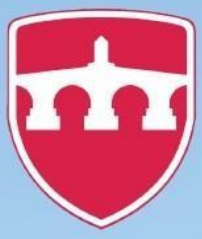

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"COMPLEXITY AND COMPOSITION IN CONTEMPORARY ARCHITECTURAL PARAMETRIC DESIGN"

Assoc. Professor PhD. Sc Viktorija Mangaroska[1]

[1] International Balkan University, Faculty of Engineering / Architecture

Abstract. *Contemporary architecture is the architecture that represents the 21st century. Architects are working in different styles, from high-tech architecture to highly conceptual and expressive styles, resembling sculpture on an enormous scale. The different styles and approaches incorporate the use of very advanced technology and modern building materials, as well as, the use of new techniques of computer-architectural aided design.*

Complexity and Composition in Contemporary Architecture incorporate a contingent assemblage of theoretical, practical, ecological, economical, political, social, and cultural parameters that presuppose the design and performance of architecture. Architecture affects these parameters. The role of architecture includes the effectiveness of sustainability. Contemporary buildings are designed to be noticed as landmarks of the place. The real complexity of architecture is an integration of parameters typified by architects integrating and practicing this complexity.

This parametric design is increasing complexity of building production increasing complex building technologies and envelopes, energy efficient techniques and technologies, software, fabrication and construction delivery methods, economic and ecological factors. Building design and building performance is a fundamental engagement with these multiple and complex contexts that condition the contemporary architecture.This parametric design strategy, which used computers for developing complex forms and construction of the buildings was often practiced in the projects of Zaha Hadid, Massimiliano Fuksas, Frank Gehry, Jean Nouvel, Daniel Libeskind. Specific attention in this research will be given to analysis of the usage of the parametric design as an algorithmic thinking that enables parameters and rules that, together, define, encode and clarify the relationship between design contents and design response. The expected outcome results in this scientific paper is to identify the contemporary design approaches and create application at the international education processes.

Keywords*: contemporary; parametric; architectural design.*

1. CONTEMPORARY ARCHITECTURE

Contemporary architecture is the architecture of the 21st century. Contemporary architects are working in different architectural styles, from postmodernism and high-tech architecture to highly conceptual and expressive styles.

The different styles and approaches have in common the use of very advanced technology and modern building materials and the use of new grtbrgtechniques of computer-aided design.

Figure 1. Contemporary Architectural Design and Parametric Forms in Architectural Design - Gugenheim Museum in Bilbao, Spain, arch Frank Gehry

Figure 2. Contemporary Architectural Design and Parametric Forms in Architectural Design - Baku Flame Towers Construction, Baku, Azerbaijan, Zaha Hadid Architects Spain, arch Frank Gehry

1.1 Complexity and Composition in Contemporary Architecture

Any building architectural project is an assemblage of theoretical, practical, ecological, economical, social, and cultural parameters that define the design and performance of architecture.

The real complexity of architecture is integration of parameters typified by architects integrating and practicing this complexity. Building design and building performance is in fundamental engagement with these multiple and complex contexts that influence contemporary architecture.

Contemporary buildings are designed to be noticed as landmarks of the place. Some feature structures have the following characteristics: very asymmetric facades, skyscrapers twist, or break into crystal-like facets, facades are designed to shimmer or change color at different times of day, in order to be presented as landmarks of the place.

Figure 3. Contemporary Architectural Design of tall buildings as landmarks of the city

Most internationally well known landmarks of contemporary architecture are works of a small group of architects who work on an international scale.

The parametric design strategy, that uses computers for developing complex forms and construction of buildings was often practiced in the projects of of the protagonists architects: Mario Botta, Frank Gehry, Jean Nouvel, Norman Foster, Renzo Piano, Zaha Hadid, Santiago Calatrava, Daniel Libeskind, Jacques Herzog and Pierre de Meuron, Rem Koolhaas, Bjarke Ingels, Massimiliano Fuksas, Peter Eisenman.

Figure 4. Contemporary Design of Gherkin Building in London, arch Norman Foster

2. COMPLEXITY AND COMPOSITION IN CONTEMPORARY PARAMETRIC ARCHITECTURE

Complexity and Composition in Contemporary Parametric Architecture incorporate the following dynamic architectural parameters that are positioned to be performed as concept in architectural parametric design:

1. Energy parameters,
2. Site parameters,
3. Climatic parameters,
4. Form parameters,,
5. Construction parameters,
6. Programmatic parameters,
7. Regulatory parameters,
8. Economic parameters, and
9. Social aspects of a project as primary parameters of the architectural design process.

This type of architectural parametric design is increasing complexity of building production increasing complex building technologies and envelopes, energy efficient techniques and technologies, effectiveness of sustainability, software, fabrication and construction delivery methods, economic and ecological factors.

Figure 5. Contemporary Architectural Design of London City Hall, arch Norman Foster

3. PARAMETRIC ARCHITECTURAL DESIGN

Parametric design is algorithmic thinking that enables parameters and rules to define, encode and clarify the relationship between design intention and response. Architects use digital technology in terms of defining complexity and composition in parametric design.

Christopher Alexander - in Community and Privacy started to set out 33 design variables for prototypical urban housing, which he organized (with the aid of 704 computers) into sequences of groupings.

This parametric design strategy, made the “insoluble levels of complexity”.

“This type of Synthesis of Form” described the analytic and synthetic model as a way to find sophisticated design methodology.

Parametric architecture is connected to algorithmic thinking: designing by explicit rules where the geometry and performance criteria are both mathematically and technically pre-rationalized with complex computation technologies.

This included computer packages like Grasshopper, Digital Project CATIA, Tekla, Inventor, and the use of SolidWorks, machines for fabrication and topographic survey machines on site for installation.

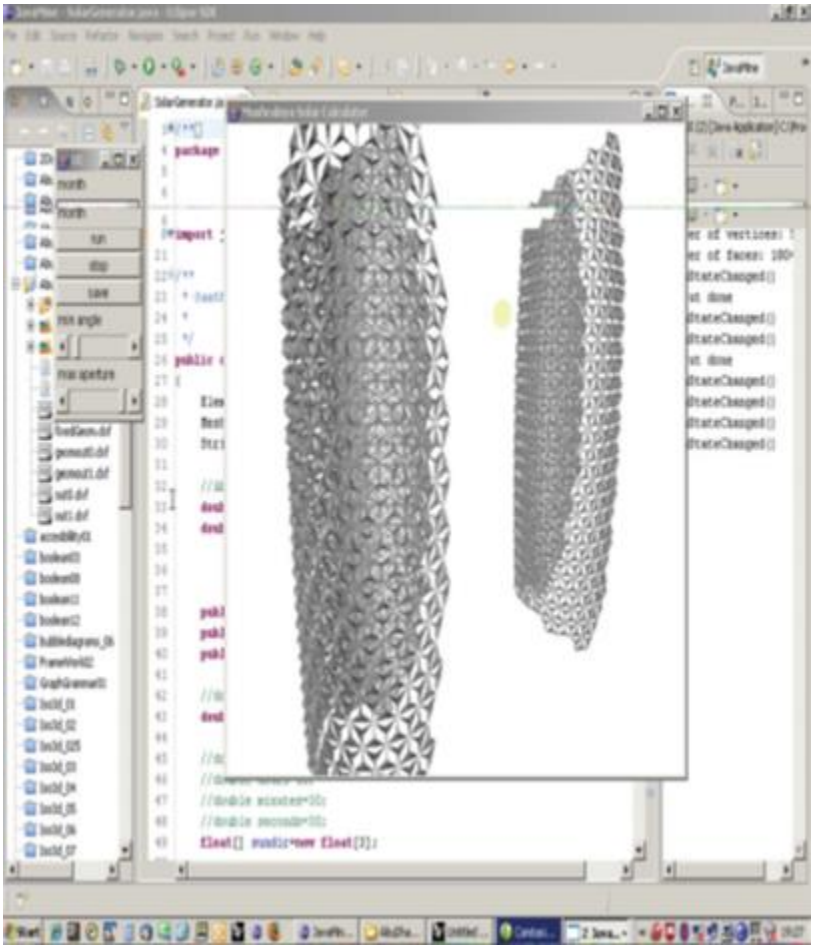

Figure 6. Algorithmic design process using computer platforms for parametric architectural design

4. PARAMETRIC DESIGN PARADIGMS

Contemporary design practices developed three different parametric design paradigms:

1. Parametric formalism that uses complex formal compositions as narrative in parametric techniques

2. Parametric BIM software and processes that allow architects and engineers to construct virtual models for the building systems and materials

3. Workflow parametric using parametric features to automate specific design workflows for projects such as façade design, environmental processes or structural procedures

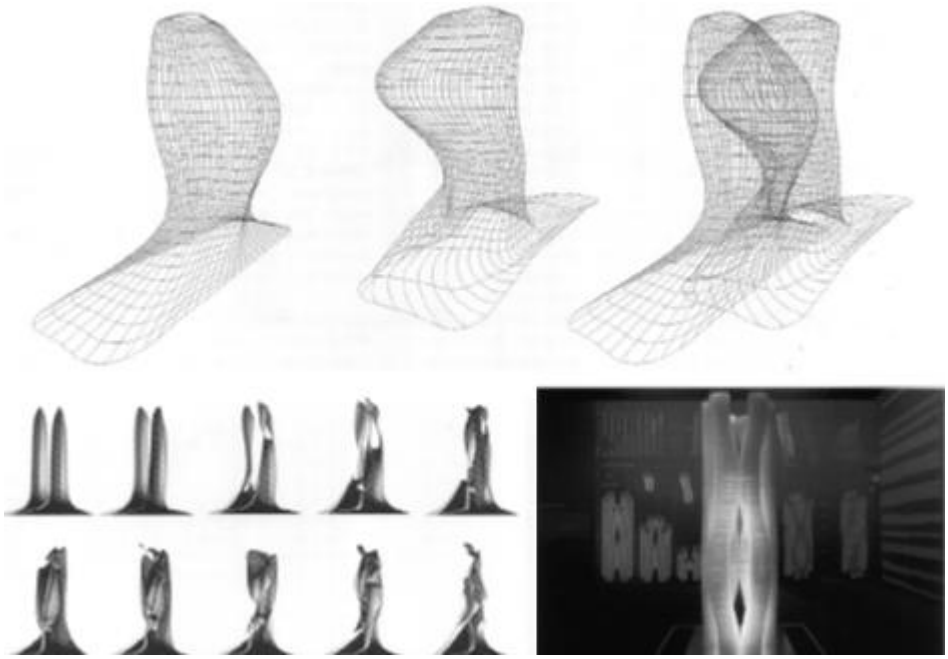

Figure 7. Geometric Design Method Analysis of Parametric Architecture

5. GEOMETRIC DESIGN METHOD ANAYSIS

The structure of the tall building exemplifies the approach in engineering, so that the central core supports much of the weight of the structure and load. Floor plates and beams connect to central core to surrounding exterior columns, each conducting a small part of the load to the ground and preventing the building from overturning or sliding when exposed to strong lateral forces such as wind and earthquake. The horizontal structure of the floors brace the entire building by tying inner core and outer frame together.

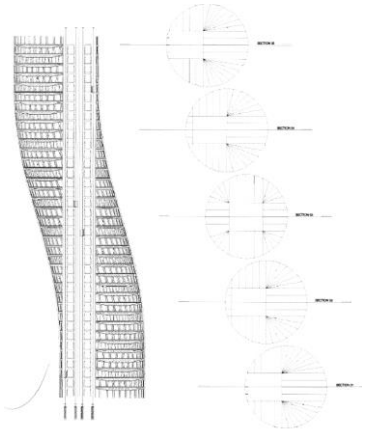

Figure 8. Geometric and Structural Analysis of Parametric Architectural Design

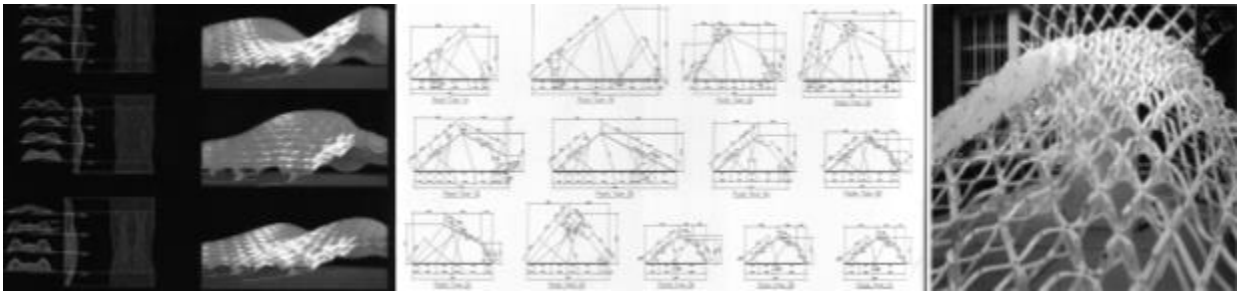

Figure 9. Engineering Complex Geometries, Algorithms and Complex Patterns in Architectural Design

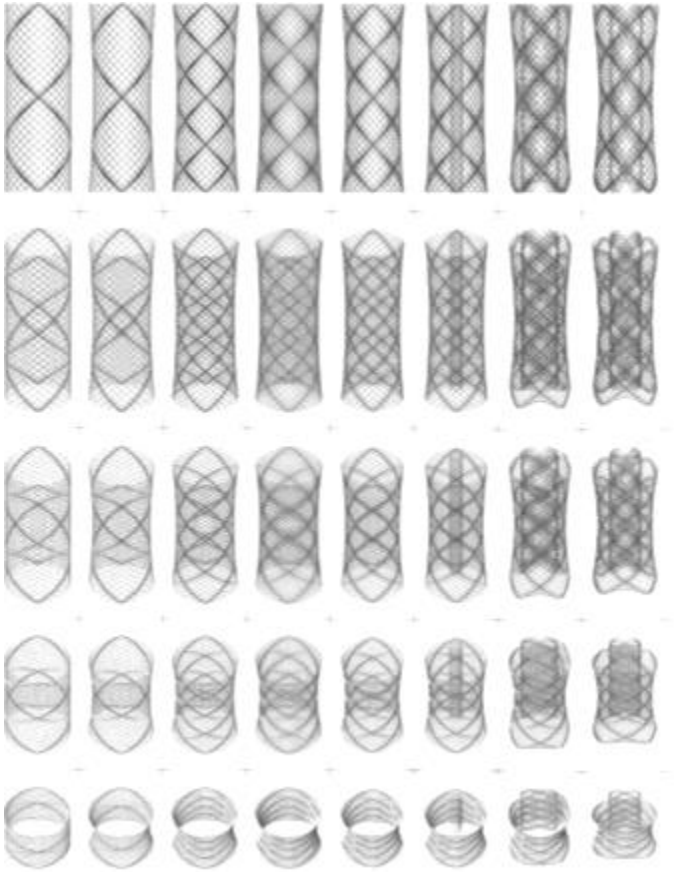

Figure 10. Architectural analysis of development of form of evolved double-helix structure

Phenotype Development by exposure of the geometry to environment in parametric design creates forms that increase structural capacity by sharing and distribution of loads.

The building envelope In the architectural design is an integral system of structure and environmental panels that adapt to the geometry and performance of the building.

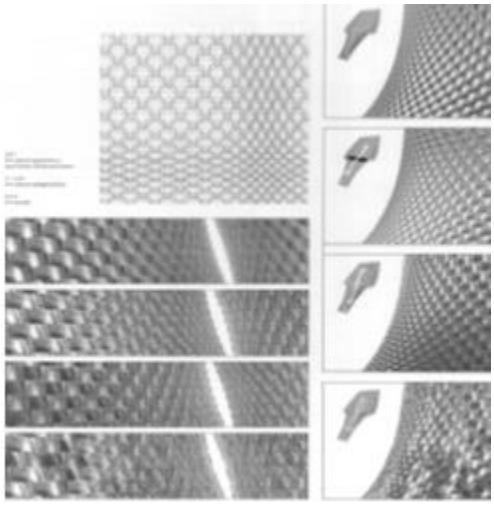

Figure 11. Phenotype Development by exposure of the geometry to environment

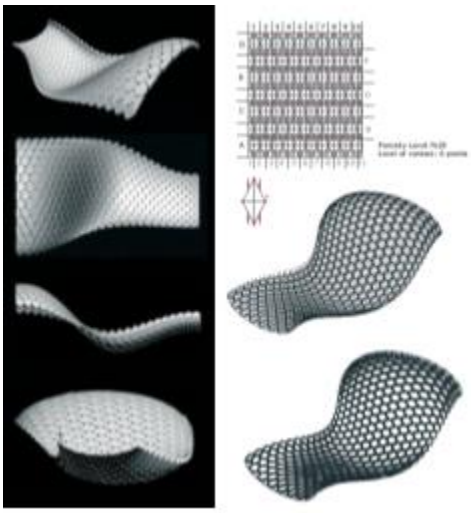

Figure 12. Parametric defined and varied digital model of double curved brick assembly

6. PARAMETRIC DESIGN PARADIGMS – GREEN DESIGN AND SUSTAINABILITY

Parametric design for modeling of integrated systems in architectural and urban scales:

- Architectural parametric design has a growing interest for the architects and engineering in designing exterior skin assembly and shapes of the building as a geometrically complex, net-zero-energy buildings, sustainable architecture,

- Urban parametric design focuses on sustainability issues (especially in the design of the infrastructure systems related to energy and water of the cities.

Figure 13. Architectural Parametric Design, Azerbaijan Cultural Centre, Baku, Azerbaijan, Zaha Hadid Architects, 2011

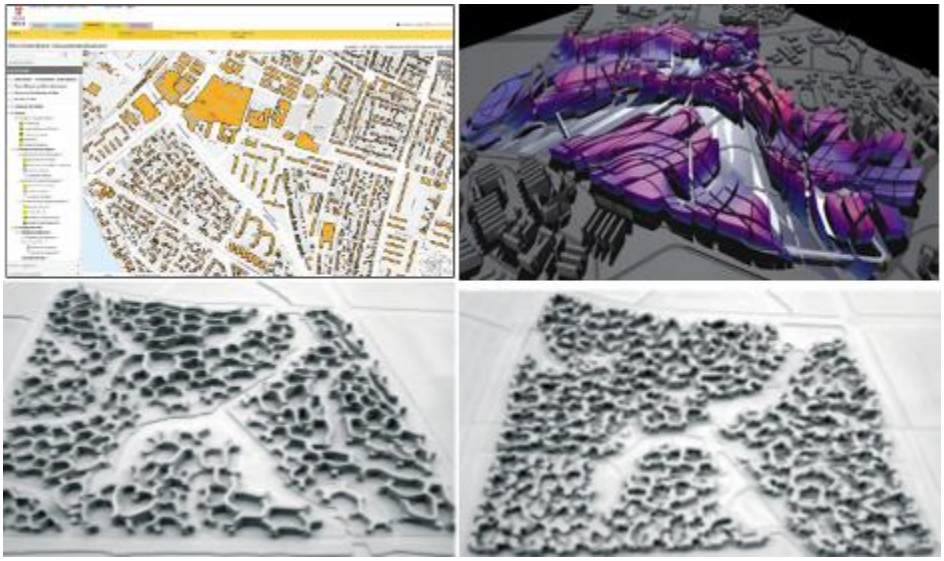

Figure 14. Urban Parametric Design - Modeling of urban infrastructure systems. Modeling software, showing resources for a proposed urban design project - Online Solar Cadastre of the City of Vienna and Urban Parametric Design

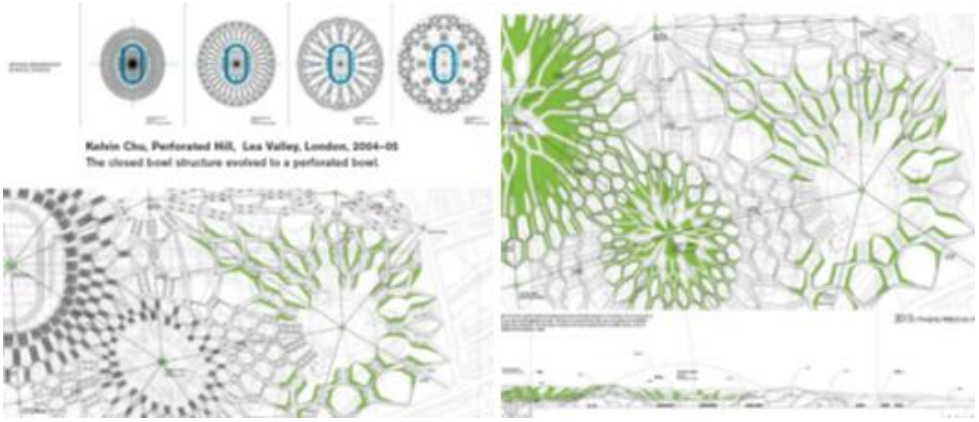

Figure 15. Urban Parametric landscape design, Perforated Hill, London - Modeling of urban infrastructure and landscape design. Modeling software, showing resources for a proposed urban design projec

Parametric design is part of prefabrication construction that plans sustainability, environmental concerns, design performance, material savings of quality products. The complex parametric design focuses on curvilinear geometries rationalized into curtain wall cladding systems.

The structural systems (including the floor slabs, perimeter columns, and sub-structural components) are designed by using algorithm design of the curtain wall system. This concept of prefabrication use can be seen in post-parametric automation in design and construction of complex buildings.

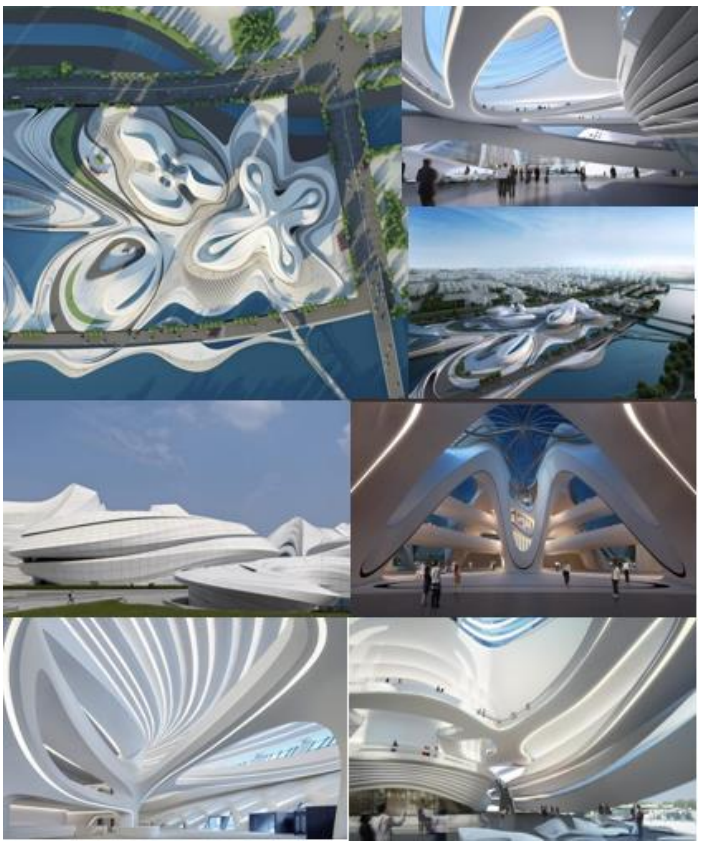

Figure 16. Urban Parametric Design and Architectural Design - Zaha Hadid Architects, Changsha Meixihu International Culture and Art Centre, China

The referent example of parametric architectural design concept of building Al Bahr Towers in Abu Dabi, Dubai responds to the fundamental issues affecting the standards of a fully glazed building in a hot climate and solves this challenge with the integration of a facade based on the traditional Islamic mashrabiya, a lattice screen used to diffuse sunlight while keeping buildings cool. Architectural designed visual code creates set of pattern and structural morphology into a telling language, social and communication aspects as semiological project. Parametric Architectural Design is complex of traditional geometric composition, sustainable technology and bio-mimetric concept, as a quantitative tool for creating biomimetic design in terms of sustainable concept of architectural design.

