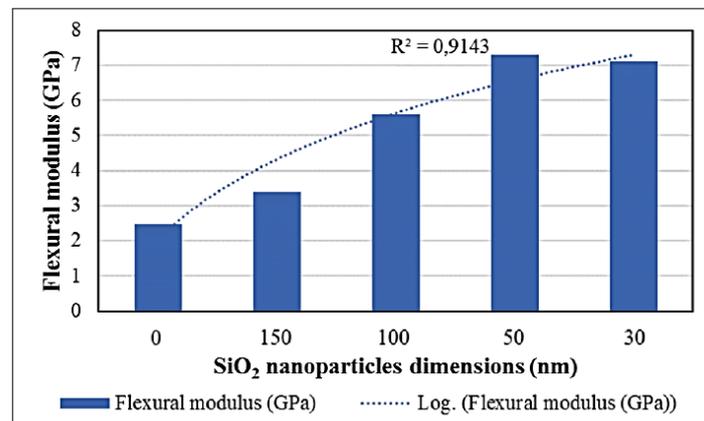


Figure 39 Flexural modulus

The flexural properties increased over 30% for the samples with 50 nm and 100 nm SiO₂ nanoparticle compared to the neat resin. At further increasing the nanoparticle size up to 150 nm, the flexural strength (Fs) as well as the flexural modulus (Ey) values of the corresponding composites began to decrease.

Flexural stability is strongly related to the interaction between polymeric chains and nanoparticles. A lower nanoparticle size will lead to a higher number of physical and chemical bonds with the polymer chains. This means that stress is uniformly distributed across the structure, and a more efficient transfer between matrix and filler is reached. On the other hand, increasing filler size will not cause a pronounced mechanical resistance, confirmed by the flexural properties of the 150 nm SiO₂ blended resin composite. However, for the sample with filler of 30 nm size, a slow decrease in flexural strength and modulus is observed. This could be a consequence of agglomeration tendency at very low nanoparticle dimensions, resulting in micro-defects in structure, which generate sample failure.

It is observed in **Figure 40**, that compressive strength was enhanced directly proportional to nanoparticle size, which is translated as a good binding strength due to filler addition

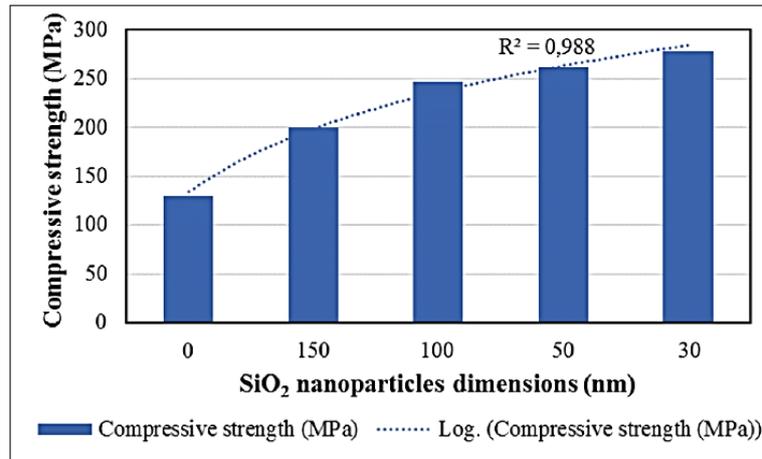


Figure 40 Compressive strength

In compressive state of the studied composite resins, nanoparticles play a different role. In the case of flexural tests, sample failure occurs in an area intentionally subjected to high stress due to opposite directions of the polymer chains movement. When discussing compression tests, mechanical stress occurs as a result of pressing polymer chains between them. Here the energy transfer between the polymer and the nanoparticle is higher and uniform throughout the structure of the material. The defects caused by the agglomeration of nanoparticles are not so obvious, because they are compacted as the load increases, which is why in the case of materials with the addition of 30 nm nanoparticles, the compressive strength is higher than in the case of other materials.

Since fracture is one of the key modes of failure for dental composites, this property is highly important to their characterization. Since most methods of obtaining materials do not offer the possibility of obtaining ideal structures, the application of specific charge allows the material to break due to structural defects. Thus the strength characteristics are reduced compared to those measured on ideal surfaces. The composites showed significant improvement in terms of work of fracture by increasing the SiO₂ nanoparticles dimension to 50 nm. Instead, due to the presence of structural defects, the fracture resistance decreases at higher and lower nanoparticle sizes (**Figure 41**).