Figure 17. Parametric Architectural Design[1], Al Bahr Towers in Abu Dabi, Dubai, 2011

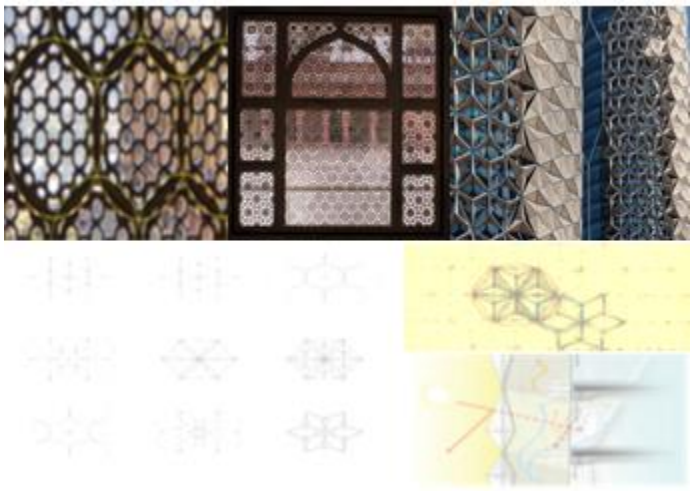

Figure 18. Architectural designed visual code creates set of pattern and structural morphology into a telling language, social and communication aspects as semiological project[2]

Parametric Design can be often used as a principle in modern contemporary interior design in shaping ceilings, flooring and often in furniture design. This principle of parametric design is often combined with wooden structural systems that are shaped in a specific algorithmic parametric design.

[1] Parametric Architectural Design is complex of traditional geometric composition, sustainable technology and bio-mimetric concept

[2] Concept of the shading screen patterns inspired from the Mashrabiya from the traditional architecture and natural adaptive systems

Figure 19. Parametric Architectural Interior Wood Design in Furniture, Wall, Ceiling Decorations

The world's largest parametric interior design in the world is the modern architectural parametric interior design of the Turkish Airlines Lounge in Istanbul Airport, from Avci Architects, located in Istanbul, Turkey. The concept of the Flow wall from Turkish Airlines unites the lounges in Istanbul Airport creating a flow concept of 19 000 square meters intuitive route with architectural space, symbolizing connecting people, culture and places. The architects studio used parametric design algorithm-based process which allowed them to test various outcomes of the design concept within a set of parameters.

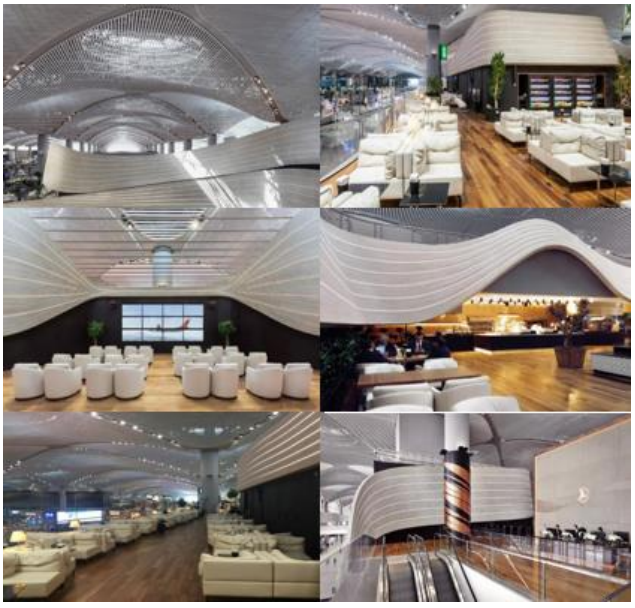

Figure 20. Modern Architectural Parametric Interior Design - Turkish Airlines Lounge, Istanbul Airport, Avci Architects, Istanbul, Turkey

The referent example of TAV Airport in Tashkent, Uzbekistan also presents architectural awarded project for parametric design concept. The concept design was inspired by traditional Uzbek architecture, the abstract colorful geometric patterns which have been shown as a stylization of forms in modern shaped architectural and interior design. The architectural design suggests linked space in order to unify, where the canopy acts as unifying element of the design, linking the roof of the building and the plaza by its dynamic and fluid form which also corresponds to the function of the building.

Figure 21. TAV Airport in Tashkent, Uzbekistan, Architects: Pinar Ilki, Dicle Demircioglu

7. CONCLUSION

Parametric design in architectural design studios emerges from the concept of new engineering and fabrication methods in a stylistic form-based and optimization processes towards new contemporary style in architecture.

Semiological articulation of parametric architectural design can map significant programmatic and morphological conceptual distinctions.

Engineering ecological concept and paradigm start to shift, in a concept that incorporates contemporary design as a modulation of environments and ecologies in architectural parametric design of the 21st century.

Parametric design is creating large number of architectural and engineering concepts which transform their practices by using parametric, BIM, and parametric automatisation design tools towards a new contemporary complexity and composition in a new trend of parametric architectural design.

The current trend from engineers for prefabrication and modularization will focus on development of 3D multi-materials and synthetic biology processes for different types of new bio-materials designed at micro and nanometer level to respond to the particular conditions according to the needs of the parametric architectural design.

This concept of parametric design in architecture will lead into contemporary transformation of the design and traditional design process of the next generations of architectural engineers of the 21st century.

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"GREEN ARCHITECTURAL PARADIGM AND ECOLOGICAL CONCEPT IN MODERN ARCHITECTURE"

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[1]*International Balkan University, Faculty of Engineering / Architecture*

Abstract. *The concept of green architectural paradigm and ecological design process is one of the architectural paradigms of the 21st century. Green architecture paradigm combines six principles that should work together with the buildings: conserving energy, climate neutral systems, minimizing new resources, respect for the users and creating green architecture that recognizes the importance of the relation between people and nature, respect for the site, where all green principles need to be embodied in a holistic approach to the built environment.*

Ecological Design in Architecture should be durable, theory based to enable environmentally holistic design approach, which will acknowledge the ecological design as a complex and involve the incorporation of a complex set of green interactions with the environment on a local and global level. General systems framework for ecological design include the concept of developing a theory for ecological design, urban environment as fundamental to the ecosystem concept in ecology, and architectural design as a crucial and essential resolution of the design process.

The sustainability conversation, achieves an urgent awareness of the global warming and the effects of climate change, in the extremes of weather and the unexpected flooding in the cities. But architects must think of sustainability in a new way. The green technology paradigm incorporates the concept of livability and the aspect how people can adapt to their environment.

One of the leading challenges for architects and urban planners today is how to deal with urban density. Cities have to design, plan, and create buildings for a population that is urbanizing at exceptional speed. Sustainable design should to be firmly grounded to the details of design and integration of ecology and design. The epistemology should rely on the deep interconnections in order to mirror nature.

Specific attention in this research will be given to analysis of ecological design process and green architectural paradigm with consideration of their urban context, adequate public access and architectural space. The expected outcome results in this scientific paper is to identify the green design approaches and create application at the international education processes.

Keywords: *green architectural paradigm; ecologic concept; modern architecture.*

1. URBANIZATION AS GLOBAL CHALLENGE

The cities nowadays have an exponential growth in their urban development. Urbanization shows that nearly half of the world's population live in urban areas. Cities nowadays are becoming economic hot-spots with nearly 80% of global GDP located in cities. Social problems are concentrated in urban spaces, as centers of environmental degradation.

Urban areas have a crucial role in tackling climate change, and there have been observed that 70% of global greenhouse gas emissions come from cities. Smart urban planning is key to ensuring safe, resilient and sustainable cities.

2. ECOLOGICAL DESIGN IN TODAY'S CITIES SHOULD MOVE TOWARDS GREENING OF URBAN ENVIRONMENT

It is very important in cities today to focus towards greening the urban environment. This is important as a preventive measure to create urban climate modification, adaptation and mitigation as a system of measures.
Benefits of the today's green cities include the following principles:

1. Ecological benefits from greening the environment in the cities:
- Temperature modification – heating/cooling of buildings,
- Air quality improvements –pollution absorption and oxygen production,
- Carbon dioxide storage,
- Storm-water– filtration and absorption of water,

2. Social benefits from greening the environment in the cities:
- Social aspects on well-being of city residents,
- Provides a connection to nature and biodiversity,

3. Economic benefits from greening the environment in the cities:
- Reduction in cooling costs,
- Regulates sunlight distribution in houses,

- Increase in real estate values,
- Improves the appearance, economic value of cities,
- Reduction in health service costs,
- Improvement in the livability in cities.

Figure 1. Sustainable Architecture and Landscape Design Projects in the Cities

3. ECOLOGICAL DESIGN PARADIGM IN ARCHITECTURE

Ecological Paradigm is defined by the architectural protagonists Brenda and Robert Vale. According to them architectural practice should focus on low-energy use, from production of materials, to thermodynamics of individual buildings, promoting a holistic approach in design.

Ecological design should be durable and have theory-base approach that will enable the design work to be environmentally holistic:

- we should acknowledge that ecological design is complex

- it specifically involves the incorporation of a complex set of "interdependent interactions" or connections with the environment (both global and local scale)

Figure 2. Green building, Nanyang Technological University, Singapore

Ecological Design Paradigm was also analyzed and defined by the protagonist Van Der Ryn. According to Van Der Ryn: "If we are to create a sustainable world, accountable to the needs of all future generations we must recognize that our present forms of architecture, engineering, agriculture, ecology and technology are connected".

4. SUSTAINABLE GREEN PARADIGM IN ARCHITECTURE

Sustainable Green Paradigm in architecture and interior design is often defined as Design in Action. According to the Green Paradigm from the architectural protagonist Van Dyk, green architecture should combine six principles that should work together with the buildings:

1. Conserving energy, (Buildings should be constructed to minimize the need for fossil fuels for buildings' functioning)
2. Working with climate (Buildings should be designed to work with climate and natural energy sources)
3. Minimizing new resources (Building should be designed to minimize the use of new resources)

4. Respect for the users (A green architecture recognizes the importance of people and nature)
5. Respect for the site
6. Holism, all the green principles need to be embodied in a holistic approach to the built environment

Figure 3. Living wall composed of individual planting cells on supporting panel system

5. REDEFINING ECOLOGICAL URBAN AND ARCHITECTURAL DESIGN RESEARCH

Architectural design with connection with the environment is one of the fundamental part in architecture. Architects nowadays are becoming a leaders towards the field of environmental design and sustainable architectural research. Applied ecological design in architectural projects reaches a growing number of architectural subjects. It creates concept of evaluating and valuing the tradition in architecture integrated in both winder academic research communities and architectural practice.

Urban Sustainable Environment shifts towards the principles of the ecological design paradigm. Ecological design paradigm and agenda can be defined also in the complex and fragmented architectural design. The design is correlated with the information communication systems in a complex and collaborative design which shifts towards complexity of these projects and their developments.

Urban and spatial planning combine the knowledge and the science in an inter-disciplinary concept, including academia, urban design and planning in a urban simulation systems.

Examples of architectural designing processes and systems can be seen in the urban design in holistic energy strategy for an innovative scheme that straddles the scales of the buildings and urbanism. In these concepts the design of the individual buildings works in urban scale towards incorporating the ideas of ecology, networks and system-based design.

Conceptualizing urban areas as sets of intersecting systems provides basis of architectural study of the organization of sustainable urban systems, in detailed analysis of the terrain configuration, insolation orientation, wind orientation, correlation between the system of buildings in a sustainable approach.

Figure 4. Sustainable Architectural Project, Zorlu Shopping Center in Istanbul

One of the main question in architecture remains: How can ecological design be redefined towards more relevant architectural approach?

There is an urgent need for new knowledge which is related to the global and multidisciplinary issue in sustainable design. In the context of sustainable architecture the challenge of building sustainability is addressed by engaging new forms of visual communications. The form of the architectural buildings start to follow energy concepts.

The focus and the need of increased level of documentation of energy, environment and various ideas of sustainability, architects are modeling, simulating and redefining the buildings, according to the energy and performances of the buildings.

During the architectural design process, the form and the shape of the building can be modified several times with advances computer programs towards design that achieves simulation of the maximum benefits of the energy performances of the building, such as solar potential for the solar photo-voltaic systems. The ecological pre-conditions will be a crucial factors in the design process of the architectural buildings.

Important part of assessing the sustainability of the building design is the method towards measuring energy, airflow, carbon production, and material performances, measurements that range form different variables according the values in the simulation models.

6. ARCHITECTURAL EDUCATION FOR SUSTAINABLE ARCHITECTURAL PROJECT DEVELOPMENT, DEPARTMENT OF ARCHITECTURE, FACULTY OF ENGINEERING, INTERNATIONAL BALKAN UNIVERSITY

Architectural education for sustainable development is currently very important theme for researching in context of architectural and urban environment

The aim and scope of the presentation from architectural studios and projects developed from students of Department of Architecture, Faculty of Engineering of International Balkan University.

Architectural project - Multicultural ecological center, course: Landscape Architecture, objectives and goal of the architectural projects are:

- To improve educational and cultural opportunities by promoting ecological content
- Education for raising public awareness for nature conservation
- Opportunity to get knowledge directly with biodiversity and natural resources with modern innovative approach
- Improve human action towards natural environment
- Organizing educational visits, eco-actions, eco-exhibitions

related to ecology in the neighbourhood, and city in general

Figure 5. Sustainable Architectural Project, course Landscape Architecture, IBU

Figure 6. Sustainable Architectural Project of Residential Complex, course Architectural Design III, IBU

Architectural Project for the course Sustainable Architecture at consisted of project that implements renewable technologies and green technologies. The title of the project is Municipality building, course: Sustainable Architecture, IBU, objectives and goals of the architectural project are:

- To improve the architectural functioning of the building with implementation of renewable technologies: solar panels, photo-voltaic panels, geothermal pumps, green roof system

- To improve the connection and between public buildings: municipality building by promoting the use of renewable technologies

- To improve educational and cultural opportunities by promoting ecological content and education for nature conservation

Figure 7. Sustainable Architectural Project of Modern Municipality Building, course Architectural Design VII Project II, IBU

Figure 8. Sustainable Architectural Project of Modern Office Building in Istanbul, course Architectural Design VII Project II, IBU

Figure 9. Sustainable Architectural Project of Modern Office Building in Istanbul, course Architectural Design VII Project II, IBU

7. CONCLUSION

Redefining Ecological Design research and paradigm shifts in two ways of approaches from the architectural professionals. There are two ways in which architects are responding to the emerging need of sustainable buildings concepts: by bringing new knowledge from outside the profession into the design teams, and secondly by attempting to create the knowledge from within design team in a holistic approach.

The increased focus on documenting energy, environment and ideas on sustainability, architects are modeling, simulating and measuring buildings, energy and performance as a holistic approach. Engineering ecological concept shifts and it incorporates contemporary design as modulation of environments and ecologies. There is an urgent need for new knowledge which is related to the global and multidisciplinary issue in sustainable design. In the context of sustainable architecture the challenge of building sustainability is addressed by engaging new forms of visual communications. The form of the architectural buildings start to follow energy concepts.

During the architectural design process, the form and the shape of the building can be modified several times with advances computer programs towards design that achieves simulation of the maximum benefits of the energy performances of the building, such as solar potential for the solar photo-voltaic systems. The ecological pre-conditions will be a crucial factors in the design process of the architectural buildings.

The current trend for architectural engineers will focus on development of sustainable elements and technologies, 3D multimaterials and synthetic biology processes for different types of new biomaterials designed at micro and nano level to respond to the particular conditions.

The research into sustainability shifts from a technological and innovation process requires contemporary sociocultural and economic transition in architectural design. The research study of the ecological and green design concepts, within the built environment of the design approaches contribute towards interior finishing materials and the surface treatment systems towards interior design from ecological and green design.

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A REVIEW OF SALIVA: SECRETION, COMPOSITION AND FUNCTION

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Abstract. *Saliva plays a central role in the complex physiological and biological processes that take place in the upper parts of the gastrointestinal tract in relation to ingestion and processing of the food. Human saliva has a number of physical, physicochemical and chemical agents that protect oral tissues against by various microorganisms and their metabolic products. Antimicrobial peptides with other innate defense molecules are fighting infection and control residents microbial populations throughout the oral cavity.*

1. INTRODUCTION

Saliva is a clear, slightly acidic mucoserous exocrine secretion. Whole saliva is a complex mix of fluids from major and minor salivary glands and from gingival crevicular fluid, which contains oral bacteria and food debris [1,2].

Mayor gland do produced more saliva than minor gland, but the quality of content endused the type of protection varies. the minor salivary gland are the most important because they have more protective components. The average daily flow of whole saliva varies in health between 1L and 1.5 L. Percentage contributions of the different salivary glands during unstimulated flow are as follows: 20% from parotid, 65% from submandibular, 7% to 8% from sublingual, and less than 10% from numerous minor glands. Stimulated high flow rates drastically change percentage contributions from each gland, with the parotid contributing more than 50% of total salivary secretions [3].

There is great variability in individual salivary flow rates. The accepted range of normal flow for unstimulated saliva is anything above 0.1 ml/min. For stimulated saliva, the minimum volume for the accepted norm increases to 0.2 ml/min. These numbers have been projected from research on general populations. Salivary flow is, a very individualized measurement and ideally should be recorded as a base reference after the age of 15 [3]. Any unstimulated flow rate below 0.1 ml/min is considered hypofunction [4]. In a 1992 study, the critical range separating persons with normal gland function from those with hypofunction was more precisely identified as unstimulated whole salivary flow rates between 0.12 and 0.16 ml/min [5]. If individualized base rates have been established, then a 50% reduction in flow should be considered hypofunction [6]. On average, unstimulated flow rate is 0.3 ml/min [3,5] with the average total for 16 hours of unstimulated flow (during waking hours) being 300 ml.

Salivary flow during sleep is nearly zero. Stimulated flow rate is, at maximum, 7 ml/min [3]. Stimulated saliva is reported to contribute as much as 80% to 90% of the average daily salivary production.

The secretion of saliva is controlled by a salivary center composed of nuclei in the medulla, [5] but there are specific triggers for this secretion. Three types of triggers, or stimuli, for this production are mechanical (the act of chewing), gustatory (with acid the most stimulating trigger and sweet the least stimulating), and olfactory (a surprisingly poor stimulus). Other factors affecting secretion include psychic factors such as pain, certain types of medication, and various local or systemic diseases affecting the glands themselves [2,5,7].

Salivary glands are innervated by both sympathetic and parasympathetic nerve fibers. Various neurotransmitters and hormones stimulate different receptors, different salivary glands, and different responses [8]. When sympathetic innervations dominate, the secretions contain more protein from acinar cells, whereas predominant parasympathetic innervations produce a more watery secretion [3]. Stimulation of 1 receptor often enhances and complements another receptor. Therefore, the separation of contributing stimuli and resulting secretory products is not absolute [8]. It must be emphasized that there is great individual variability in salivary stimulation and secretion from cell type to cell type, thereby affecting the content of saliva regionally and as a whole.

2. SALIVARY FUNCTION

Saliva serves multiple functions that are important for the maintenance of oral and systemic health. The fluid characteristics and viscoelastic properties of saliva are essential for the mechanical cleansing of the oral cavity, clearance of food debris and microorganisms, dissolution of tastants and dilution of hot, cold or spicy food, as well as for the lubrication and moistening of teeth and oropharyngeal mucosa, which facilitate the processes of chewing, bolus formation, swallowing and articulation of speech.

Saliva consist of more than 99% water and less than 1% solids such as proteins and electrolytes. [9,10,11]. Salivary constituent include sodium chloride, potassium, calcium, magnesium, phosphate and bicarbonate as well as trace elements. the composition of saliva , especially the concentration of various ions is depend of the flow rate [12]. This concentrations of sodium chloride bicarbonate and total calcium are higher and the concentrations of potassium and total phosphate are low in stimulated saliva compared to unstimulated saliva [9,10,11]. The physical chemical properties of the inorganic salivary components and hereby their role information of the oral surface biofilms and has on the resident oral microbiota.

Analysis of the human salivary proteome has characterized about 3000 different proteins and peptides [13]. More than 90% in weight of the about 3000 protein components are present in saliva from the parotid, submandibular and sublingual glands, belonging to the classes of acidic and basic proline-rich proteins, α-amylases, mucins, cystatins, histatins, statherin and host defence peptides and accounting for about 200 proteins and peptides. The remaining 10% in weight are compo- nents deriving from the minor glands (labial, palatine, buccal and lingual glands) [14], and from gingival crevicular fluid, e.g. α-defensins and products of mucosal exudates.

Salivary function can be organized into 5 categories that serve to maintain oral health and create an appropriate ecologic balance: (1) lubrication and protection, (2) buffering action and clearance, (3) maintenance of tooth and oral mucosa integrity, (4) antibacterial activity, and (5) taste and digestion.[15,16].

(1) THE ROLE OF LUBRICATION

The complex mix of salivary constituents provides an effective set of systems for lubricating and protecting the soft and hard tissues [17]. The best libricated components of saliva are muffins that are excreted from salivary glands. Mucins are complex protein molecules that are present predominantly in 2 molecular weight types [17,18] and formed by polypeptide chains that stick together. These mucins have the properties of low solubility, high viscosity, high elasticity, and strong adhesiveness. Any intraoral contact between soft tissues, between soft tissues and teeth, or between soft tissues and prostheses benefits from the lubricating capability of saliva supplied largely by these mucins [3]. Mastication, speech, and swallowing all are aided by the lubricating effects of mucins [18].

The lubricating and antimicrobial functions of saliva are maintained mainly by resting; saliva results in a flushing effect and the clearance of oral debris and noxious agents [19]. Saliva is a complex fluid, which influences oral health through specific and nonspecific physical and chemical properties [20]. Saliva contains numerous antimicrobial proteins that help protect the oral ecosystem from infectious agent [20]. Proteins can move from blood circulation into salivary glands through active transportation, passive diffusion, or ultrafiltration; some of which are then released into saliva and hence can potentially serve as biomarkers for diseases [21]. Saliva covers the oral hard and soft tissues with a conditioning film which governs the initial attachment of microorganisms, a crucial step in the setup of the oral microflora [22].

(2) BUFFERING ACTION AND CLEARANCE

Saliva buffers acids and its buffer capacity originates from the content of bicarbonate, phosphate and proteins [23, 24]. Salivary pH is maintained at a relatively constant physiological level, that is 6.5–7.4, by buffering dietary acids and acids derived from bacterial fermentation of carbohydrates and thereby diminishing the rate of tooth demineralization [23]. The concentration of bicarbonate in saliva, the salivary pH and the buffer capacity are highly dependent on the salivary flow rate, and they increase when the salivary flow rate increases and *vice versa* [23,25].

Salivary pH and the levels of calcium and phosphate are important factors for maintaining sa- liva supersaturated with respect to hydroxyapatite [26]. In the stimulated state, the bicarbonate buffer system is responsible for about 90% of the buffer capacity, whereas in the unstimu- lated condition, the phosphate concentration is nearly equal to the bicarbonate concentration and they contribute almost equally to the buffering capacity. At lower flow rates and salivary pH below 5, proteins constitute the major buffering capacity [23]. Saliva also contains certain proteins

including acidic proline-rich proteins, histatins, cystatins and statherins, which are among the first proteins that adhere to a clean enamel surface to initiate enamel pellicle formation. They display high affinity for hydroxyapatite as they bind calcium ions, and inhibit precipitation of calcium phosphate salts from saliva supersaturated with respect to hydroxyapatite, thus protecting the teeth from demineralization and calculus formation [27].

The ions in saliva, including calcium, are also important to the function of salivary α-amylase [28]. In addition, oral bacteria help to buffer saliva by breaking down urea to ammonia and carbon dioxide resulting in an increase in pH [28].

(3) MAINTENANCE OF TOOTH AND ORAL MUCOSA INTEGRITY

Maintaining tooth integrity is a third function of saliva, one that facilitates the demineralization and remineralization process. Demineralization occurs when acids diffuse through plaque and the pellicle into the liquid phase of enamel between enamel crystals. Resulting crystalline dissolution occurs at a pH of 5 to 5.5, which is the critical pH range for the development of caries [3]. Dissolved minerals subsequently diffuse out of the tooth structure and into the saliva surrounding the tooth. The buffering capacity of saliva greatly influences the pH of plaque surrounding the enamel, thereby inhibiting caries progression [30]. Plaque thickness and the number of bacteria present determine the effectiveness of salivary buffers. Remineralization is the process of replacing lost minerals through the organic matrix of the enamel to the crystals. Supersaturation of minerals in saliva is critical to this process. The high salivary concentrations of calcium and phosphate, which are maintained by salivary proteins, may account for the maturation and remineralization of enamel [2]. Statherin, a salivary peptide, contributes to the stabilization of calcium and phosphate salts solution, serves as a lubricant to protect the tooth from wear, and may initiate the formation of the protective pellicle by binding to hydroxyapatite.[3,6]. Proteins in the protective pellicle, such as statherin, histatins, cystatins, and proline-rich proteins, are too large to penetrate enamel pores. Therefore, they remain on the surface, bound to hydroxyapatite, to aid in controlling crystalline growth of the enamel by allowing the penetration of minerals into the enamel for remineralization and by limiting mineral egress [31,32]. The presence of fluoride in saliva speeds up crystal precipitation, forming a fluorapatite-like coating more resistant to caries than the original tooth structure. In that sense, small amounts of demineralization have been suggested as advantageous for the tooth because enamel components of magnesium and carbonate are replaced with the stronger, more caries-resistant fluorapatite crystals [3]. Fluoride in salivary solution works to inhibit dissolution of apatite crystals.

(4) ANTIBACTERIAL ACTIVITY

Immunologic and nonimmunologic antibacterial salivary content come from 2 different sources namely, plasma and ductal cells with different responses to stimulation and different content levels.

Salivary glands are exocrine glands, and, as such, secrete fluid containing immunologic and non-immunologic agents for the protection of teeth and mucosal surfaces. Immunologic contents of saliva include secretory IgA, IgG, and IgM. Non-immunologic salivary contents are selected proteins, mucins, peptides, and enzymes. Secretory IgA, the largest immunologic component of saliva, is an immunoglobulin produced by plasma cells in connective tissues and translocated through the duct cells of major and minor salivary glands. IgA, while active on mucosal surfaces, also acts to neutralize viruses, serves as an antibody to bacterial antigens, and works to aggregate or clump bacteria, thus inhibiting bacterial attachment to host tissues[33,34]. Other immunoglobulins present in saliva are in low quantities and probably come from gingival crevicular fluid [2]. It seems unlikely that host complement response could act generally in the oral fluid [3]. IgA itself does not activate complement[5], but oral fluids can be augmented by gingival crevicular fluid host complement components when gingivitis is present around existing teeth[1,15]. Non-immunologic antibacterial salivary contents such as proteins, mucins, peptides, and enzymes (lactoferrin, lysozyme, and peroxidase), all products of acinar gland cells, help protect teeth against physical, chemical, and microbial insults [35].

Antimicrobial peptides include: mucins, histatines, defensines, lactoferrin cathelicidins,, calprotrctin, lysozymes and oral peroxidase.

Mucins

The main role of mucins is in mechanical protection of mucosa, but the research showed their antimicrobial activity. Low molecular mucins of saliva in "*in vitro*" conditions show effect against different kinds of fungus (*Candida*

albicans, Cryptoccocus neformans), gram-positive (*Streptococcus mutans*) and gram-negative bacteria that cause periodontal deices (*Porfyromonas gingivalis*)[36, 37].

Because they are able to aggregate bacterial microflora, mucins represent the important factor of dental caries. Literature data show that low molecular mucins are more effective than high molecular ones. The indicator for this is that, high molecular mucins are predominant in saliva of caries sensitive persons, while in saliva of caries resistant persons higher concentration of low molecular mucins is established [38].

Histatines

The main source of histatines are salivary glands. The representatives of this family proteins are: histatine1, histatine 3, histatine 5. The specially articulated anti fungal effect in "*in vitro*" conditionals, has histatine 5 against different kinds of fungus (*Candida albicans,Candida krusei, Candida glabrata, Sacharmyces cervisiae, Cryptococcus neoformans*). These protein doesn't behave like classic antibiotic, by forming pores of ionic chanels in *c.albicans* membrane, but in its mechanisms of anti fungal effect there are a couple od phases: bonding for the specific receptors on membrane, transport trough membrane and entering the cell mobilization of ions K^+, Mg^{2+}, I ATP from the cell. The target for histatine to act inside *C.albicans* is mithochondria, where it inhibits respiratory chains [39].

Defensives

Defensives shows antimicrobial activity because they are able "to kill" all kind of gram-positive and gram-negative bacteria, the fungus (C*andida albicans)* as well some viruses (*Herpes simplex*) [40,41].

The mechanism od antibacterial defensives can be divided into couple of phases:

1. Electrostatic connection between defensives as a cations at the surface of bacteria cell membrane, which has anon characteristics.

2. The increasing of permeability of bacteria membrane is achieved in two ways: the first one is to form ionic channels with dimension depend of the type of the cell; the second is called "*carpet model*" which means aggregation of those peptides with positive electrified parts of membrane and in this way formation of a transit path for their pass.

3. Disturbance in a protein synthesis in bacteria cell [41].

Because of the great potential in "killing" bacteria, defensives are popularly called "*natural antibiotics*". In some studies is suggested the possibility of their use in oral disease therapy [41].

Lactoferrin

Lactoferrin is an important component for unspecific antimicrobial mucosa protection, because it demonstrates bacteriostatic and bactericidal effect towards gram-positive and gram-negative bacteria. It has an outstanding affinity in bond with ferritin, so it made it inaccessible for bacteria and so they are deprived of these bio element necessary for them. The phenomena is cold "*nutritive immunity*"and these is a way that lactoferrin prevents the growth and reproduction of bacteria [42].

Lactoferrin demonstrated antiviral activity, because in (*in vitro*) conditions it could inhibit replication of viruses. However, research show that lactoferrin primary stops virus infection of host cells and to the smaller extend, it inhibits the replication of viruses. Lactoferrin achieves the prevention of the infection of the host cells in two ways:

1. By direct bonding of lactoferrin to the virus (hepatitis C virus, polyvirus, rotavirus, herpes simplex virus and human immunodeficiency virus (HIV)).
2. By bonding of lactoferrin to the host cells, especially for those biomolecules in the structures of plasma membranes witch serve for viruses as a receptors or coreceptors (HSPGs) [43].

Lactoferrin has the same effect like *Candida albicans* bacteria. It refers to ferrous bonding as a direct interactions of lactoferrin and it peptides with this fungus, which provoke disturbance in porousness of it membranes [44].

The patients with progressive periodontal decease where one of the causes is *Actinobacillus actinomycetemcomitans*, negative correlation is found between the number of those pathogens and concentration of lactoferrin in saliva. After the appropriate periodontal disease therapy the level of lactoferrin in saliva and gingival fluid is significantly decreased. This shows that lactoferrin can be sensitive biomarker for the parodontopathy level and the efficiency of therapy applied [45].

Calprotectin

Calprotectin has antimicrobial effect which is achieved by zinc bonding, and that is why, microorganisms are the deprived of this essential element and their survival can be prevented [46]. The presence of calprotectin is proved in saliva. The main source of these saliva proteins are the gum fluid mucosa transudate and gum keratinocytes. These protein is included in unspecific antimicrobial protection of oral environment because of its antibacterial and anti fungal effects. The increased concentration of calprotectin in saliva is proved in some of oral diseases, so it could be considered as a valid marker for those diseases [47]. In addition of direct antibacterial effect of calprotectin the data shows that this defensive protein has a role in protection of oral mucosa from bacterial colonization. This multifunctional protein lessens the possibility of bacterial bonding for the epithelia cells on the oral mucosa [48].

Lysozime

Lysozyme is part of the innate salivary defense mechanisms. The lysozyme present in whole saliva originates from the major and minor salivary glands, and to a minor extent from gingival crevicular fluid, and salivary leukocytes. Lysozyme is present in the salivary pellicle as well as in the dental plaque [49]. Lysozyme exerts enzymatic activity via hydrolysis of the β-1,4-glycosidic bonds between N-acetylmuramic acid and N-acetyl-d-glucosamine in the polysaccharide layer of the gram-positive bacterial cell wall. Apart from this well-known bacteriolytic activity, and a highly cationic protein, lysozyme also has the ability to aggregate oral bacteria, e.g. streptococci, thereby affecting their adherence to the oral surfaces and promoting clearance of microorganisms from the oral cavity. In addition, lysozyme can activate bacterial autolysins which destroy the bacterial cell walls [50]. Lysozyme of saliva presence are important factor of unspecified environment. A couple of studies show that concentration of saliva with accumulation of dental plaque and appearance of gingivitis in children and young. The other studies pointed out an increase of lysozyme in saliva from the population with oral candida, in addition to its importance in defense of oral environment against bacteria and fungi, it also inhibited the adherence of bacteria streptococcus mutant and anguish for the acquired dental periclle, with lessons accumulation of dental plaque.

Oral Peroxidase

Oral peroxidase is saliva enzyme with consist of two peroxidase enzymes: saliva peroxidase 80% and mieloperoxidase 20%. Saliva peroxidase is secreted from the main saliva glands mostly parotid gland. The role of peroxidase is to catalyze reaction between H_2O_2 (product of oral bacterial metabolism) and tiociyant ions. The product of these reaction is hipotiociyant acid and hipotiocianates, witch blocade sulfurhydric groups of bacterial enzymes, glycolyse, hexokinase, aldolases and pyruvate kinase. The enzymes show antibacterial effect against of number of gram-positive (Streptococcus mutant) and gram-negative bacteria (P.Nucleatum, P. gingivalis, Prevoteles, Actinobacillus, actinomycetem comitans). Besides the role of unspecific antimicrobial protections of oral environment, these enzyme also contributes effective elimination of H_2O_2 from oral environment.

Mielooperoxidase is HEM-dependent enzyme witch is part of leukocytes (neutrofiles and monocytes). In the presence of H_2O_2 and mieloperoxidase a compex enzyme-substrate is formed and it has the ability to oxidase iodides and chlorides, making toxic products. Because of the great diffusion of chorions in biological systems, its oxidation gives the hypochloric acid (HOCL). This acid has expressive oxidative capacity and during the reaction it makes products witch have, not only bacterial capacity but they also participate in demolishment of uninfective substance toxin and inflammatory mediators. [51]

In order to enhance the antimicrobial effects of saliva, the lactoperoxidase system and other proteins have been added to oral health products [52,53]. Studies have shown that regular use of lactoferrin and lactoperoxidase-containing tablets, or toothpaste, mouth rinse or gel containing peroxidase system as well as colostrum results in a shift in the microbial ecology that may contribute to improvements in oral health, including oral malodour and gingival conditions [54,55,56]. On the other hand, a study by Kirstilä et al. [57] on the effects of a lactoperoxidase-system-containing toothpaste (BioteneTM), found no effect on salivary flow rate, peroxidase activity, thiocyanate/hypothiocyanite, bacterial counts or on the dental plaque levels compared with the placebo toothpaste. However, the toothpaste was only used for a very limited period of two weeks. In addition, with new technologies including 16S rRNA gene high-throughput sequencing, proteomics, transcriptomics and metabolomics, allowing in depth analysis, it is more likely to identify differences. Thus, a recent randomised clinical study, comparing the use of fluoride toothpaste containing enzymes, proteins and fluoride toothpaste without these ingredients for a 14-weeks period, showed a shift in the ecology of the oral microbiome at species level after the use of the toothpaste with natural enzymes and proteins.

Accordingly, 12 taxa associated with gum health including *Neisseria* species had increased, whereas 10 taxa including *Treponema* species associated with periodontal disease had decreased [57]. These results have recently been supported by larger clinical studies, demonstrating that persons having used a fluoride toothpaste with enzymes and proteins for 3 months and at least one year, respectively, had better gingival state than persons having used a fluoride toothpaste without these enzymes and proteins [57].

Amilase

Alpha-amylase is one of the most abundant enzymes of human saliva, and it is also present in the salivary pellicle and dental plaque [58,59]. It is mainly secreted from the serous acinar cells in the parotid glands and to a lesser extent from the serous cells in the submandibular glands [60,61]. Salivary α-amylase breaks down ingested starch by cleavage of the α-1,4-glycosidic lin- kages of starch molecules into maltose, maltotriose and dextrins. Salivary α-amylase is active at a pH above 6, and it is inactivated in the acidic environment in the stomach [58,59]. Maltose can be fermented by oral bacteria, and hydrolysis of maltotriose leads to ad- ditional glucose for metabolism by bacteria in dental plaque. The resulting lactic acid production lowers the pH within the biofilm, which contributes to tooth demineralisation and development of carious le- sions [61]. Amylase also facilitates the dissolution of starch-containing food debris retained in the oral cavity after a snack or meal by forming more soluble compounds which can dissolve in the saliva. Salivary amylase not only facilitates bacterial fermentation of carbohydrates and adherence of bacteria to oral surfaces, it also binds specifically to certain oral bacterial species. Thus, amylase can complex with sIgA in the salivary pellicle to form a binding receptor for *S. sanguinis* [62]. In addition, *Streptococcus gordonii* and *Streptococcus mitis* encode specific amylase binding proteins (adhesins) [63]. Through these various mechanisms, salivary amylase plays an important role in modulating the adhesion, co-adhesion and colonisation of microorganisms, and in supporting the host-microbiome symbiosis. The function of salivary amylase may be compromised in conditions associated with salivary gland hypofunction, impaired oral clearance and saliva buffering, where low pH in the biofilm lead to a shift in the balance of the microbiota towards a more acid-tolerating and acid- producing and thus potentially cariogenic microbiota and dysbiosis [64].

(5) TASTE AND DIGESTION.

Saliva plays an important role in the digestive processes of taste, initial breakdown of foods, chewing, bolus formation and swallowing [65].

During mastication, or the act of chewing, food is broken down into smaller fragments and mixed with saliva. The food particles are thereby lubricated and softened and exposed to digestive enzymes, processes which are essential for the formation of a food bolus suitable for swallowing [66]. Mastication, which requires involvement of the teeth, the masticatory muscles, the temporomandibular joint and the tongue, facilitates the subsequent gastrointestinal absorption of food particles. Mastication is under the control of the central pattern generator located in the brain stem, which is regulated by the extensive sensory inputs evolving from the oral cavity during ingestion and chewing of food, in order to constantly adjust the act of chewing to the food properties (texture) and facilitate formation of a bolus ready for swallowing [68].

The optimal moment for swallowing appears to occur when the cohesive forces between the food particles in the bolus are strongest. The cohesiveness and adhesiveness are determined by the food particle size, the liquid in the food and the salivary secretion [68]. The most prominent salivary enzyme is α-amylase, which breaks down starches to soluble maltoses and dextrins by cleaving the α-(1- 4) glycosidic bonds [69]. This breakdown to simple hexoses occurs in two phases. The luminal phase starts in the oral cavity with the initial digestion of starch by salivary α-amylase, and the second phase occurs in the upper small intestine as pancreatic α-amylase reaches the chyme. Salivary α-amylase is considered to be of minor significance in polysaccharide digestion due to its rapid inactivation in gastric acid and its pH optimum at 6.8, but short-chain glucose polymers in the diet may stabilize the enzyme and allow maintenance of activity at acid pH during the first period in the stomach [70]. Furthermore, that salivary amylase plays a significant role in gastric digestion.

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ALL ON FOUR. PROSTHETIC CONSTRUCTION IN MANDIBULA

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Abstract. *In the clinical dental practice, often, we are faced with patients that have very few teeth, or they haven't got any at all – total tooth loss. The prosthetic is the future of these problems. With its many possibilities, it has a scientific basis to solve all these cases with mobile or fixed prosthodontics. In these cases we're doing reconstruction and rehabilitation of the mouth with prosthodontic appliance in order to make up for the lost teeth and to set up functional and aesthetic harmony of the patient's mouth. Nowadays, the prosthetic treatment of the total tooth loss combined with oral – surgical procedure called ALL ON FOUR is ideal, practical and safe reality to solve such a problem. Metal – ceramic fixed construction is placed over the 4 integrated implants. The crucial question is the biomechanical loading of the fixed construction, which asks extensive analysis and planning of the case. At the very beginning, based on the panoramix X-ray images and studio models, we are marking the most suitable static positions for the implants on our model. In advance, we have to keep in mind the action of horizontal and vertical strength. They act like flipping mastication strength and we have to calm and balance them. The augmentation of the ridge, correct designing and forming of the suprastructures, as well as the stable and polygonal orientation of the occlusion, are inevitable. Later, with oral – surgical treatment the implants are placed, together with ridge augmentation and its voluminous enlargement. After a 3-6 month period we're starting with producing of the future fixed metal ceramic construction that at the end is going to be screwed like suprastructure over the implants.*

1. INTRODUCTION

In the nature everything is perfect and in harmony, but in the reality it isn't that simple and ideal. We, the dental therapist, wish to get closer to her and that specific perfection is the challenge for progress in our profession. That way, more or less successful in our cases, we, like imitators of the perfect nature, are trying with our professional engagement and knowledge to solve different kind of dental problems. With our commitment to the work, every day and unstoppable we are moving the borders towards better, more beautiful and more natural.

In the clinical practice, often, we are facing patients with handicap, which from different reasons have very few teeth or they don't have it at all – total tooth loss. The dental prosthetic is really a magic and the future with lots of possibilities. It has scientific base for rehabilitation of these lost teeth. In these cases we are reconstructing the total loss with mobile or fixed prosthetic tool. The goal is to replace the lost teeth, so we can set a long term functional and aesthetic harmony in the patients mouth. The prosthetic treatment of the total teeth loss like multidisciplinary combination with oral surgery intervention is known in the world with popular short name ALL ON FOUR. This is not just a fantasy without proofs, but contrary, safe reality and ideal modern solution of this kind of problems. This technique is practical combination for quality rehabilitation for the disappointed patients.

Over the minimal number of 4 implants, comes fixed bridge construction with maximum of 12 teeth. This theme is a subject of discussion for the last few years, so here, we are going to describe the whole process form the beginning to the end from prosthetic aspect. This case is presented after a real distance of time with detailed description of all the work phases.

2. MATERIAL AND METHOD

The crucial question is the biomechanical loading of prosthetic construction, it needs thoroughly analysis and planning. According to the panoramix X-ray images and the studio models, we are looking for the best static positions for the future 4 implants. We have to take into account the influence of the horizontal and the vertical forces. They, like flipping and masticatory forces need to be calmed and balanced. For this, we need appropriate natural height of the intermaxillar space, basically we need interjaw space splited in equal halves. We have to have visual 3D image for the future teeth and which need ideal prosthetic plain. With selective grinding of the antagonists we get the wanted space for the regular position of the teeth. Planning the suprastructure at this point results in stabile and polygonal positioned occlusion with multi – point contacts. This quarantee long lasting of the structure. With these kind of contacts we would get the wanted balanced positioning of the masticatory and non – masticatory forces in wider zones./Pic.1 Starting position ,Pic.2 Studio model /

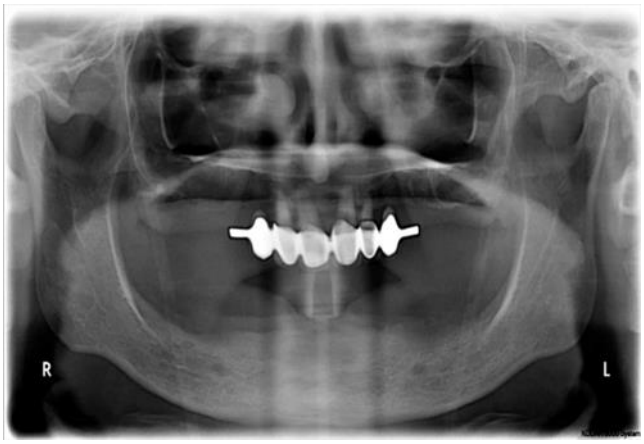

Figure 1. Starting position

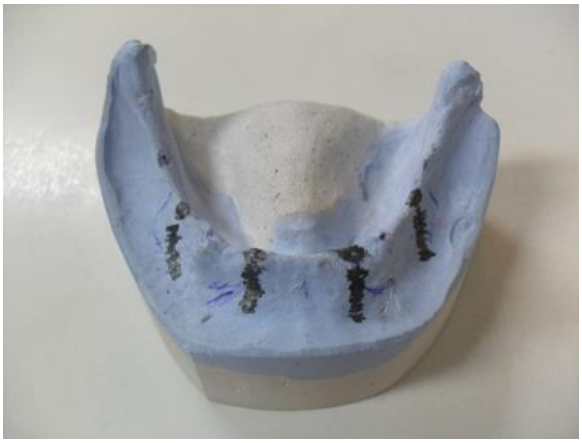

Figure 2. Studio model

After this extensive analysis, according to work protocol, we proceed with oral surgical intervention and implantation of 4 implants. During the intervention we have to be very careful, so the implants are placed in the middle of the bone cliff, if possible on positions 2-2; 5-5. With this kind of positioning we are avoiding the compromitation of foramen mentale, as well as canalis mandibularis. Basically, that is the reason why the posterior implants are inserted under angle of around 30 degrees. At the same time we are getting implant length in the bone /Pic.3 Post implantation status – 4 implants /.

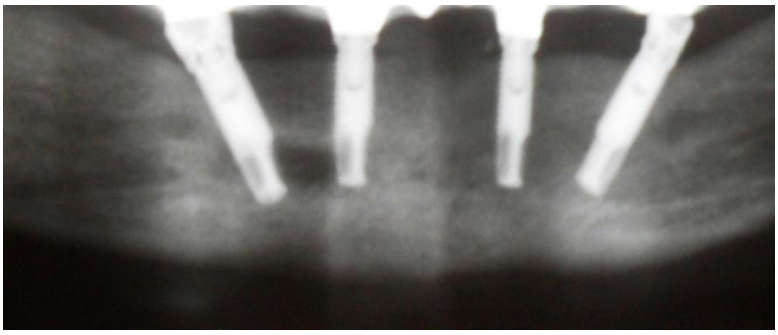

Figure 3. Post implantation status – 4 implants

We compensate the inclination of the distal implants with 30 Angled Multi – Unit abutments which are screwed over the implants right after their insertion.