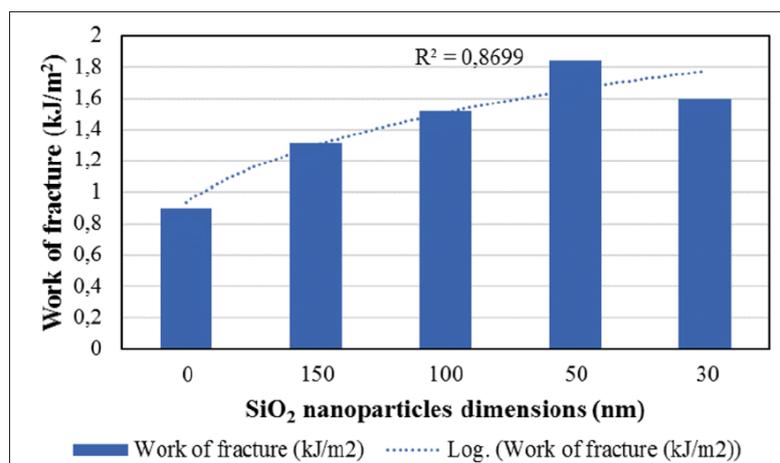


Figure 41 Work of fracture

The strong chemical bond between biomaterial and nanoparticles results in a uniform stress distribution and is able to minimize the occurrence of stress concentration, leading to a significant increase in the mechanical properties of the resulting composites .

DISCUSSIONS

The basic requirements of biomaterials are mechanical characteristics, biocompatibility and resistance to corrosion in body fluids and tissues. Biocompatibility is the ability of the substance to interact with fluids and tissues of the body without causing undesirable harm to the body, such as toxicity and irritant effects, inflammatory and allergic reactions (Roshanali et al., 2020).

In the production of novel biomaterials for dentistry applications, biocompatibility and biodegradability are considered main characteristics (Canche-Escamilla et al., 2014).

In addition, using inorganic nanofillers to improve the polymer matrix properties is a widely used technique to achieve improved performance (Sideridou et al., 2005). Commonly used additives in the preparation of composite materials that are often processed with silane coupling agents are silica nanoparticle (Moszner et al., 2001).

G. Canché-Escamilla et al. studied the incorporation of nanoparticles with silica and PMMA through a polymerization process used as dental biomaterials. They observed that the use of hybrid filler nanoparticles allowed to incorporate a larger amount of inorganic filler. In this case, the hybrid nanoparticles did not show agglomerations of material, obtaining a uniform distribution.

Monomers used in the matrix of composite materials for dental purposes are divided into two broad categories: strongly viscous monomers, such as Bis-GMA, urethane dimethacrylate (UDMA); and diluent monomers, such as hydroxyethylmethacrylate (HEMA), TEGDMA, etc (Krifka et al., 2013; Floyd et al., 2006). Depending on the polymerization of the monomers, composite materials have various physical, chemical properties and clinical performance (Sun et al., 2010). The biomaterials obtained were studied by the photo-differential scanning calorimetry (DSC) system for the reactivity of monomeric molecules and the dependence of the conversion of the double bond on the structure of the monomer. They observed that UDMA resins were significantly more reactive than Bis-GMA resins (Liu et al., 2014).

The global growth in tolerance to antibiotics contributes to the use of new infection prevention methods, and the use of metal oxides may be an interesting method for the production of antimicrobial biomaterials, since they have a significant antibacterial effect (Liu et al., 2014).

Coupling agents, like vinyltriethoxysilane and methacryloxypropyl-trimethoxysilane, increase the adherence between the resin and the surface of the filler particles. To reinforce the bond to the interface, modifications to the surface of the filler particles were also carried out (e.g., roughening and aggregation of the particles, resulting in mechanical retention).

Nanoparticles have been available for some time, but the early ones, formed agglomerations during the production process, thus limiting their use for dental composites. Subsequent research has led to the possibility of particle separation, generating a uniform dispersion offering the possibility to be incorporated into composites.

Liu et al. has studied the influence of SiO₂ nanoparticle concentration in the poly(Bis-GMA)-grafted silanized hydroxyapatite whisker (PGSHW) (Liu et al., 2014). Light permeability and filler packing density were enhanced through the incorporation of s-SiO₂ nanoparticles in PGSHW (mass ratio 2:4), which effectively improved water sorption and solubility of the biomaterial. Physical and mechanical properties as well as in vitro bioactivity were significantly improved by the obtained PGSHW/s-SiO₂ (Liu et al., 2014)

CONCLUSIONS

The study showed that the presence of silicon dioxide nanoparticles can significantly improve the properties of composite biomaterials compared to the control sample. The mechanical strength of resins with the addition of SiO₂ nanoparticles has been improved, due to the strong chemical bond between the resin matrix and the nanoparticles. The greatest improvement in mechanical properties was observed in samples with the addition of SiO₂ nanoparticles with a size of 50 nm in Bis-GMA / HEMA resin. By changing of SiO₂ dimension above or below 50 nm, the interface

between the nanoparticles and the neat resins can restrict the enhancement of the mechanical properties of the composites, as observed in the case of SiO₂ nanoparticles with 150 nm size or in the case of the 30 nm size particles, which could be linked to nanoparticle agglomeration.