The same day, when the implantation is finished, we are taking one-phase impression with syringe technique, with the principles of the open tray method, so we can start the preparation of the hybrid bridge. Immediately, before taking the impression, in the patient mouth we are placing respectively the chosen transfers. /Pic.4 Placing of the transfers/.

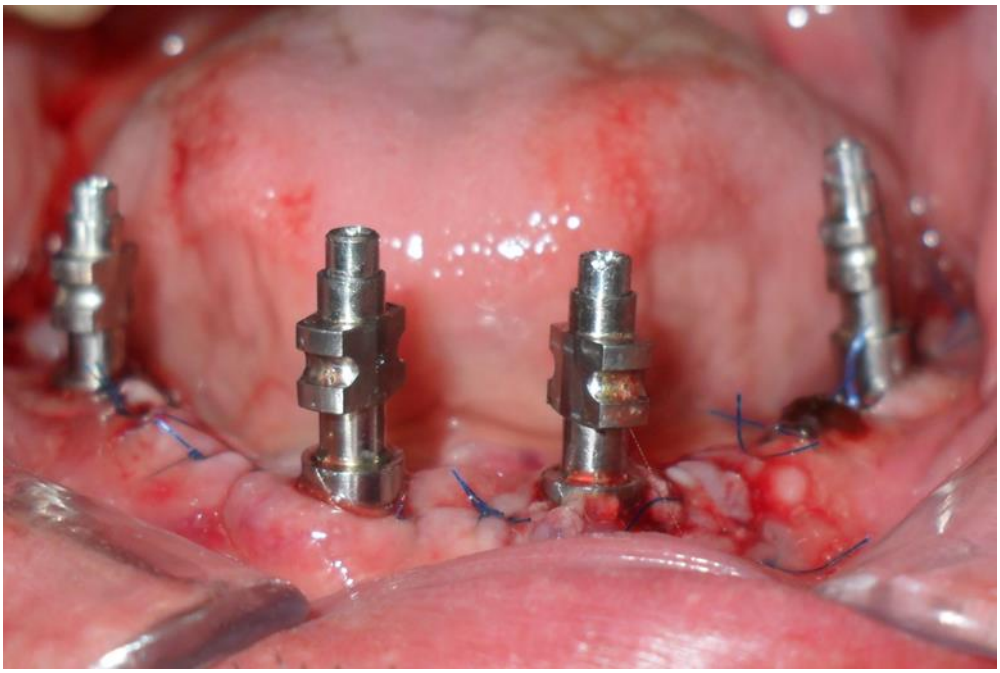

Figure 4. Placing of the transfers

When the impression is taken, very precisely, we are placing the appropriate analogues in the directions of the transfer caps. Carefully, we are controlling their mobility. /Pic.5 impression with analogues,Pic.6 impression with transfers/.

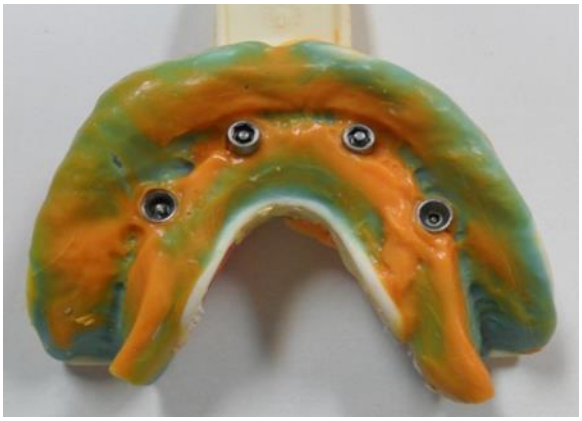

Figure 5. Impression with analogues

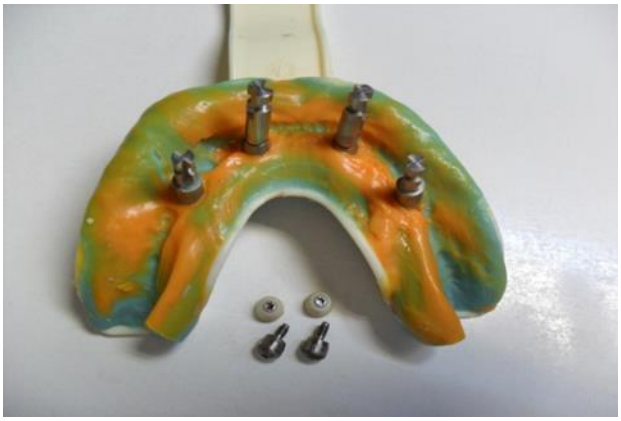

Figure 6. Impression with transfers

The next step is spilling the impression and preparing the working model. At the beginning the spilling is with silicone gingival masque between the analogues and the transfers and all around the cliff. The silicone has elastic abilities and it simulates the reziliation of the gum. The other parts of the impression are spilled with hard gypsum with zero expansion – zerostone. /Pic.7 gum mask, Pic 8 working model/.

Figure 7. Gum mask

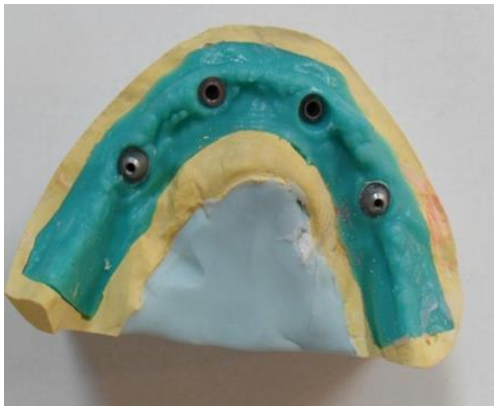

Figure 8. Working model

When the working model is finished, we are making test template made of acrylic base in which are placed temporary titanium abutments. They are finished factory product that is used in the phases for the hybrid bridge, so they are captured in the acrylic base. /Pic.9 test template/.

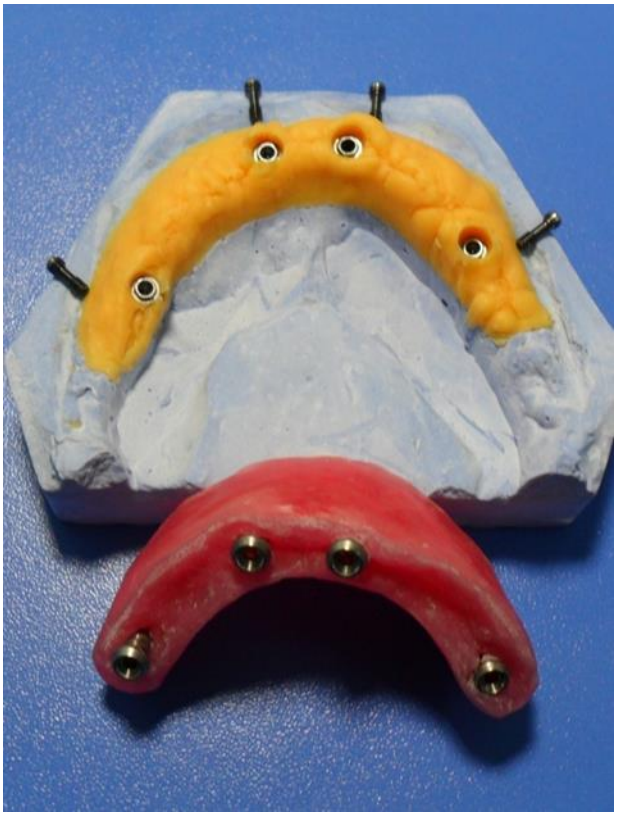

Figure 9. Test template

The next step is to build rose wax turret on the acrylic template. We use the turret to determinate the needed height of the interjaw space into equal halves. Because we need easy manipulation and perspicuity we release the holes for screwing./Pic.10 rose wax turrent/.

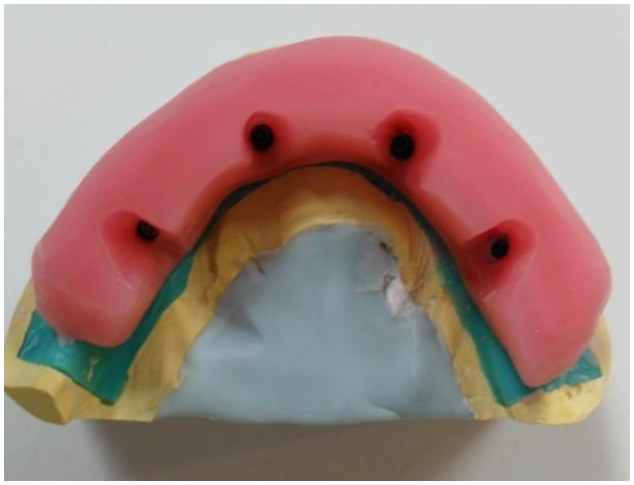

Figure 10. Rose wax turrent

When the test template is prepared, we fix it in the patience's mouth with hexagon screws that are shown above. The template is multi - functional, we use it like a test control for the impression preciseness. In some bad cases, if the impression is wrong, the template won't work, so in this early phase we have opportunity to fix it. If the correction is needed we should follow the next procedure: first, we remove the wax form the turret, then we separate the acryl from the base of the template. The separated fragments are fixed with screws in the patience's mouth and we connect them with thermoresin. When the template is fixed we are taking new precise impression.

We proceed to the next phase, to determine the needed height, but at that point we have to be sure that everything is fine whit the test template. For better stability, always, we are fixing it in the patient's mouth. After that, we are determinating the height. The intermaxillar rate is determined according to classical principles, minus 2-3mm from the physiological standby, with soften wax, in occlusion. /Pic.11 rose wax turrent/

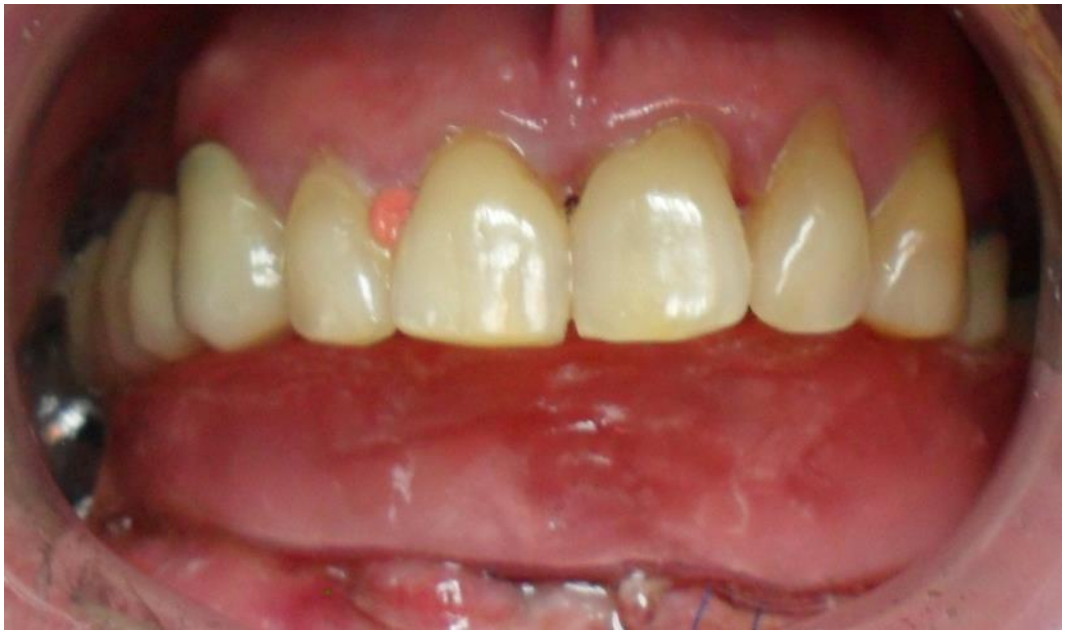

Figure 11. Rose wax turrent

We transfer the fixed height together with the models in half – individual articulator. The fixing of the models has to be with special gypsum for that purpose – artifiks that has not expansy. If the fixing is with ordinary white gypsum, depending on the producer, its expansy may increase the height up to 1mm. In the following phases that would be a problem because it increases the determinate height. When the fixing is finished, we start to position the teeth in the wax. For that purpose we use acrylic factory teeth, we are using the same type of teeth in the mobile prosthetic. The the positioning of the teeth is classical, also like in the mobile prosthetic. Of course, during this step we pay attention the teeth to be positioned according to the functional and the aesthetic needs, in the middle of the comb, without Spee - curve. Depanding on the conditions and when the implants have more lingual position on the comb, we use back stage placing of the teeth. They are placed frontally, but the screwing hole in behind them. After this laboratory phase, we try the teeth in the patience's mouth, with prior fixation. This step, asks fast corrections, so the wax does not melt from the mouth warmth. We recommend their cooling in the fridge and a glass of cold water between the work phases. There is a possibility for reocclusion with selective seizure of the antagonists and increasing the agonists from the wax. The procedure is repeating until we get ideal occlusion, visibility of the teeth while smiling and their natural playfulness. The tried and fixed teeth are moving back on the working model. It comes the making of the metal constructional splint and changing the wax for acrylic material. This step ends with polishing the hybrid bridge. Nowadays, this is a hit in our profession, but because the short amount of time to execute it, the team work and its efficiency are needed. Although the final construction becomes fixed, during all the work phases, the mobile and the

fixed prosthetic are mixed, which asks solid knowledge of both disciplines. Everything that is said above has to be done very precise and in a period of seven days to be fully finished. The hybrid bridge should not has reassigned juga alveolaria in the acryl of the mesostructure because every single facial pressure can affect the structure. This like extra side pressure can disfigure the immediate loading of the implants. Next, follows the trying of the finished hybrid bridge in the patients mouth with additional reocclusion, polishing to high shine and its fixation with hexagon screws. /Pic.12 The hybrid bridge /

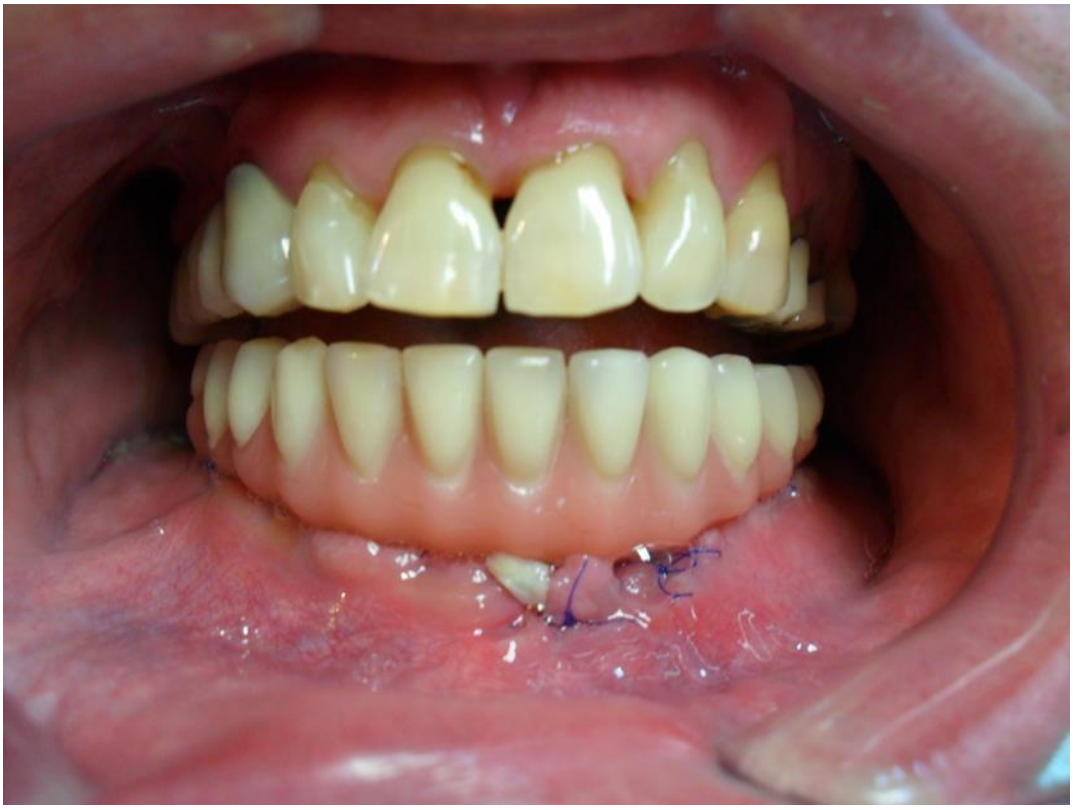

Figure 12. The hybrid bridge

For the immediate loading we use the defensive power of the organism, for its self – reparation with regenerative power towards the surgical zone. For maximum 7 days we have to load the implants with the hybrid bridge for the limited time of osteointegration in function of chewing. For the patients this is a practical transient solution because of the fact that they got teeth immediately. They are happy and the satisfaction sees in their eyes. They are full with spontaneous optimism and totally psychologically relieved. This way we can extend the transitory period without unnecessary forcing. The benefit of the immediate loading is in the fact that there is bigger contact between the bone and the implant (bone-to-implant) which is even for 64,2% bigger compared with delay loading implants.

The most optimal is the early or immediate loading of the implants to be done in a period from 48 to 72 hours. This frame can be extended to maximum 168 hours (7 days), but no longer than that. This recommendation is supported with in vivo and in vitro experiments (McCracken et al., 2001) that show that the biggest uptake of necessary minerals on metabolic level are in this specific time interval. After the seventh day, there is rapid decrease of the metabolic processes, so loading after that period will be disaster.

The stitches can be removed later, even after two to three weeks without removing the hybrid bridge, with inevitable irrigation and laser therapy.

After a period of at least 6 months, when the osteointegration is accomplished, comes new impressions for the final metal – ceramic construction. When the impression is taken, we put the sulcus formers with hexagon screws in the patients mouth. /Pic.13 sulcus formers /

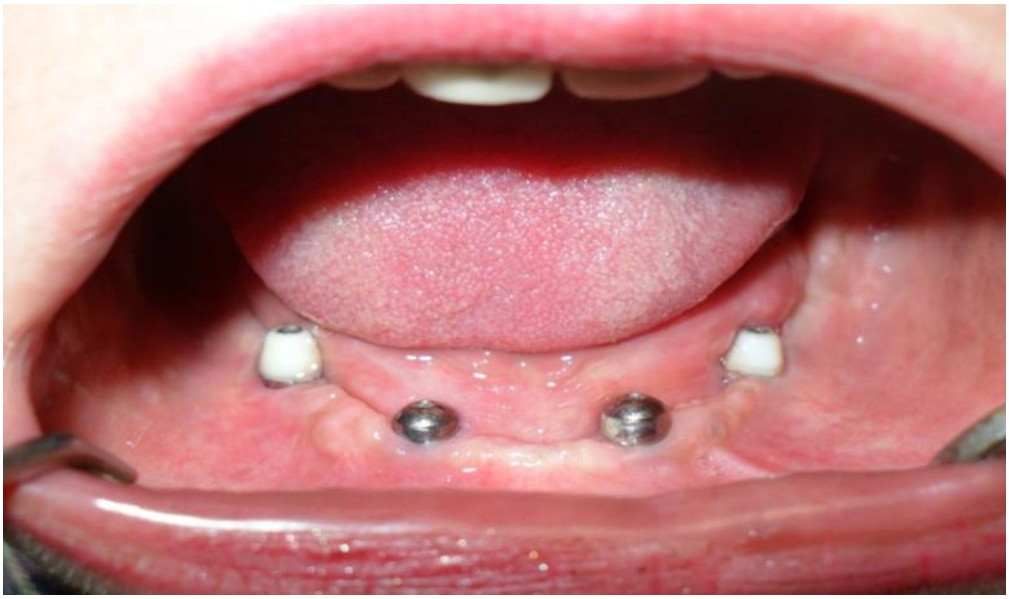

Figure 13. Sulcus formers

The following step is in the dental lab, where with help of the hybrid bridge on the working model, we are putting secure keys and we are forming forgus from optosil. These keys are guaranteeing the stability of the forgus for identical transfer of the condition and the inclination of the teeth for the future wax modelation of the fixed construction./Pic.14 forming forgus from optosil stability /

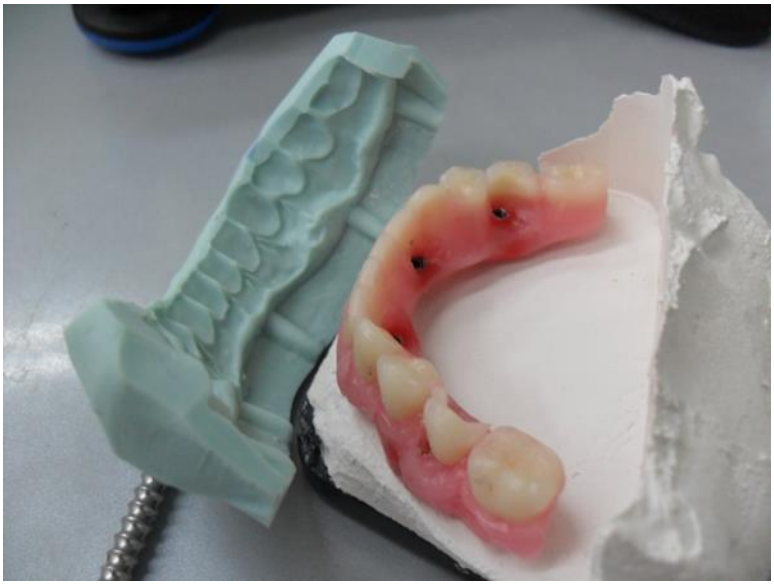

Figure 14. Forming forgus from optosil stability

First, on the working model we are screwing the factory manufactured CASTABLE UCLA ABUTMENTS. They are connecting and fixing between them with thermoresin, which presents nucleus of the construction in a shape of splint./Pic.15 thermresin splint and Pic.16 grey wax modelation /.

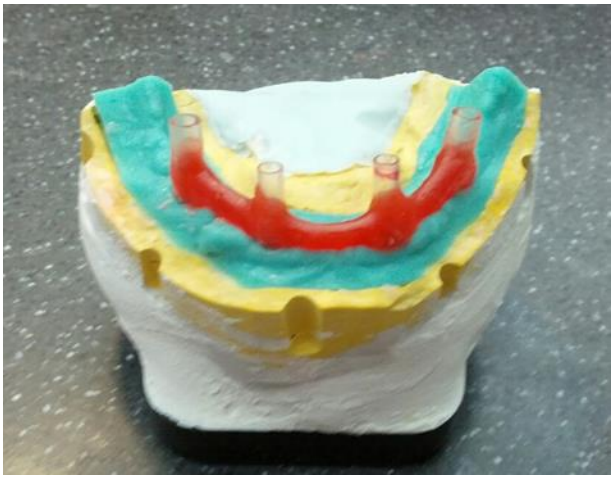

Figure 15. Thermresin splint

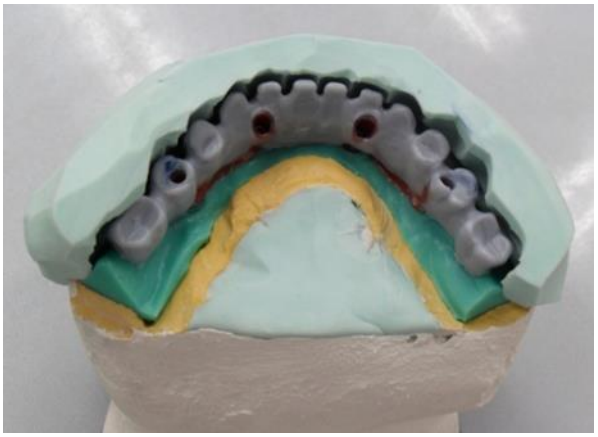

Figure 16. Grey wax modelation

When this is done, we proceed to wax modelation – CROW WAX. In half – individual articulator, we are checking the occlusion and we are modeling the final shape of the wax construction, so the thermoresin split stays in its nucleus./Pic.17 modeling contol in articulator /.