SECTION II FUTURE PROGRESS AND DEVELOPMENT PLANS UPON CAREER AND RESEARCH ACTIVITY

The second section of this habilitation thesis outlines short, medium as well as long-term research directions and development projects, concentrating on the comprehensive and challenging interrelation between professional, academic and scientific research.

II.1 Future directions in research activity

On short, medium and long-term, my research activity will be guided toward:

- Dissemination of results in ISI / indexed international databasis journals;
- Continuing and expanding the collaboration with the preclinical disciplines such as Immunology, Biochemistry, Pharmacology and other dental disciplines (Prevention, Caryology, Endodontics, Periodontology, Prosthetics, Dental materials,), addressing new proposals that could provide real funding through joint research projects;
- Attracting funds to improve the means of research at the Ergonomics discipline;
- Expanding collaboration with other research laboratories outside the faculty;
- Organizing and participating in national and international scientific events;
- Developing applications for international research programs and grants;
- Organization of student scientific events, for the purpose of their involvement and inclusion in the research activity and participation in scientific events, as well;

The main trends in my research activity in the next few years will focus on several priority areas, as follows:

Prevention of musculoskeletal disorders in dentistry (MSD), because MSD have become increasingly common worldwide during the past decades and, in the mean time, a common cause of work-related disability among dentists with not only physical, psychological, and social consequences, but also economic.

MSD issues related to dental profession are related to exposure and stress to many mechanical factors including prolonged vicious positions, force activities, repetitive movements and vibrations.

In future studies I intend to increase the number of enrolled subjects as this is an important element that gives relevance to the results obtained; I also intend to diversify the evaluated parameters, in order to be able to reach valid conclusion and be able to generalize results.

Although the closer bidirectional relationship between cranio-mandibular disorders and posture imbalances is intensely debated, there are still unmet needs. Thus, I intend to develop new directions of collaboration with high-performance simulation and research laboratories in order to design a 3D analysis model, which brings together TMJ, different types of occlusion, posture, and musculoskeletal impairment; moreover, I want to perform a complex analysis of general, locoregional and local specific markers.

I also intend to:

- *reopen, refresh and upgrade the information in the Musculoskeletal pain academy website (develop in one educational IASP grant);*

- to exploit all the research results by publishing books with various topics, developing subjects with profound impact in dental practice such as hand pathology, given the importance of its involvement in the professional act

Despite abundant technological and medical advances in recent years, a significant amount of occupational health problems still exists in modern dentistry *such as: exposure to infectious diseases, radiation, skin dermatitis, respiratory disorders, eye injuries, psychological impact, and hearing problems.*

Remaining in the same register of the dentist's exposure to occupational diseases, I propose to add different studies that will take into account the analysis of other organs and systems exposed in its professional activity.

Prevention of hearing problems; in addition to the common daily noise levels, dental professionals are exposed to supplemental noise which is related to their area of work. Thus, sound sources which might affect hearing in a dental practice include high-speed and low-speed turbines, high volume suction devices, ultrasonic instruments, compressors, autoclave and air-conditioning.

Besides its effects on hearing, loud noise may also impair other organic systems, such as: behavioral, neurological, vestibular, digestive, cardiovascular disorders, among others negatively impacting their quality of life.

Taking in mind all these issues, I want to analyze the relationship between the intensity of the noises in the dental office, the professional hours, the time of professional activity and the hearing loss in that profession.

Prevention of eye injuries; dental clinic may also be a source of eye-related injuries because of the constant risk of **infection**, mechanical trauma, exposure to various chemicals and electromagnetic stress. The direct contact between the eye and various splashing material including aerosols, saliva, organic particles like plaque, calculus, and tissue residues and bacteria-rich flora is responsible for infection-related injuries.

Another important aspect to consider is the advent of modern technologies that magnify the details represented by magnifying glasses or electron microscopes.

Both the studies that will approach the visual and the auditory analysis will be carried out in an interdisciplinary vision that will involve an important number of members in the research teams.

Evaluation of the link between chronic inflammatory rheumatic disorders (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic sclerosis) and Periodontal Disease

Another future direction of research I want to develop is the dynamic analysis of rheumatic pathology in the context of periodontal pathology; I intend to realize a complex immunological approach and to assess the bidirectional relation between chronic periodontitis and rheumatic conditions in various therapeutical settings.