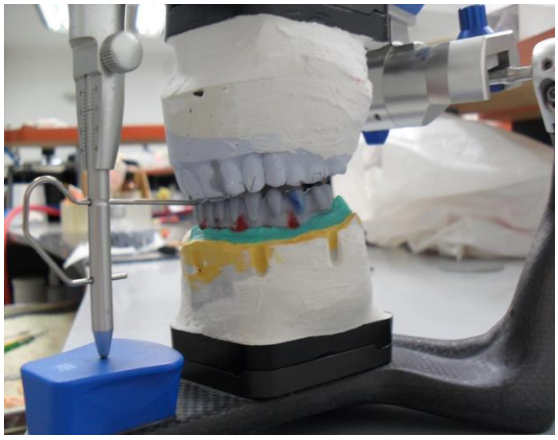

Figure 17. Modeling contol in articulator

When the wax modeling is over, we are pouring form appropriate compatible metal together with original abutments that stay stuck in it. Then comes the finishing of the metal and its sanding. /Pic.18 . metal construction/

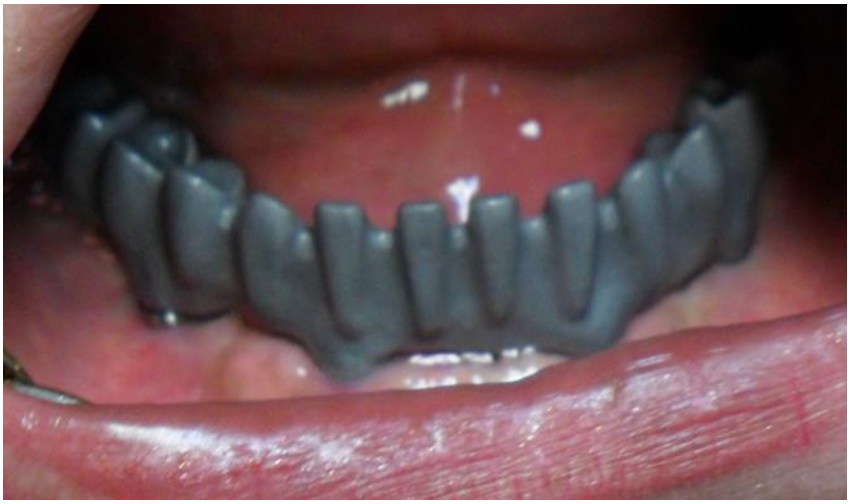

Figure 18. Metal construction

The prepared construction is used for the metal trying in the mouth. In the mouth, we check its stability, the laying on the gum and the prosthetic plain in parallel towards the ridges. The final check is the intermaxillar relation in horizontal and vertical dimension which ends with new impression in soften wax.

We are defining the color and the shades of the ceramic, as well as the color and the shades of the gum mask like mesostructure. It comes the shaping in ceramic in the dental laboratory and its baking in many layers. While modeling there should not be too many morphological characteristics over the occlusal surfaces – in other words soft modeling of the tubers. When we try the construction in the patients mouth, before the final glazing, we do the reocclusion. With the reocclusion we should give freedom over the sliding ridges of the occlusal tubers, known as FREEDOM IN CENTRIC. It is very important to relax the stress occlusal contacts between the agonists and antagonists, so we get multiple contacts with at least 3 to 4 contacts per tooth. This kind of polygonal occlusion softens the lateral strengths and provides stabile occlusion which is priority for stability and long – lasting of the suprastructure. /Pic 19 and 20 pre-glazing/

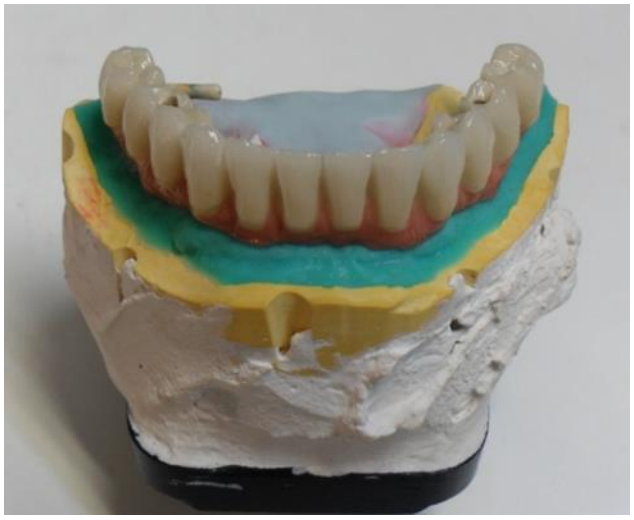

Figure 19. Pre-glazing

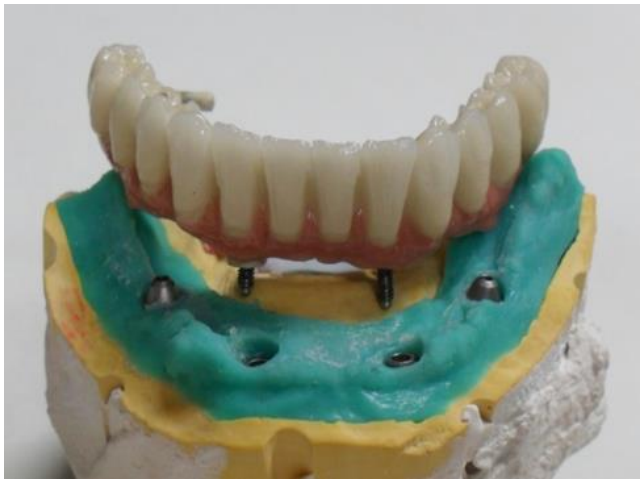

Figure 20. Pre-glazing

Following procedures are shading and final glazing of the ceramic in the dental laboratory /Pic.21 metal cermic bridge/.

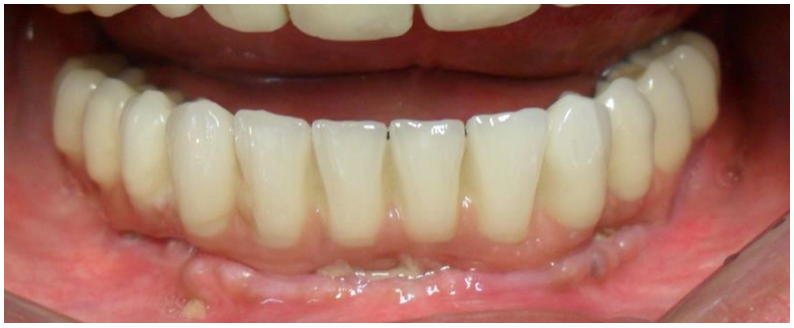

Figure 21. Metal cermic bridge

When the construction is glazed and polished, we put it in the patience mouth and we fix it with hexagon screws. The holes for manual manipulation are temporary closed with gutta-percha or cotton tampon covered with cavit. The screwing should be step by step, so in the end it finishes with strength by 20 N. For this purpose we use special tools (sirindge) according to the recommendation of the manufacturer.

After a certain period, comes the regular check of the tenseness of the screws. Afterwards it is followed by their closing, in the lower parts with gutta – percha or cavit and in the higher parts they are sealed with layer of nano composite. The composite color should be chosen according to the ceramic and the occlusal shape should be in the same style like the ceramic construction.

3. RESULTS

The case is worked in 2013, but after a distance of time, it is now presented. Because of the quality control, surely, we can confirm its stability and permanency to the bone and the surrounding tissues. There aren't any noticeable changes during the normal everyday activities of the patient. How it looks today, it can be seen on the last picture that is taken recently during the regular check.

We recommend the checks to be more frequent, when we use oral jet and profi jet for cleaning the construction. The regular check, also includes occlusion check, as well as polishing to high shine if there are pigmented deposits. At home, the patient should do regular wash with device under water pressure called water pik. We also recommend using mouth washes for refreshing the oral cavity that in their components have chlorxesidine /CHX/.

4. DISSCUSION

It is valuable to mention the real interest for the time of waiting for the osteointegration of the implants. This pause for the patients is very important factor because of their real psychological tense. Thay have been with teeth problems for so many years, so their patience and faith are finished. Another 6 months of waiting for osteointegration of the implants for them is too much time to be without teeth. Everyone of them want to get teeth sooner, so any kind of convincing for the patient is unacceptable.

The period for osteointegration can pass with two options: eighter classical total temporary prosthesis adapted to the newly mouth conditions after the implantation or hybrid bridge with immediate loading. Nowadays, the immediate loading is used more often like practical transient method. It is always followed by the final metal ceramic construction.

The permanent construction, depending on the patients financial possibilities, can be made of non – metal, full ceramic (ZIRCONIA). Basically, the phases remain the same until the moment of the shaping in wax. In this case, this step is made on previously scanned model and its modeling on computer on some of the world programs for designing such as Exocad or 3 D Shape. Then, with CAD – CAM machines from Zirconium Oxide block is cut the whole construction. /Pic.22/ Followed by modeling and baking the ceramic in multiple layers. When the construction is made of zirconia, it is recommended to use transfer caps and replicas for a single use – laboratory analogues. For better precision in the phases of scanning, it is very important to use scan abutments for each laboratory sample.

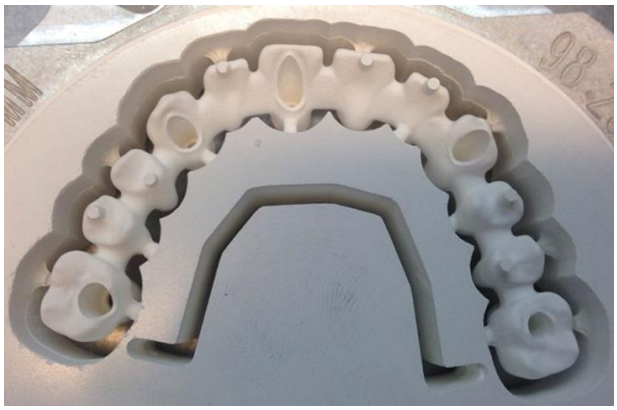

Figure 22. Zirconium Oxide block

No matter if the construction is made of metal ceramic or zirconia, the recommendation is for each implant to be used two pairs od identical screws, one for the phases in the dental laboratory and the other for the phases in the patient mouth. Over all this is for sterility during the work, but as well as for the possible damage of the hexagon in the dental laboratory.

5. CONCLUSION

The curtail characteristic for the shown techniques is that there is always possibility for screwing and unscrewing (remove) of the construction. That gives us space for any corrections in future, inside or out the patient mouth, in our dental office or in the dental laboratory. The constructions that are fixed with classical cement don't have that possibility, for corrections outside the patient mouth. In these cases, removing the bridge with separation is the worst case scenario, because we have to make new construction. Our experience gives us right to conclude that it is a great difference and huge advantage compared to the other techniques of fixing of the construction, so we share like benevolent recommendation.

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4. Dental Implant Restoration: Principles and Procedures http://www.quintpub.com/display_detail.php3?psku=B8842 - 38.5kb
5. Quintessence Dental Implant Logbook http://www.quintpub.com/display_detail.php3?psku=B6027 - 34.5kb [91.18%] Preview: Quintessence Dental Implant Logbook Quintessence Preview Close Window Title: NQuintessence Dental Implant Logbook http://www.quintpub.com/preview.php?psku=B6027 - 1.2kb
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COVID 19 AND PATHOGENESIS IN ORAL MANIFASTIONS REVIEW IN LITERATURE

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Abstract. *It is well known that coronavirus COVID-19 comprises a single plus strand of RNA (+ss RNA). SARS-CoV-2 is a β-CoV and mainly infects the respiratory, gastrointestinal and central nerves system of human and mammalians. It is transmitted trough respiratory droplets, aerosols, contact and vomits. Along with these symptoms, this virus can affect other organs including skin, olfactory system and oral cavity. The most common well recognized oral manifestations is dysgeusia leading to alteration of the taste, as a pathognomic symptoms. The reason for the loose of taste of COVID-19 are unknown and questionable. Some have speculated that the increasing number od ACE2 receptors on the tongue receptors keranocytes and association cell death and desquamation may block the taste perceptions. The same in the patients with SARS-CoV-2 (COVID-19) may be attack the mayor and minor salivary gland and the other oral mucosa with different lessons.*

1. INTRODUCTION

Coronaviruses (CoVs) are enveloped viruses with a positive sense RNA genome, that belong to the subfamily *Coronavirinae* within the family *Coronaviridae*, which is part of the *Nidovirales* order. They are classified in four genera (α, β, γ, and δ) and four lineages are recognized within the β-CoV genus (A, B, C and D). CoVs cause a variety of respiratory and enteric diseases in mammalian and avian species. Until recently, CoVs were considered to be pathogens with a largely veterinary relevance but with limited impact on human health [1]. Until recently when global pandemic burden has emerged by the human to human transmissions of a novel corona virus decease Covid-19. The most common symptoms are fever, and dry cough and in some cases shortness of breath dysosmia, and dysgeusia [2].

Current research shows that coronavirus invades human cells via the receptor angiotensin-converting enzyme 2 (ACE2) through scRNA-seq data analyses. The study identified the organs that are at risk and are vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [3]. Therefore, cells with ACE2 receptor distribution may become host cells for the virus and cause inflammatory response in related organs and tissues, such as the tongue mucosa and salivary glands [4,5,6,7,8]. SARS-CoV-2 interaction with ACE2 receptors may also impair taste bud sensitivity, which could induce dysfunctional gustatory responses [9]. Available evidence has not yet established an efficient and safe pharmacologic therapy against COVID-19, and the potential ones are related to several adverse reactions [10].

2. ACE2 AND ITS ANTI-INFLAMMATORY PROPERTIES

The human ACE2 protein is a zinc metallopeptidase, an ectoenzyme (family of dipeptidyl carboxydipeptidase), which contains 805 amino acids. This protein is a type I transmembrane glycoprotein and its expression is ubiq- uitous with a single extracellular catalytic domain that predominantly localizes at the plasma membrane [11, 12].

There are two functional forms of the ACE2 protein. The first form is the full-length ACE2 protein, which con- tains a structural transmembrane domain and spikes its extracellular domain to the plasma membrane. The sec- ond form is the soluble form, which lacks the membrane anchor and circulates in small amounts in the blood. ACE2 has also been shown to regulate cardiovascular functions in brain regions [13]. The soluble form rep- resents the circulating ACE2 blood vessels. ACE2 plays a major role in balancing the levels of Angiotensin II (AngII) and Angiotensin-(1–7) (Ang (1–7) [14].

Angiotensin-converting enzyme (ACE) 2 is a common binding site (“receptor”) for both SARS- CoV and SARS-CoV-2 [15]. The SARS-CoV-2 entry into host cells begins with its viral spike (S) protein binding to the host cell’s surface transmembrane ACE2, followed by a down regulation of membrane ACE2 expression [16]. The normal level of ACE2 is important to protect vital organs; However, as demonstrated in the models of acute lung injury (ALI) and ARDS [17, 18], the abnormal ACE2 levels were suggested to aggravate COVID-19 via the renin-angiotensin system (RAS), including promoting pathological changes in ALI [18] and being involved in inflammatory and fibrotic responses [19]. ACE2 exists in two forms, the full-length transmembrane ACE2 (ACE2) and the soluble ACE2 (sACE2). sACE2 is cleaved from ACE2 by ADAM17 (a disintegrin and metallopeptidase domain 17) and then released into the extracellular environment [20].

ACE2 is the predominant enzyme regulating the ACE2/Ang-(1-7)/Mas receptor (MasR) axis. The functi`on of sACE2 remains unclear. ACE is a close homolog of ACE2 with a 42% identical sequence in the catalytic domains, which function in an opposite manner to ACE for balancing [21]. ACE2 was identified as the binding "receptor" of SARS-CoV and SARS-CoV-2. ACE2 is expressed SARS-CoV-2, ACE2, and multiple organ failure predominantly in the epithelial cells of the lung and intestine, suggesting that these organs may be the primary infected sites of SARS-CoV-2. ACE2 is also present in arterial and venous endothelial cells [22]. These distributions of ACE2 are very likely associated with the characteristics of COVID-19: respiratory failure, colitis, microvascular injury, and inflammation. These data suggested that the intestine might also be an entry site for SARS-CoV-2, and the virus ability to be transmitted via the mouth/food intake is thus worth investigating.

ACE2 is widely expressed in many different cells of the body. In 2002, Harmer et al. [23] studied the expression of ACE2 and found that the mRNA is expressed in 72 different tissues obtained from three human donors. It was observed to be highly expressed in endocrine tis- sues, gastrointestinal tract (e.g. ileum, liver and gallbladder), cardiovascular tissues, kidney and urinary bladder, testes and muscle tissues. It was observed that central nervous system and lymphoid tissues express relatively low ACE2 levels. They found that that the receptor it is not expressed in red blood cells. In the lung, high mRNA ACE2 expression was detected in the parenchyma and in primary and tertiary bronchi. Relevant for the transmission and respiratory manifestations of SARS-CoV-2, ACE-2 positive cells were observed in oral, nasal, and nasopharynx epithelia, and in type I and type II alveolar epithelial cells (AT1 and AT2 cells).

3. ORAL MUSOCA MANIFESTATION

The first remarkable finding was that ACE2 was present in endothelial cells from small and large arteries and veins in all the tissues studied. Moreover, arterial smooth muscle cells were consistently positive for ACE2. Positive staining for ACE2 was also noted in myofibroblasts and the membrane of fat cells in various organs. Furthermore, ACE2 was found at specific sites in each organ as described below[23]. In nasal and oral mucosa and the nasopharynx, the ACE2 expression in the basal layer of the non-keratinizing squamous epithelium is found.

The most common well recognasized oral manifestations of COVID-19 is chemosensory dysfunction, leading to alterations of taste (dysgeusia) either with, or without, olfactory involvement (anosmia). There are now several reports and reviews in the literature on dysgeusia that could be characterized as a pathognomonic symptoms of COVID-19.[24]

Including meta analysis of 31 reports by Dos Santos et al.[25], they noted the global prevalence of taste disorders, 45% of COVID-19 patients, 24% with ageusia, 35% with hypogeusia, 38% dysgeusia. They also found that taste disorders are associated with COVID-19 positively, mild-to-moderate deceases in female sex. Some have evaluated the specific loose of different flavours, in COVID-19 - related dysgeusia, reported 77% with changes in their ability to taste spice, 80% softness, 79% of sourness and 91% for sweetness. However the veracity of these are questionable because they will obtained from a web based questionnaire survey [26]. The reason for the loss of taste in COVID-19 is unclear. Some have speculated that the increasing number of ACE-2 receptors on the tongue keratinocytes and the associated cell death and desquamation may block the taste buds and adversely affect taste perception [27,28]. Whether the dysgeusia is due to direct damage to the taste buds located in the filiform, fungiform and vallate papillae by the SARS-CoV-2 virus is unclear as yet. Dysgeusia is almost always temporary, and normal taste sensation returns by 4–6 weeks after recovery from the acute COVID-19 illness. Additionally, some reports indicate that women experience the condition more than men, although confirmatory evidence is required [29, 30]. Pathohistology for dysgeusia is some what speculative at present.

One contributory reason of dysgeusia or ageusia could be reduction in salivary flow or xserostomia associated with COVID-19. Considering that salivary tissue replayed with ACE2 reception witch are portals of cellular entry for SARS-COV-2 [31]. It is not surprising that salivary gland are profoundly affected by COVID-19, leading to a reduction of the salivary secretion. Other secondary cofactors for COVID-19 induce xserostomia are trough to be impaired nasal breathing due to nasal congestions and or rhinorrhea due to deceases with in term, may induce atheling of oral dryness and sense of xserostomia other apparent of real [32]. Pandemic induced physiological factors and chronic stress maybe contributed to the functionally of salivary glans and quantitative reductions of salivary secretions [33, 34].

Oral manifestations included ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and

spontaneous bleeding. The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, EM-like, mucositis, drug eruption, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome. One of the most common oral complications associated with COVID-19 confirmed or suspected individuals is erosion and ulcerative lesen of the oral cavity [34-42].

Tongue (dorsum and lateral boarder) is the most common reported site followed by hard palate and buccal mucosa. Irregular and painful ulcers either appear alone (single ulcers) or in the form of multiple tiny ulcers. Clusters of ulcers either resemble herpetiform ulcers or multiple apthoid ulcers with diffuse erythematous base. These multiple apthoid ulcer later on coalesce to form large ulcers with yellowish fibrin covering them, resembling erythema multiform-like disease.[43]. Candidal plaque-like lesions are also observed in association with Covid-19. Both red and white plaques were observed. They are located on the dorsum of the tongue and palate. They were also observed along with multiple tiny ulcers, taste changes, tongue and masticatory muscles pain [43]. Immune system suppression as a result of antibiotic therapy, deteriorating general health and neglected oral hygiene can be possible causes of these plaques.

Many times the blisters are observed in the soft palate and the cheek in the patients with COVID-19. Gingival changes such as general erythematous and edematous gingiva, gingivo-periodontal bleeding, necrotic interdental papillae and desquamative gingivitis are reported in literature. Symptoms such as halitosis, tongue and masticator muscle pain and swelling, geographical tongue, hyperplasia of papilla associated with taste changes and macroglosia are also reported along with fatigue and mayor symptoms of COVID-19 in case reports. There seem to be at least four possible pathways by which SARS- CoV-2 infection leads to dysgeusia,

as outlined below:

- As ACE-2 receptors for SARS-CoV-2 are common in the epithelium of taste buds, as well as in the human salivary glands, it is likely that these entities may be targeted in the pre-symptomatic phase of the infection, resulting in salivary gland dysfunction. The resultant impairment of the quality and the quantity of salivary flow may be reflected as dysgeusia (see below).
- A neurological pathway, where it has been hypothesized that, as dysgeusia and anosmia are closely linked, impairment of the olfactory system (with an abundance of ACE-2 receptors for SARS-CoV-2) may have an indirect impact on taste sensation, leading to dysgeusia.
- The infection could directly damage peripheral taste neurosensory chemoreceptors through the cranial nerves responsible for gustation and, in particular, the chorda tympani (CN VII) nerve. It has been posited that the virus could access the chorda tympani, first by travelling from the nasopharynx to the eustachian tube and then colonizing the middle ear from where it could access the chorda tympani, eventually causing dysgeusia.
- Lastly, another inflammatory response pathway has been proposed wherein the SARS-CoV-2 virus enters ACE-2-expressing epithelial cells of the taste buds, triggering an inflammatory response, leading to cellular changes that could alter taste.
  The interaction of SARS-CoV-2 with gustatory components and ACE2 receptors supports a direct effect in COVID-19-related taste disorders. First, the peripheral nervous system is affected by the new coronavirus, and as gustatory buds are innervated by cranial nerves, related functions may be impaired, resulting in taste disorders [44, 45]. Second, SARS-CoV-2 may bind essential salivary mucin components, such as sialic acid, consequently accelerating taste particle degradation and disturbing gustatory sensation [46]. Moreover, the tongue presents a high expression of ACE2 [22], and its interaction with SARS- CoV-2 may affect normal gustatory functions through dopamine and serotonin synthesis pathway coregulation [44, 45]. In addition, ACE inhibitors and ACE2 blockers are frequently associated with impairment of taste sensation [46, 47]. These drugs play a role in taste disorders by G protein–coupled and sodium channel inactivation. Similar to what patients with COVID-19 experience after infection recovery, the effect on gustatory sense by ACE inhibitors regresses a few weeks after discontinuation. Furthermore, ACE2 high expression was demonstrated in the taste buds of rats and was associated with angiotensin II production in mice taste buds. These findings might also suggest the inability of ACE2 to degrade this protein during COVID-19 infection, resulting in disorderly taste responses [48, 49].