Autoimmune rheumatic diseases remain a heterogeneous group of conditions characterized by immune tolerance breakdown and production of autoantibodies and of a number of substances responsible for lesions in several body structures.

Evaluation of the link between systemic disorders such as diabetes mellitus and cardiovascular disease and and Periodontal Disease

Diabetes mellitus and periodontal disease: Known as a genetically and clinically heterogeneous metabolic conditions, diabetes mellitus (DM) is widely associated with serious complications that can affect the quality of life and life expectancy of the patient due to significant damage of eyes, nervous, cardiovascular, and renal systems. Various oral health issues are already recognized in DM comprising a wide spectrum: burning mouth and tongue sensation, dry mouth,

abnormal oral microbiota with the predominance of *Candida Albicans*, *Hemolytic Streptococci* and *Staphylococci*, *Actinomyes species*, increased frequency of dental caries, gingivitis and periodontitis.

The association between diabetes mellitus and periodontal disease has been extensively studied in the last years, and several studies conclude that DM may be a risk factor for the development of gingivitis and/or periodontitis, irrespective of the type of diabetes - type I is insulin-dependent (more frequently found in young patients) and type II is non-insulin dependent.

Moreover, both diabetes and periodontal disease share a genetic background based on HLA genotype and both are characterized by a hyper-inflammatory phenotype with high levels of inflammatory cytokines such as IL-1 and TNF- α . Thus, it seems that the understanding of the mechanisms responsible for periodontal destruction and periodontal healing in patients with DM is essential to the future development of new treatment strategies for patients with diabetes and periodontal disease

Cardiovascular disease and periodontitis: Cardiovascular diseases (CVD) or atherosclerotic diseases are principally coronary heart disease, cerebrovascular disease and peripheral vascular disease and represent one of the main causes of death worldwide. Many studies have already demonstrated the association between periodontal disease and ischaemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation and peripheral artery disease.

The potential role of chronic infection in the complex pathobiology of CVD was recently investigated, mainly related to the link between chronic inflammatory processes and atherosclerosis. Furthermore, recent studies have also provided serological evidence that infections caused by major periodontal pathogens such as *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* are associated with future stroke, increased risk of myocardial infarction, and acute coronary syndrome.

In my future research I intend to demonstrate:

- the link between the prevalence of bacteraemia and plaque/gingival indices;
- the presence of periodontal pathogens in atherothrombotic lesions, and a correlation with periodontal status;
- a correlation between the subgingival flora and pathogens detected in atheroma.

Evaluation of the link between chronic inflammatory rheumatic disorders and temporomandibular joint (TMJ)

Another future research direction is based on the continuation of the research carried out within my doctoral thesis "TMJ changes in rheumatic diseases". I want to retake the research and to perform a detailed analysis of TMJ morphology in various rheumatic conditios, through modern paraclinical examinations such as CBCT and scintigraphy.

Since detection of inflammatory synovitis of the TMJ is an efficient way to evaluate whether the joint is affected in rheumatic disease, bone scintigraphy can be effectively use as a sensitive tool for the detection of inflammatory lesions and high osteoblastic activity. Because bone scintigraphy is considered a real-time evaluation, similar to an estimation of the levels of serum inflammatory markers I consider that this method will be of significant value in assessing the progression of inflammatory process in TMJ in rheumatic patients.

Finally, I would like to be able to develop this research on other coordinates with other pathologies, thus extending the area of corroboration of data in the interdisciplinary sphere.

III.2 Future directions in academic activity

From educational activity aim to:

- enhance editorial activity with the publication of teaching materials, both course notes, but also practical papers; proposal for updating of the information addressed, in native language but also new editions in English and French; thus we will facilitate the access by a high quality information through new textbooks and the use of E-learning platform;
- improving the didactic practice approaches by applying an active-participatory strategy with the student's involvement in the teaching-learning process;
- identify the student profile with consistent interest in ergonomics for research in this field, focusing on topics of interest;
- coordinate and encourage medical students in the development of scientific papers;
- keep up-to-date the curriculum content, clinical traineeship and provision of the information, in line with ergonomics novelties and technology capabilities;
- propose new line in education (optional courses);
- coordinate and encourage medical students in the development of scientific papers;
- encouraging students to participate in inter-institutional educational exchanges
- *reopen, refresh and upgrade the information in the Musculoskeletal pain academy website (develop in one educational IASP grant).*

***Trebuie să încerci necontenit să urci foarte sus, dacă vrei să poți să vezi foarte departe.
You have to constantly try to climb very high if you want to be able to see very far.***

By Constantin Brancusi

SECTION III

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