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EVALUATION OF KNEE SPORT INJURIES WITH MAGNETIC RESONANCE IMAGES

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Abstract

Introduction: *The knee is one of the major weights bearing joint that provides not only mobility and stability during physical activity, but also balance while standing. Sport injuries are injuries caused by sports activities and may lead to severe pain and disability. Magnetic resonance imaging (MRI) is established as the leading modality for noninvasive evaluation of the sports knee injuries with its multi-planar capabilities and excellent soft-tissue contrast.*

The aim of the study: *To investigate the accuracy of MRI in assessment of sport related knee injuries.*

Materials and methods: *This is a prospective study which includes 50 patients with knee injuries during sport activities from period of May 2020 to September 2021.All patients came to department of traumatology at University clinic for Surgery " St. Naum Ohridski "– Skopje , and after physical examination were sent for MRI examination at the department of radiology at the same clinic. In all patients magnetic resonance images (MRI) was performed at 1.5 T MR in SAG T2 weighted images, SAG proton density(PD) weighted images, COR STIR weighted images, COR T1 weighted images, AX PD weighted images and additional weighted images if it is needed for evaluating the anterior cruciate ligament. The results from MRI were evaluated and also compared with the results from arthroscopy or surgery.*

Results: *50 patients with knee sport injuries were included in study, from them 35 male and 15 female from age of 16 to 35. Depending on the sport which cases the injury 20 patients get knee injury while preforming handball, 10 football, 7 patients during ski activities, 3 patients during running and jumping, and the rest 10 patients from bicycling and other different sport activities. Depending from the MRI results: in 33 patient lesion of anterior cruciate ligament (ACL) was detected on MRI, from which 7 patients were with complete lesion and 26 were with partial lesion. 3 patients have founding of bone edema and cartilage injuries. 2 patients have retinaculum lesions, 7 patients have meniscal lesion and 5 patients were with combined injuries of meniscal lesion and lesion of ACL. With comparison of the results from MRI finding with arthroscopy or surgery findings which were taken as a gold standard we get the accuracy of MRI in 66.7% of finding the meniscal complete lesion and 85.7% of meniscal incomplete lesion. The accuracy of MRI in detection the ACL lesion was 85.7 % in complete ACL lesion and 80.8% for detection the ACL partial lesion. 100 % for bone edema and cartilage lesion and also 100 % for retinaculum lesion.*

Conclusion: *MRI is noninvasive diagnostic tool with high accuracy and it is the primary approach in sport knee injuries. Thus MRI is superior to the diagnostic arthroscopy and we recommend MRI as the primary diagnostic tool for the evaluation of sports knee injuries. This study has shown total accuracy of MRI in finding the sport knee injuries at 87%, which makes it valuable noninvasive diagnostic tool for primary sport injuries.*

1. INTRODUCTION

The knee is one of the major weights bearing joint that provides not only mobility and stability during physical activity, but also balance while standing. Sport injuries are injuries caused by sports activities and may lead to severe pain and disability.[1]

Although plain radiographic films have traditionally been the first diagnostic imaging study performed in the evaluation of the painful knee, today they are useful only for evaluating joint space narrowing, alignment, and major trauma which results with bone fractures.[2]

Magnetic resonance imaging (MRI) is established as the leading modality for noninvasive evaluation of the sports knee injuries with its multi-planar capabilities and excellent soft-tissue contrast.[3]

Magnetic resonance imaging is a high accepted imaging modality in the initial diagnostic approach of patients with knee complaints. Also MRI has largely replaced diagnostic arthroscopy at this point. It is because is the top imaging and diagnostic tool for the knee joint as a result of its ability to evaluate a wide range of anatomy and pathology varying from ligamentous injuries to articular cartilage lesions.[4,5]

Imaging of the knee especially for evaluation of sport injuries requires excellent contrast, high resolution, ability to visualize very small structures, multiplanar projection all of which can be provided by MR imaging. The development of advanced diagnostic MR imaging tools for the joints is of increased clinical importance has been recently shown that musculoskeletal imaging is a rapidly growing field in MR imaging applications .[6]

Although arthroscopy is established as ‘‘the gold standard’’ for the diagnosis of traumatic intra-articular knee injuries, by its nature is an invasive procedure that requires hospitalization and anesthesia, thus presenting all the potential complications of a surgical procedure. [7]

Over the past 20 years, since its beginning in radiology in the 80s years of the last century magnetic resonance imaging have become first-line imaging study that should be performed in the evaluation of the painful knee. [8]

MRI has gained in popularity as a diagnostic tool for knee injuries. It is general opinion between surgeons that MRI is an accurate, non-invasive method to diagnose knee injuries, and gives adequate information to support decisions for conservative treatment and save the patient from unnecessary arthroscopy.[9]

2. MATERIALS AND METHODS

This is a prospective study which includes 50 patients with knee injuries during sport activities from period of May 2020 to September 2021.All patients came to department of traumatology at University clinic for Surgery “ St. Naum Ohridski “– Skopje , and after physical examination were sent for MRI examination at the department of radiology at the same clinic. In all patients magnetic resonance images (MRI) was performed at 1.5 T MR in SAG T2 weighted images , SAG proton density (PD) weighted images, COR STIR weighted images, COR T1 weighed images , AX PD weighed images and additional weighted images if it is needed for evaluating the anterior cruciate ligament. The results from MRI were evaluated and also compared with the results from arthroscopy or surgery.

3. RESULTS

50 patients with knee sport injuries were included in this study, from them 35 male (70%) and 15 female (30%) (Table 1)

Table 1. Distribution of patients by gender

Distribution of patients by gender			
Gender	Male	Female	Total
Number	35 (70%)	15 (30%)	50

The age of the patients range from 16 years to 35years , 5 patients were at the range to 20ty , 28 patients were at the age between 20ty and 30ty , and 17 patients were at the age between 30ty and 40ty.(Table 2)

Table 2. Distribution of patients by gender and age in decades

Distribution of patients by age						
Gender	AGE					TOTAL
	up 10	10-20	20-30	30-40	over 40	
Male	0	3	19	13	0	35

Female	0	2	9	4	0	15
Total		5	28	17		50

Depending on the sport which cases the injury 20 patients get knee injury while preforming handball, 10 football, 7 patients during ski activities, 3 patients during running and jumping, and the rest 10 patients from bicycling together with other different sport activities. (Table 3)

Table 3. Distribution of patients by gender and the sport that causes the trauma

Distribution of patients by gender and the sport trauma			
Trauma during sport	Male	Female	Total
Handball	14	6	20
Football	10	0	10
Skiing	4	3	7
Running	1	2	3
Bicycling and others sports	6	4	10
Total	35	15	50

Depending from the MRI results, MRI findings for distribution of the type of injuries of the knee: in 33 patient lesion of anterior cruciate ligament (ACL) was detected on MRI, from which 7(21.2%) patients were with complete lesion and 26(78.8%) were with partial lesion. 3 patients have finding of bone edema and cartilage injuries. 2 patients have retinaculum lesions. 7 patients have meniscal lesion, from them 3 patients (42.85%) have complete lesion and 4 patients (57.15%) have incomplete lesion.5 patients were with combined injuries of meniscal lesion and lesion of ACL. (Table 4 and 5)

Table 4. Distribution by the type of injuries of the knee elements

Distribution by the type of injuries of the knee elements			
	Complete lesion	Incomplete lesion	Total
ACL	7 (21,2%)	26 (78,8%)	33
Meniscal lesion	3 (42.85%)	4 (57.15%)	7
Retinaculum lesion			2
ACL + Meniscal l	1 (20%)	4 (80%)	5

Bone edema			3
Total	35	15	50

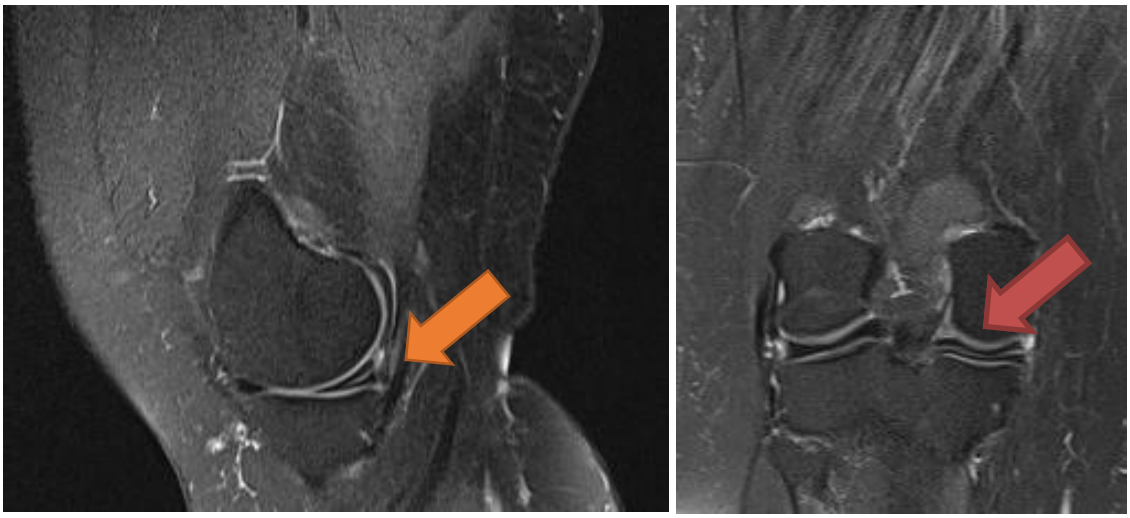

Figure 1. MRI of knee, SAG and COR proton density (PD) weighted images. Incomplete lesion of posterior horn of medial meniscus.

With comparison of the results from MRI finding with arthroscopy or surgery findings which were taken as a gold standard we get the accuracy of MRI in 66.7% of finding the meniscal complete lesion and 85.7% of meniscal incomplete lesion.

Table 5. Distribution by the degree of the lesion: Gr. 0 - intact, Gr. I - low-grade partial tear, Gr. II - high-grade partial tear, and Gr. III - complete tear.

Distribution by the degree of the lesion						
ACL	Incomplete lesion			Complete lesion		
	Gr. 0	Gr. I	Gr. II	Gr. III		
	0	9	17	7		
Meniscus	Medial			Lateral		
	Gr. I	Gr. II	Gr. III	Gr. I	Gr. II	Gr. III
	5	2		2	1	

The accuracy of MRI in detection the ACL lesion was 85.7 % in complete ACL lesion and 80.8% for detection the ACL partial lesion.100 % for bone edema and cartilage lesion and also 100 % for retinaculum lesion. (Table 6)

This study has shown total accuracy of MRI in finding the sport knee injuries at 87%.

Table 6. The accuracy of MRI findings in correlation with arthroscopy and surgery

The accuracy of MRI findings in correlation with arthroscopy and surgery				
Type of injuries	**Overestimated**	**Correct**	**Underestimated**	**Total**
ACL complete	1 (14,3%)	6 (85,7%)		7
ACL partial	1 (3,8%)	21 (80,8%)	4 (15,4%)	26
Meniscal complete	1 (33,3%)	2 (66,7%)		3
Meniscal partial		6 (85,7%)	1 (14,3%)	7
Bone edema		3 (100%)		3
Retinaculum		2 (100%)		2

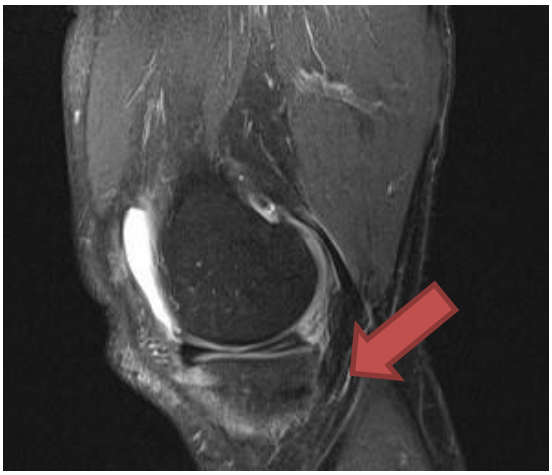

Figure 2. MRI of knee, SAG proton density (PD) weighted images. Complete lesion of posterior horn of medial meniscus.

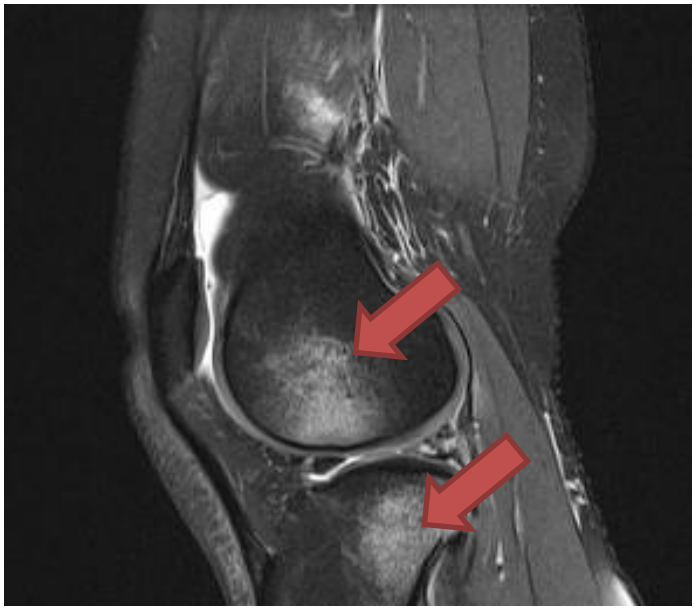

Figure 3. MRI of knee, SAG proton density (PD) weighted images. Bone edema on medial condyle of tibia and femur.

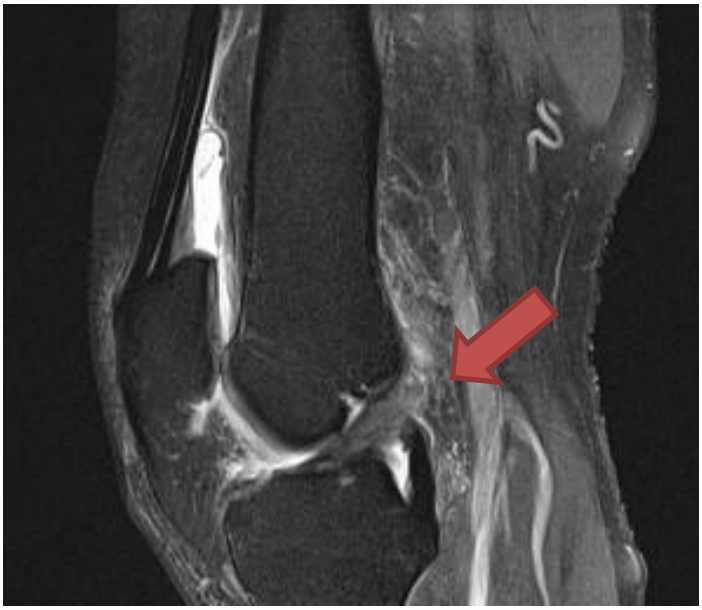

Figure 4. MRI of knee, SAG proton density (PD) weighted images. Partial lesion of ACL Gr. I.

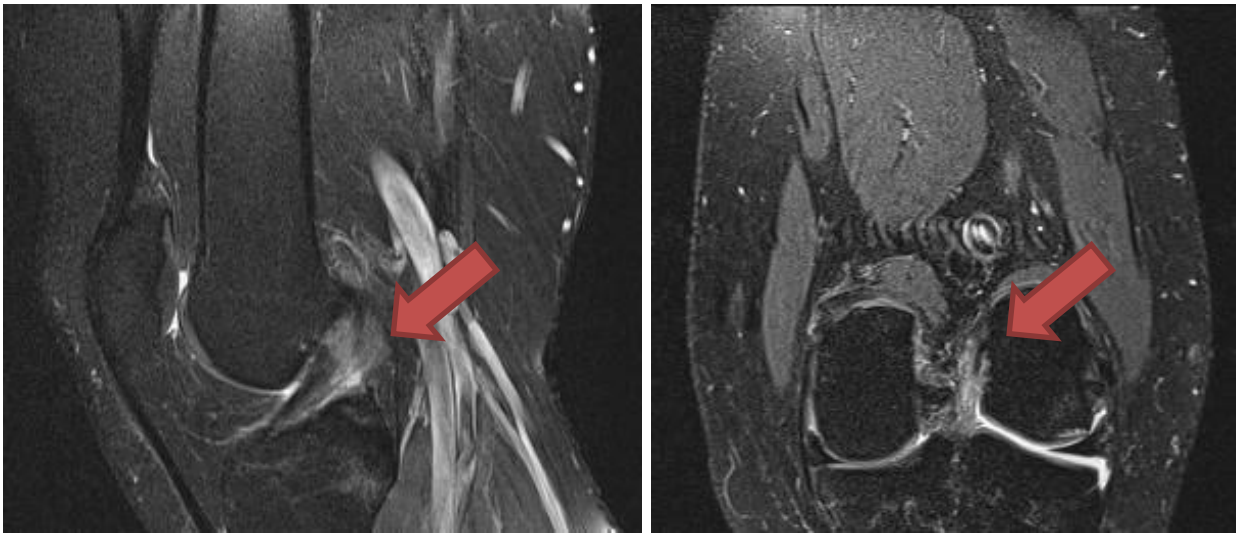

Figure 5. MRI of knee, SAG proton density (PD) weighted images. Partial lesion of ACL Gr. II.

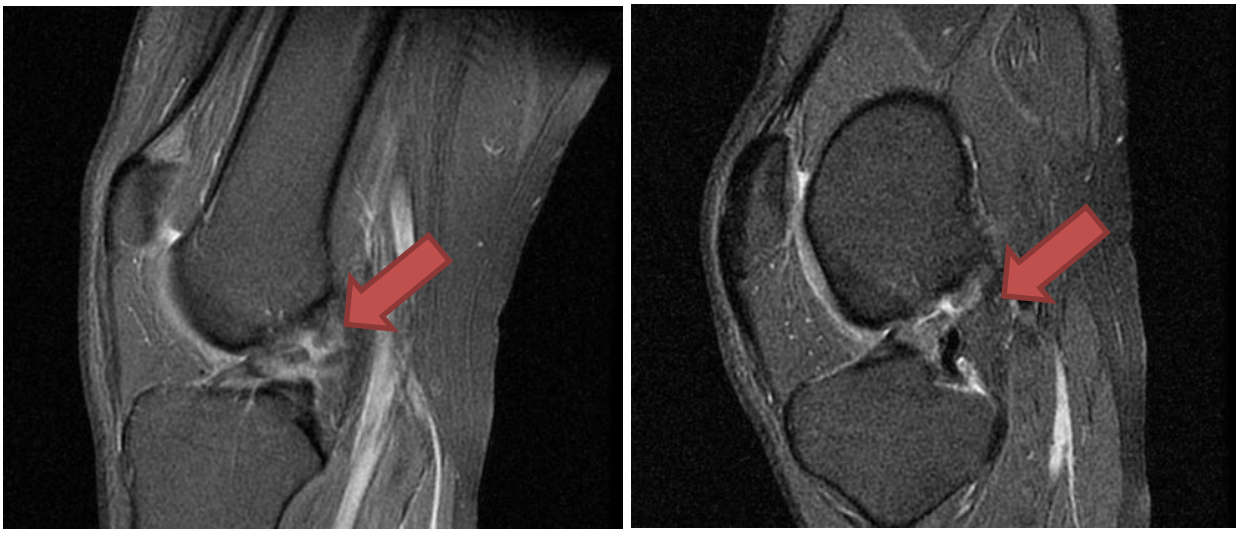

Figure 6. MRI of knee, in sagittal plane proton density sequence. Complete lesion of ACL Gr. III.

4. DISSCUSION

MRI of the knee is the basic tool in the detection of knee injuries especially in sport activity and younger patients. Injuries to menisci and cruciate ligaments can be diagnosed on MRI with a high degree of sensitivity and specificity, but it is shown that the accuracy of MRI decreases in patients with multiple injuries.[10]

Although arthroscopy is established as the Gold Standard in diagnosis of meniscal and ligament injuries, MRI remains a high sensitive, non-invasive diagnostic method, which can reduce the use of diagnostic arthroscopy.[11]

For the adequate evaluation of the internal knee elements, the knee must be scanned in the axial, coronal, and sagittal planes using thin sections (3-mm thick) with a combination of T1- and T2-weighted techniques as well as at least one 5-mm thick short tau inversion recovery (STIR) or T2-weighted image with fat suppression and proton density.[12]

The anterior and posterior horns of the medial and lateral menisci appear as wedge-shaped, low-intensity structures pointing toward each other on sagittal and coronal views. High signal within the meniscus, extending to the superior or inferior articular surface, constitutes a meniscal tear.[13]

Horizontal-oblique tears are considered the results of myxoid degeneration and are called "degenerative" tears. Those oriented in the vertical direction, which involve both the superior and inferior articular surfaces, are considered "traumatic" tears. Tears do not need to be seen in both the sagittal and coronal planes, as they are only visualized when they are perpendicular to the plane of the section. In fact, tears running oblique to both the coronal and sagittal planes may well be visualized only by a notch on the articular surface. This "notch sign" has served us very well over the last decade in diagnosing subtle meniscal tears.[14]

Occasionally, a large piece of meniscal fibrocartilage will become detached from its capsular attachment and flip back-to-front or centrally into the intercondylar notch. Clinically, these patients present with a locked knee. These "bucket-handle" or "flap" tears are recognized on the basis of two findings: An absence of the normal meniscus in its expected position and abnormal meniscal-intensity material in an unexpected location. [15]

Bucket-handle tears flipping from posterior to anterior appear as arrowheads pointing posteriorly in the position of the anterior horn of the meniscus, with nothing at all in the expected position of the posterior horn. This pattern is more common for bucket-handle tears of the lateral meniscus. Tears flipping from the periphery into the intracondylar region of the knee appear as an extra structure adjacent to the cruciate ligaments, with an absence of meniscal signal in the expected position of the posterior horn. Typically, this pattern is seen with bucket-handle tears of the medial meniscus. When the displaced meniscal fragment lies parallel to the posterior cruciate ligament (PCL), it may produce the "double PCL sign." [16]

The anterior cruciate ligament (ACL) may be seen on sagittal images; however, it is always seen as an upside-down "V" on coronal images. The ACL is lateral to the rounded dark posterior cruciate ligament (PCL).[17]

The ACL is most commonly injured by valgus stress to the knee while the leg is in external rotation, e.x a "clipping" injury in football or getting hit laterally coming down from a layup in basketball.[18]

In addition to the medial distraction resulting from valgus stress during an ACL injury, there is lateral impaction. This may lead to bone marrow contusions of both the femoral and tibial surfaces of the lateral compartment. [19]

Bone marrow contusions (also called "bone bruises" and "trabecular fractures") cannot be seen on plain films and can be a major source of pain. They should be suspected in the patient with an acutely injured knee without a meniscal or ligamentous injury in the absence of plain-film findings of fracture. Because their water content is higher than that of adjacent fatty bone marrow, these contusions are best detected on fat-suppressed T2-weighted images.[20]

In evaluating bone marrow contusions, it is important to determine if they extend to the articular surface, as this is usually an indication that the patient must rest for 30 days. Continued activity in this setting could convert a bone bruise with intact cartilage (type I) to one in which the cartilage becomes disrupted (type II), leading to early osteoarthritis.

Bone bruises can be seen whenever abnormal forces are applied to normal tissue or essentially normal forces are applied to weakened tissue, e.x, osteoporotic bones in middle-aged "weekend warriors."[21]

An interesting pattern of bone marrow contusion can be seen with traumatic dislocation of the patella. After the patella dislocates laterally when the knee is in hyperextension, the quadriceps contracts, jamming the medial patellar facet against the lateral femoral condyle, resulting in bone marrow edema on both surfaces. Usually, this is also associated with disruption of the black line of the medial retinaculum, which, acutely, may have associated bleeding or edema. Such injuries are seen in football and basketball players who come down on a hyperextended knee.[19,20]

Lesions of the PCL and the lateral collateral ligament are much less common than their anterior counterparts. The PCL is recognized as a dark C-shaped structure on sagittal images and is visualized as a dark, rounded structure seen en face on coronal images. The coronal images are best for visualizing partial PCL tears (which show increased signal in a normally black structure), while the sagittal view may better illustrate complete disruption.[20,21]

5. CONCLUSION

MRI is noninvasive diagnostic tool with high accuracy and it is the primary approach in sport knee injuries. Thus MRI is more adequate to the diagnostic arthroscopy and we recommend MRI as the primary diagnostic tool for the evaluation of sports knee injuries.

Over the past 20 years, MRI has become the leading imaging method for the evaluation of the painful knee following a sports injury. It can detect soft tissue abnormalities (meniscal and cruciate/collateral ligament tears) and fractures

that cannot be detected by plain film. These findings are critical for the therapeutic decisions to be made by the orthopedic surgeon and traumatologist.

This study has shown total accuracy of MRI in finding the sport knee injuries at 87%, which makes it valuable noninvasive diagnostic tool for primary sport injuries.

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HYPODONTIA OF LATERAL INCISORS PROSTHETIC THERAPY WITH IMPLANTS

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Abstract. In the diagnosis of the agenesis of the lateral incisors, it is essential a good clinical examination and a proper x-ray image, which will define not only the agenesis of the teeth, but it will rule out any other anomalies that can be associated with this condition. When we make plan for the treatment, whether we use opening or closing the space, we need to take in consideration the aesthetic, skeletal, dental, periodontal and functional factors. There are clinical cases in which the residual space is minimal and the patient is satisfied with the aesthetic look. In other cases, the patients are not completely satisfied with the aesthetics of their teeth, but due to the price and the time consuming therapy, they do not undergo the procedure. The resolution to this problem should be multidisciplinary. Any type of experimenting may lead to mistake and it will compromise the final look.

Keywords: hypodontia; x-ray; implant; aesthetics.

1. INTRODUCTION

Many etiological factors are related to agenesis of lateral incisors such as: physical barrier, rupture of the dental lamina, limited amount of space and functional anomalies. Besides the factors given, the etiopathogenesis of the hypodontia of the lateral incisors still remains idiopathic. There is evidence which states that the congenital absence of the incisors may be due to the environmental or hereditary factors, or both combined.[1]

Early diagnosis is essential due to the evaluation and treatment plan of the patient. There are direct and indirect significant clinical signs that will lead us to the right diagnosis. Seeking help from orthodontist is primarily from aesthetic reasons since there are no lateral incisors. Furthermore, another significant sign are the persistent deciduous lateral incisors in the dental arch combined with the late eruption of the permanent successors. This is the indirect clinical sign of the agenesis of the lateral incisors.[2] For definite diagnosis it is essential to do an x-ray, which will confirm the absence of the lateral incisors. Panoramic x- ray in these cases is the method of choice. It can be done in individuals that are younger than 8 years old and in individuals that do not have presence of lateral incisors in the dental arch. This is one of the early diagnostic methods in the agenesis.[3]

2. MATERIALS AND METHODS

There are clinical cases in which the residual space is minimal and the patient is satisfied with the aesthetic look. In these cases, we do not treat the patients radically. In other cases, the patients are not completely satisfied with the aesthetics of their teeth, but due to the price and the time consuming therapy, they do not undergo the procedure.

In this case, we had 25 year old male patient with hypodontia of the lateral incisors. The hypodontia was diagnosed with clinical examinations and with an x-ray image. The patient asked for orthodontic and prosthetic treatment to correct the hypodontia. The therapy plan was made, and we have decided to use the straight arch orthodontic therapy by Roth. The goal of this therapy was to achieve mesialization of the central incisors and distalization of the canines, which will result with bigger space to place the dental implants. The patient was aware that the therapy is very time-consuming and it might last a long time period. We have collaborated perfectly fine with this issue. After 18 months of continuous one month dental check up, we have decided that is time to do the next step. We have removed the fixed appliance. The patient was examined by dental prosthetist and oral surgeon, and finally we have decided to place the dental implants. Nine months after the procedure, with the patient's full collaboration, we have placed the crowns. Short time after the procedure, the patient was very satisfied with the result and he wanted to finish his look with crowns on the central incisors. The patient was very pleased with his final aesthetic look.

3. RESULTS AND METHODS

Whether the agenesis of the lateral incisors aesthetically doesn't satisfy the orthodontist, there are two possibilities – opening or closing the space. It is not easy to make a decision on which of these treatments the patient will undergo. It will rely on the maxillary disharmony with crowded teeth in the front, class I with crowded teeth, with indicated extractions in the mandible, also mesializated canines that can easily be remodeled into lateral incisors and malocclusions that do not seek for extractions in the mandible. In most cases, the presence or absence of malocclusion indicates to open or close the space. Some factors such as the proportion of the molars, the degree of protrusion of the incisors, the skeletal ratio of the alveolar ridge, the configuration of the dental arch, the inclination of the teeth, the form of the teeth, the incisal contact, the contour of the marginal gum, the form of the lips and the aesthetical result should be taken in consideration when the plan of the therapy is being made.

3.1 Closing the Space

This procedure represents the definite orthodontic treatment with mesialization of the canines, replacing them with lateral incisors and in the same time closing the gap between the central incisors. For many authors, this treatment is the method of choice in which adequate aesthetics is being achieved. When we decide to close the gap, it is essential that the canines are remodeled to look and have the function of the lateral incisors. The benefits of this treatment are that no dentures are needed, the limited orthodontic treatment, and the price is lower due to the cost of the prosthetic treatment. On the other hand, there are some consequences and the main flaws are the loss of the function of the canines and the loss of the class I in the same region.

3.2 Opening the Space

Placing an intraosseous implant and finishing it with a crown is a method of choice in case of orthodontic space opening or preserving the one in adults. The diagnosis and the treatment in children that have no presence of lateral incisors is a problem since the placement of the implant is impossible due to the facial growth and development. Female patients mature faster, so their adolescent development finishes quicker [4]. The space needed for placing the implant is defined by the occlusion. It should be from 5 – 7 mm for ideal placement of the lateral incisor. Some authors state that the minimal interdental space should be 6 mm in mesio - distal width and 5 mm in labio – lingual spread [5]. Anyhow, there are biological restrictions in which the bone between the implant and the bordering tooth should be 1.5 mm. Whether this minimal space is not preserved, the attachment of the soft tissue to the tooth will be compromised and will lead to reduction or loss of the interdental papilla, which will have repercussion in the final aesthetic look. In most cases of lateral incisors hypodontia there is not enough amount of bone mass. It might lead to high risk of recession of the soft tissue around the implant and the prosthetic restoration. Therefore in these cases augmentation of the dental ridge is essential [6].

4. CONCLUSION

In the diagnosis of the agenesis of the lateral incisors, it is essential good clinical examination and proper x-ray image, which will define not only the agenesis of the teeth, but it will rule out any other anomalies that can be associated with this condition. When we make the plan for treatment, whether we use opening or closing the space, we need to take in consideration the aesthetic, skeletal, dental, periodontal and functional factors. The therapy decision depends on the experience of the doctor specialist in orthodontics, and of course on the collaboration with the dental implantology and the dental prosthetics specialists. The resolution to this problem should be multidisciplinary. Any type of experimenting may lead to mistake and it will compromise the final look.

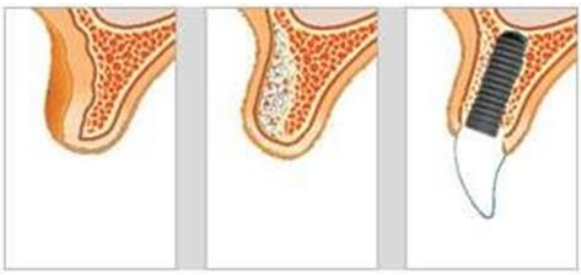

Figure 1. Augmentation of the dental ridge

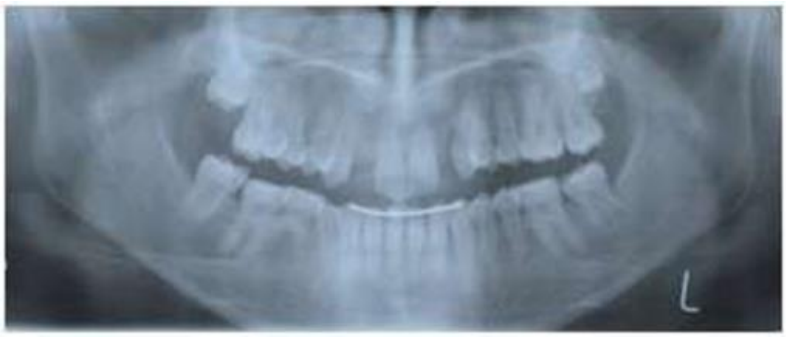

Figure 2. An x-ray image as proof of the existing malocclusion. It is clear that the hypodontia in lateral incisor is present

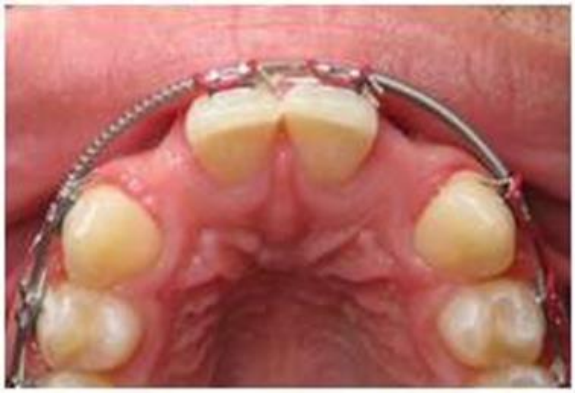

Figure 3. The patient during the orthodontic treatment. It is clear that the hypodontia in the lateral incisors is present

Figure 4. Picture of the patient's teeth after placing the crowns on the later and the central incisors

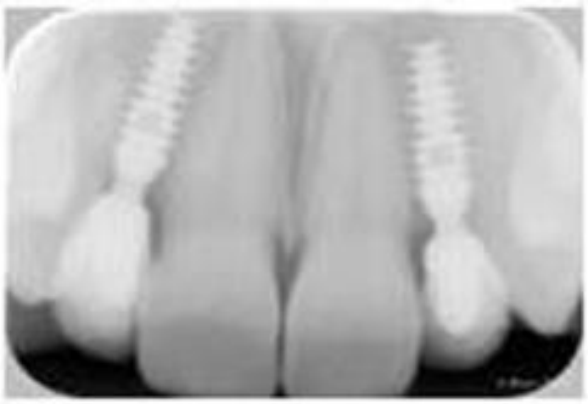

Figure 5. An x-ray image after placing the implants

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PHYSIOLOGICAL AND PATHOLOGICAL DARK PIGMENTATION IN ORAL MUCOSA

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Abstract. *The presence of melanocytes in the oral epithelium is a well established fact but their physiological functions are not well defined. milline provides protection from environmental stressors such as ultra violet radiation and reactive oxygen and melanocyte function as a stress sensors having capacity to react and to produce variety of micro-inveremental cytokines, and growth factors modulating immune inflammatory and antibacterial responses. There is wide range of normal and pathological variations in melanin pigmentations of the oral mucosa. Oral pigmentation can be physiological or pathological and endogenous and exogenous. Such lesions represent a variety of clinical entities, ranging from physiologic changes to manifestation of systemic illnesses and malignant neoplasms.The color of oral mucose depend upon the epithelial thickness, the keratin status, the vascularity and the density of the underlying fibrous tissue. Dark or black pigmented lesions can be focal, multifocal or diffuse macules. The pigmented lesions including entiteties such as physiological pigmentation, smokers melanosis, melanotic macule, drugs pigmentation, Peutz-Jeghers syndrome, Kaposi`s sarcoma, pigmentation related to heavy-metal ingestion (lead, mercury, bismuth amalgam), endocrinopathic pigmentation, and melanoma malignum.*

1. INTRODUCTION

Oral mucose is not uniformly colored. the color varies in different physiological or pathological conditions[1,2,3,4,5,6]. physiological pigmentation is frequent in asians, africans and mediterranean people[3].

These lesions represent a width variety of clinical entities, ranging from physiological changes to manifestation of systemic illnesses and malignant neoplasm. It can be important symptoms, sometimes the first symptom or accompanied symptom in some diseases. Therefore oral pigmentation needs to be assessed carefully by a medical professional.

Pigmentation of oral mucose membrane may be endogenous or exogenous in origin. Endogenous pigments included melanin, hemoglobin, hemosiderin and carotene. Melanin is produced by melanocytes in the basal lear of the epithelium and its transferred to adjacent keratinocytes via membrane-bound organelles called melanosomes. Melanin is also synthesized by nevus cells, which are derived from the neutral crest and are found in the skin and mucosa [7] Pigmented lesions caused by increased melanin deposition may be brown, blu, grey or black, depending of amount and location of melanin in the tissues [8]. Exogenous pigmentation (heavy metals, drugs, foreign bodies), may also promote pigmented lesions, which can vary in intensity and extension and can occur in any sites in the oral cavity.

2. PHYSIOLOGICAL PIGMENTATION

Physiologic pigmentation is common in darker skinned individuals, African, Asian and Mediterranean population, is due to greater melanocyte activity rather than a greater number of melanocytes [3]. The color of physiological pigmentation can range from light brown to almost black. Microscopical examinations of physiological pigmented oral mucosa show increased melanin in the basal cell types and sometimes in the upper portion in lamina propria with him melanophages or simply as extracellular melanin particles [9]. This microscopical features are very similar to those found in melanotic maculae and smokers melanosis [3]. Physiological oral pigmentation and pathological oral pigmentation that may be similar in appearance should be differentiator. deceases that may be confuced with physiological oral pigmentation include Adison decease neurophybromatosis oral melanotic maculae ray mucosal mellanoma, drug-induced oral mucosa pigmentation, and too as much lesser extended Kaposi sarcoma, vascular malformation and angioma of the oral mucosa [10]. The pigmentation is symmetrically distributed, especially on the gingival [Fig. 1] and buccal mucosa, on the hard palate, lips and tongue may also be seen as brown patches with well-defined borders.

Physiological melanin pigmentation of the oral mucosa affects males and females equally, as asymptomatic, solitary or multiple brown maculae with well-defined borders [Fig. 1] [11]. It may involve any part of the oral mucosa but most frequently the gingiva [3, 11, 13]. Oral pigmentation gradually appears during the first two decades od life.[11] but affected subject maybe unaware of it. [11,13]. The extend and intensity of oral pigmentation increase with age [13,14] concurrently with increase of the number of melanocytes, perhaps because of the effects of potential melanogenic stimuli such recurrent minor functional injury inflammatory conditions medication, or tobacco smoke cumulative [15]. Physiological pigmentation increases with age and color intensity, and can be influenced by smoking, hormones and systemic medication [16]. The attached gingiva is the most common location, but physiological pigmentation can be noted anywhere in the oral cavity (buccal mucosa, hard palate, lips and tongue). This pigmentation is asymptomatic and no treatment is required [17]. Pathological oral melanin pigmentation are divided in two group benign, malign and hereditary. Most common benign oral mucosa pigmentation.

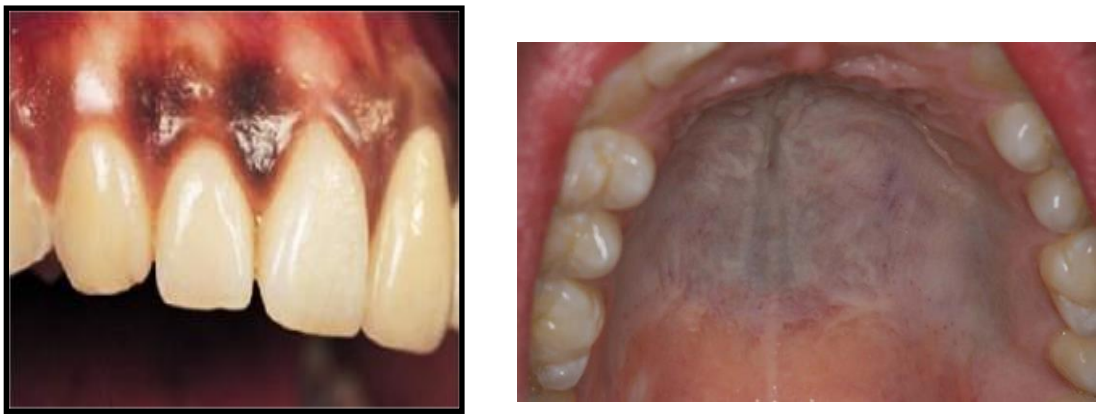

Figure 1. Physiologic pigmentations in gingiva

3. DRUG INDUCED PIGMENTATION

A variety of drugs can induce oral mucosa pigmentation [13, 14]. This pigmentation can be localized, usually to the hard palate, or they can be multifocal throughout the mouth. The pathogenesis of drug-induced pigmentation varies, depending on the causative drug. It can involve accumulation of melanin, deposit of the drug or one of its metabolites, synthesis of pigments under the influence of the drug deposition on iron after damage to the dermal on mucosal vessels. Chloroquine and other quinine derivates are used in the treatment of malaria, cardiac arrhythmia and a variety of immunoglobulin's diseases including systemic and discoid lupus erythematosus and rheumatoid arthritis. Mucosal discoloration associated with this group of drugs is described as blue-grey or blue-black, and in most case only the hard palate is involved [25,26]. [Fig.2] female patient with typical discoloration of the teeth after prolong use of tetracycline.

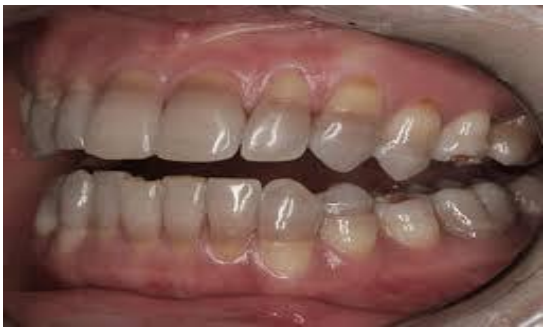

Figure 2. Tetracycline discoloration of teeth

In predisposed patients, drugs may cause inflammatory reaction and subsequently induce post inflammatory hyper-pigmentation, a non-specific reaction that is the basis of pigmentary change seen in fixed drug reaction [27]. Drugs such as arsenic can directly induced pigmentation by combining with sulfhydryl groups in the epithelial cells causing promotion of the action of tyrosine. Other such as the phenothiazines and minocycline may be deposited in mucosa and directly react with melanin to from a drug-pigment complex. Cortimozole was the most common drug associated to oral pigmentation followed by tetracycline: however, many others have been implicated, including colchicines, ketoconazole, pyrimethamine and barbiturates [28]. Fixed drug eruptions are more commonly seen in people with dark skin and often present as a slate brown color due to pigmentary incontinence of melanophages in the upper dermis. Pigmented macules of the tongue have also been described, occurring as a result of a fixed drug eruption [29].

4. MELATONIC MACULE

The oral melanotic macule is a small, well-circumscribed, brown-to-black that occurs commonly on the lips and gingiva, followed by palate and buccal mucosa [18,19]. Melanotic maccules are usually smaller than 1 cm in diameter and show a well demarcated smooth border [Fig.3].

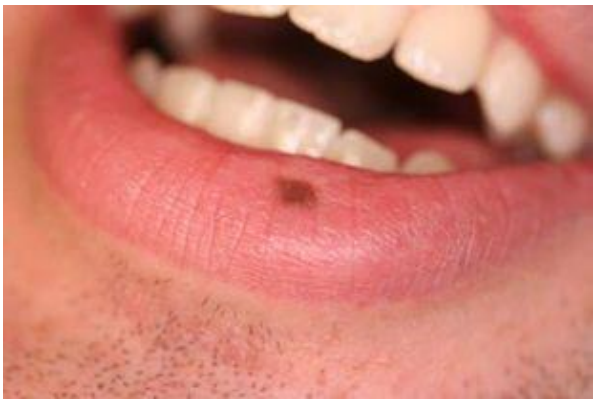

Figure 3. Melanotic macule

They usually occur as single lesions, but multiple lesions are sometimes seen [10]. The color may be light or dark-brown and is homogenous within each lesion. Melanotic macules are more common in women and yang adults. These are benign pigmented lesions and are not know to transform into melanoma [20]. Biopsy may be indicated to rule out melanoma and no treatment in otherwise indicated.

5. HEAVY METAL PIGMENTATION

Increase in heavy metal (e.g. lead, bismuth, mercury, arsenic and gold) levels in the blood leads to oral mucosal discoloration. It is mostly seen in individuals exposed to heavy metal occupational, or patients taking drugs containing heavy metals such as arsenic, mercury or silver.[7]. The pigmentation appears as a blue-black line along the gingival margin and seems to be proportional to the amount of gingival inflammation as stated by Esen et al. [8,30]. Other oral mucosal sites may also be involved [Fig. 4].

A variety of systemic signs and symptoms may be seen depending on the type of heavy metal exposure [8]. Malignant transformation of oral pig- mentation due to heavy metal pigmentation has not been reported. Yet care should be taken regarding severe systemic toxicity.

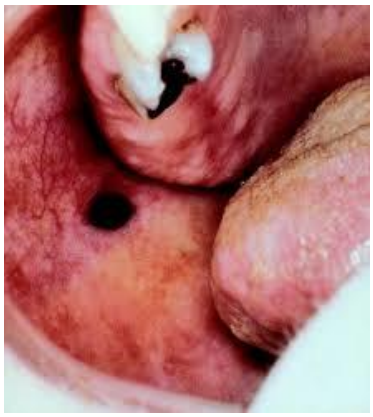

Figure 4. Heavy metal pigmentation

6. SMOKERS'S MELANOSIS

Smoking may cause oral pigmentation in light-skinned individuals. Smoker's melanosis occurs in 25-31% of tobacco users. There is increased production of melanin which may provide a biologic defense against the noxious agents present in tobacco smoke [21]. Lesions are brown-black and most often on the anterior labial gingiva, followed by the buccal mucosa. There are irregular, some are even geographic or map like on configuration. The intensity of the pigmentation is the related to the duration and amount of smoking [21, 22]. Women are more commonly affected than man, which suggest a possible synergistic effect between the female sex hormones and smoking [21]. Biopsy should be performed if there is surface elevation or increased pigment intensity or if the pigmentation is in an unexpected site [23].

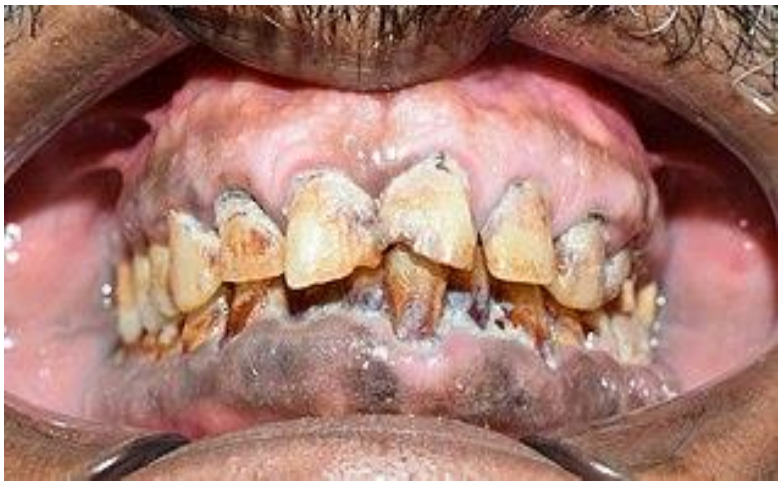

Figure 5. Smoker`s melanosis

7. AMALGAM TATTOO AND OTHER FOREIGN-BODY PIGMENTATION

Many metals have been implicated in the production of pigmentation in oral mucose. Lead, mercury and bismuth have all been shown to be deposited in oral tissue if ingested in sufficient quantities or over a long course of time [31, 32]. These ingested pigments tend to extravagate from vessels in foci of increased capillary permeability such as inflamed tissue. Thus in the oral cavity, the pigmentation is usually found along the free marginal gingiva, where it dramatically outlines the gingival cuff, resembling eyeliner. The metallic line has a gray to black appearance.

Graphite may be introduced into the oral mucosa through accidental injury with graphite pencil. The lesion occurs most frequently in the anterior palate of yang children, appearing as an irregular grey to black macule [23].

An amalgam tattoo is a localized, blue-gray lesion of variable dimensions most commonly cited on the gingiva or alveolar mucose, or less commonly of the floor of mouth or buccal mucosa. Amalgam tattoo is one of the most common causes of intraoral pigmentation. The lesion does not disappear with pressure, and there are no signs of inflammation at the periphery of the lesion. If the deposits of amalgam in the tissues are large enough, they may be show up radiographically as radiopaque debris in the soft tissues or superimposed on hard tissue.

a history of injures confirms the diagnosis otherwise a biopsy should be performed to exclude the possibility of melanoma. as amalgam filings still are ubiquitous and amalgam tattoos remain one of the most common causes of intramural pigmentation, we consider amalgam tattoos to be an important differential diagnosis consideration, when assessing patients suspect for mucosal melanoma of oral cavity. information regarding previous prosthetic dental work should be included in the patient medical history and x ray showing metal deposits in the mucosa

As amalgam fillings still are ubiqui- tous and amalgam tattoos remain one of the most common causes of intraoral pigmentation, we consider amalgam tattoos to be an important differential diagnosis considera- tion, when assessing patients suspected for mucosal mela- noma of the oral cavity. Information regarding previous prosthetic dental work should be included in the patient's medical history, and an X-ray showing metal deposits in the mucosa can safely rule out mucosal melanoma. But when in doubt, we recommend a diagnostic biopsy for histopathological examination [10]. This lesion is just a localized reaction to metal deposition in the mucosa.

8. ENDOCRINOPATHIC PIGMENTATION

Patchy melanosis on the oral mucose and bronzing of the skin are signs of Adison`s diseases and Cusing`s syndrome. In both of these endocrine disorders, the cause of hyperpigmentation is over secreting of ACTH, a hormone with melanocyte-stimulating properties.

Primary hypoadrenalism is due to progressive bilateral destruction of the adrenal cortex by autoimmune disease, infection or malignancy. A decreased level of adrenocortical hormones in the blood stimulates ACTH production in the anterior pituitary. Increased ACTH induces melanocyte-stimulating hormone, resulting in diffuse pigmentation of the skin and oral mucose. Intraorally, this presents as a brown patches on the gingiva, buccal mucosa, palate and tongue [Fig.6] These lesions may resemble racial pigmentation, but they developed during adult life and are progressive. Oral pigmentation may be the first, sign and oral biopsy show acanthosis with silver positive intracellular granules in the stratum germinatuvum and melanin in basal layer. Addisons may give systemic manfestations such as weakness, nausea, vomiting, abdominal pain, constipation or diarrhea, weight loss and hypertension. Management is cause related and corticosteroid replacement therapy.

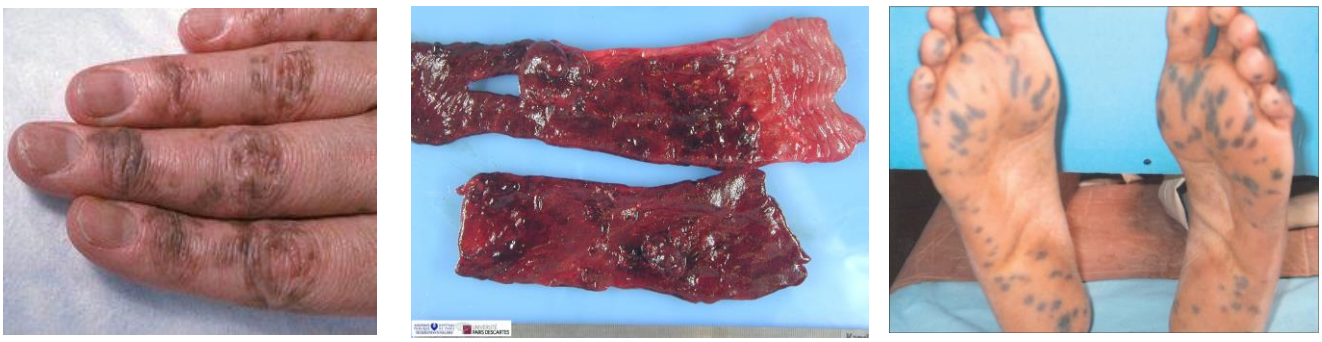

Figure 6. Addison disease

In Chushing`s syndrome, adrenocortical hyperactivity is observed, and if such activity is caused by a cortical secretory adenoma or cortical hyperplasia of adrenal origin, ACTH secretion will be shut down. Patients with Cushing`s syndrome may be hypertensive and hyperglycemic and may show facial edema “moon face”. Oral pigmentation may be the first sign on the gingiva, palate and bucall mucose. These changes in pigmentation are due to an accumulation of melanin granules, as a consequence of increased hormone dependent melanogenesis.

9. MUCOCUTANOUS MELATONIC PIGMENTATION AND GASTROINTESTINAL POLYPOSIS (PEUTZ-JAGHERS SYNDROME)

The hereditary intestinal polyposis syndrome is an unusual condition which is of the interest to the dentist because, pigmentation in oral cavity is usually patognomic sign, for these syndrom. The cause of human herpes virus 8, and the lesion most commonly occurs on the hard palate present from birth and appears as a small brown macules. On the lips, especially the lower and oral mucosa can be seen round, oval, or irregular, rarely confluent macules of blush-gray pigment of variable intensity. They vary of size from 1 to 12 mm, in general, larger than those on the cutaneus surface, which diameter is 1 to 5 mm. Intraorally the buccal mucosa is most frequently involved, with the gingival and hard palate next. Selom does the tangue show this pigmentation. On the face the spots tend to be grouped around the eyes, nostrils and lips.
Histologically, these lesions show basilar melanogenesis without melanocytic proliferation. The melanotic spots do not require treatment and are not associated with increased risk of melanoma. Such oral lesions help in early diagnosis and should alert the clinician to prompt the patient to screen for cancers in organs implicated in this syndrome.

Figure 7.Peutz-Jeghers syndrome

10. KAPOSI'S SARCOMA

This is a multifocal malignancy seen mostly in HIV infected patients. Appearance of Kaposi`s sarcoma is considered a heralding event for progression to AIDS [Fig.8a]. The cause is human herpes virus 8, and the lesion most commonly occurs on the hard palate, gingival and tang. Early lesions are macular, brown to purple and often bilateral[fig.8]. Advanced lesions are dark red to purple plaques or nodules with or without ulceration, bleeding and necrosis. Biopsy shows a proliferation of spindle shaped cells surrounding poorly formed. Vascular spaces or slits with numerous extravagated erythrocytes.

a) Typical Kaposi`s sarcoma* *b) Kaposi`s sarcoma attached to gingiva

Figure 8. Kaposi`s sarcoma

11. ORAL MELANOACANTHOMA

Oral melanoacanthoma is uncommon benign pigmented lesion of the oral mucosa, characterized by proliferation of dendritic melanocytes dispersed throughout the thickness of an acanthotic and hyperkeratotic surface epithelium [15,33]. Clinically, the lesion appears hyper pigmented black or brown, flat or slightly raised. This lesion, in contrast to most of the benign pigmented lesions has a tendency to enlarge rapidly, which raises the possibility of a malignant process in the clinical differential diagnosis [34]. Howeverits tendency to occur in young black females distinguishes it from melanoma, which is uncommon in this age and racial group. Goode et al. stated that the buccal mucosa is the most common site of occurrence, which may be related to greater frequency of trauma in this area [33]. Oral melanoacanthoma appears to be a reactive lesion with no malignant potential. In some cases, the lesion disappears after incisional biopsy or removal of the offending stimulus [34].

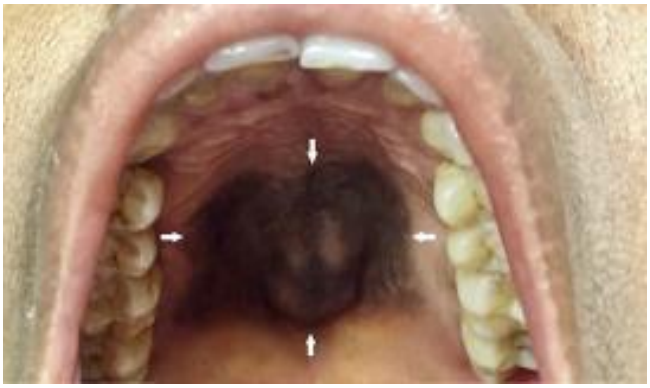

Figure 9. Oral melanoacanthoma

11. ORAL MELANOME

Oral mucosal melanoma is rare, accounting for less than 1% of all oral malignancies. Clinically, oral melanoma may present as an asymptomatic, slow-growing brown or black patch and bone destruction. In approximately one-third of the cases, oral manifestations are characterized by a prolonged radial growth phase followed by a vertical growth phase, whereas others exhibit a faster progression into a vertical growth phase [35]. The most common site it's the hard palate, with 30%, followed by gingival, which account for 1/3 of case [36]. Oral mucosa melanoma is generally encountered between fourth and seventh decade of life, with a greater incidence in man than in women. Histologically, the radial growth phase represents in situ and superficial melanoma and the vertical growth phase represent the modular or invasive melanoma [Fig.10].

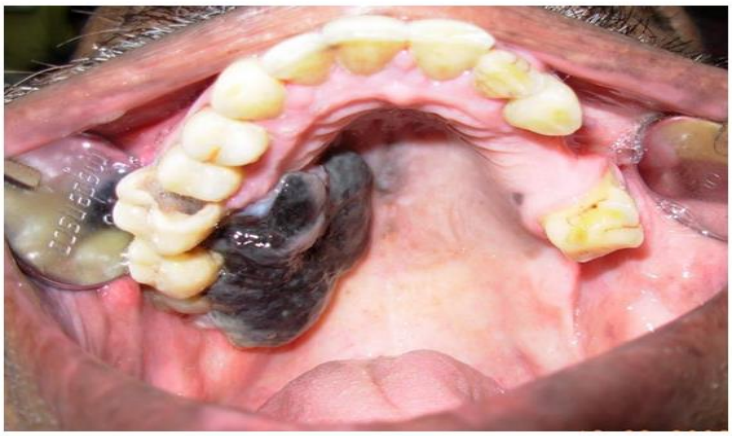

Figure 10. Oral melanoma

The oral melanoma is not subdivided into the classical cutaneous melanoma categories, which include superficial spreading melanoma, nodular melanoma and acral lentiginous melanoma [37]. Treatment involves radial surgical excision with clear margins. This may be difficult to accomplish because of anatomic constrains and proximity to vital structures. Radiation and chemotherapy are ineffective, which adds to the difficulties associated with management on this malignancy. Distant metastases often affect the lungs, brain, liver or bones. The prognosis for patients with oral melanoma is much worse than for those with cutaneous lesions and the overall 5-year survival rate is 16% [38].

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REVIEW OF INFLAMMATORY CYTOKINES IN DENTISTRY

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Abstract. *Pro-inflammatory cytokine is a type of signaling molecule that is secreted from immune cells like helper T cells and macrophages, and other cell types that promote inflammation like interleukin 1(IL-1), (IL-12) (IL-18), TNF-α, interferon gamma, granulocytes, macrophages and colony stimulating factor (GM-GSF). They play important role in mediation in initiate immune response. Inflammatory cytokines are predominantly produced and are involved in up regulation of inflammatory reaction. Most frequently Inflammatory diseases in dental medicine are periodontal diseases. Many studies have indicate that biological activity of variety of cytokines may be directly relevant to periodontal destruction. Draw of the initiation is well documented and the end result is destruction of alveolar bone and periodontal connective tissue. This is readily observe but the events between this two points in time remain obscure and are the focus of this paper. Bacteria from plaque formation induces tissue destruction indirectly by activating host defense cells, and tissue breakdown components of dental plaque have the capacity to induce the initial infiltrate of inflammatory cells including lymphocytes macrophages, PMNs. Bacteria can cause damage directly and indirectly. Cytotoxic cellular immune responses to self and pro-inflammatory responses are involved in releases of many cytokines and chemokines.*

1. INTRODUCTION

The first line of defense against molecules that are either pathogen-derived or endogenous danger signals (or quite often both) has evolved over millions of years. It is composed of players and mediators that are common to most vertebrates and invertebrates, as well as even plants [1]. In general, immunity does not only differentiate between self and not-self but also between dangerous and not dangerous [2]. Inflammatory cytokines play a role in initiating an inflammatory response and to regulate the host defense against pathogens mediating the innate immune response. Some inflammatory cytokines have additional rules such as acting as a growth factors. Pro-inflammatory cytokines such a IL-1 beta, IL-6 and TNF-α also trigger pathological pain. While IL-1 beta is released by monocytes and macrophages it is also present in nociceptive DRG neuron. IL-6 plays a role in neuronal reaction to an injury. TN-alpha is well known pro-inflammatory cytokine present in neurons and the glia. TNF alpha is often involved in different signaling pathways to regulate apoptosis in the cell. Excessive chronic production of inflammatory cytokines contribute to inflammatory decease that have been linked to different decease such a arteriosclerosis and cancer. This regulation of pro-inflammatory cytokines have also been linked to depression and other neurological decease. Pro-inflammatory and anti-inflammatory cytokines should be in balance for health to be maintained. Aging and exercise also play a big role in the amount of the release of pro-inflammatory cytokines.

Summarized, the messenger molecules such as cytokines are highly important in the orchestration of the inflammatory response to self- or not-self danger molecules. Meanwhile, the role of the immune system in various inflammatory diseases, in dental medicine as a periodontal decease, pulpitis bone pathologies such as atherosclerosis and distraction. But most frequently decease in dental medicine are periodontal diseases.

Periodontal diseases or periodontitis, are heterogeneous group of diseases characterized by inflammation and subsequent destruction of the tooth-supporting tissue. Today it is quite clear that periodontal diseases are of an infection nature and that the microorganisms present in the sub gingival bacterial plaque are the primary etiological agents [3, 4, 5, 6]. Initiation and progression of periodontitis are dependent on the presence of gram-negative anaerobic bacteria localized in the sub gingival region and include typically, *Porphoromonas gingivalis* (Pg), *Prevotela intermedia* (Pi), *Actinobacillus actonomycetascomitans* (Aa), and *Bacteroides forshytas* (Bi). One periodontal pocket can contain more than 700 microorganisms. The bacterial colonizing the sub gingival region multiply and extend in the apical direction, and, in the process, bring about loose epithelial and connective tissue attachment. The bacterial may give rise to destruction process by both direct and indirect mechanisms due to the activation of the hosts ' immunological and inflammatory reaction.

Although is not possible to attribute the etiology of periodontal diseases in a specific bacterial agent, there are a number of studies pointing to a group of bacteria believe that play a special role in the triggering and subsequent development of the disease.

There are over 500 bacterial species capable of colonizing in the sub gingival region, but the number of these commonly implicated in the disease process is around 10 or 15 gram negative anaerobes and spirochetes. The designation of periodontal pathogen applies to those bacteria that possess specific mechanism to break down the host's defense systems and cause destruction of the periodontal tissues.

The bacteria are considered to play significant role in the pathogenesis of periodontal diseases and the formation of the periodontal pocket, destruction of connected tissues and desorption of alveolar bone. Oral pathogens are necessary to initiated periodontitis, but they are not sufficient to insure progression of disease, unless it parallels inflammatory responses, in a susceptible host. There is, however, specific host defense mechanism to the bacterial challenge in the adaptive response of the immune system [7, 8]. Innate immunity is the first line of host defense and includes a number of relatively non-specific mechanisms, including the barrier effect of intact epithelium.

The host immune response may be conveniently divided into innate and adaptive immunity. Both innate and adaptive immunity operate together and not in isolation, complementing each other to maintain health and prevent disease.

Oral mucosa bathed in saliva, which contains number protective factors. Bacteria can be recognizing by non-clonally receptors, otherwise known as pattern recognition receptors. These receptors recognize substances such as lipopolysaccharide (LPS) from gram-negative bacteria and peptidoglycan from gram positive bacteria. Innate responses are relative non- specific and there is therefore greater potential for bystander damage of tissues.

Neutrophils appear to be crucial for the maintenance of periodontal health, as disease severity is increased the neutropenia, agranulocytosis and where cellular function in impaired, such as leukocyte adhesion deficiency, lazy leukocyte disease, Papillon Lefèvre and Downs syndromes, as well as diabetes mellitus.

The adaptive immune response is characterized by specificity, memory and the capacity to distinguish self from non-self. One recognition of microbial agents has taken place by the appropriate receptor on macrophages or dendrites cells, then cytokines are released which activate T and B cells, thereby engaging cell- mediated and humeral immune responses..The two arms of immunity therefore function together: the earlier responses being predominantly innate, subsequently helping to focus adaptive immune responses. In humeral or cell-mediated immunity, specificity of the responses is thought to limit by standard damage by focusing the adaptive or specific immune system.

2. CYTOKINES

Cytokines and (chemotactic cytokines) are the messages between the cells. the immune response to infection is regulated by cytokines and chemokines signals. Cytokines are low molecular - weight proteins involved in the initiation of further stages of inflammation, in witch they regulate the amplitude and duration of the response. The genetic regulation leading to the secretion of pro inflammatory cytokines from a variety of cells is generally dependent of the activation of transcription Nuclear factor-kappa B (NF-κB). the Nuclear factor-kappa B (NF-κB) regulation is regulated pathways are activated by pathogen associated molecular pattens, and such as lipopolysaccharides, trough the tall-like receptor pathway. A network of secreted cytokines led to activation of lymphocytes, but the progression of periodontal lesions is caused by deregulations of molecules released by specific cell populations. Many of these secreted factors are involved in bone regulation and maintained, and their imbalance leads to altered periodontal bone remodeling. Thus enhanced osteoblast activity without increase in bone formation occurs and drives the alveolar bone loss [6].

Inflammatory process gives rise to macrophage activation as well as leukocyte infiltration. The activated immunocompetent cells produce and secreted cytokines. These activated host cells include monocytes, macrophages, lymphocytes and fibroblast [9, 10].

Cytokines, are substances that are secreted by specific cells of immune system which carry signals locally between cells, and thus have an effect another cells. The biological effects of cytokines and are extremely diverse as they influence not only the immune response but also inflammatory processes and hematopoiesis.

Various studies have shown that IL-1 alpha, Il-1beta and TNF-α stimulated bone desorption and inhibit bone formation. Research work has sown that IL-1 beta expression is elevated in gingival cervical fluid at sites bone and attachment loss in patients with periodontitis. In another study, it was shown that the exogenous application of recombinant human IL-1 beta in a rat ligature model accelerated alveolar bone loss destruction and inflammation.

Cytokines can be classified into following categories: a. Proinflammatory cytokines; b. Cytokines with predominant immunoregulatory functions; c. Cytokines that regulate lymphocyte growth, activation and differentiation; d. Cytokines that help in hematopoiesis; f. Chemokines.

a. Proinflammatory cytokines: There are cytokine that mediate natural immunity. In this group there are soluble factors that influence inflammatory reaction. These include: interleukin-1 (IL-1), Tumor necrosing factor alpha (TNF-alpha), interleukin 6 (IL- 6), interleukin 8 (IL-8), Macrophage inhibitor factor (MIF).

Interleukin 1(IL-1)

This cytokine exist in two molecular form IL-1 alpha (IL-1 alpha) and IL-beta (IL-1 beta), encoded by two separate genes and displaying only 20% homology to one another. Cells of the monocytemacrophage lineage are the main cellular source of IL-1, while IL-1 beta, synthesized as inactive precursors, is released from the cells after being processed post translational by a cysteine-asparagine protease. IL-1 beta is a proinflammatory cytokine expressed by monocytes, macrophages and dendrite cells. It signals through two receptors, IL-IRI and IL-IRII., both of which are shared with IL-1 alpha. It I multifunctional molecule that effects ranging from inflammation, immunity and haemopoiesis.IL-1 has diverse activities and roles in immunity, inflammation, tissue breakdown, and tissue homeostasis [11, 12].

Interleukin 1 (IL-1), is a proinflammatory multifunctional cytokine, which among its many logical activities enables ingress of inflammatory cells into sites of infection, promotes bone resorption, stimulates eicosanoid (specifically,PGE-2) release by monocytes and fibroblasts stimulates release of matrix metalloproteinases that degrade proteins of the extracellular matrix and participates in many aspects of the immune response [13]. Interleukin-1 levels in general are elevated in both tissues and GCF from diseased [12, 13]. The predominant form in the periodontal tissues is IL-1 alpha, which is produced primary by macrophages. [14].

Release of interleukin-1 beta by epithelial cells, monocytes, macrophages and resident fibroblasts, is accompanied with increased production of prostaglandin E-2, induce osseous resorption by osteoclasts. IL-1 and TNF-alpha increase the production of PGE-2 by epithelial cells, monocytes and fibroblasts. These products can subsequently trigger degradative pathways such as a matrix metalloproteinase (MMPS), plasminogen–depended, and phagocytic polymorphonuclear serine proteinase pathways. The examination of Armitage and Ofenbucher show that MMPS are highly expressed in gingival cervical fluid [15, 16]. MMPS are released in an attempt to kill bacteria: nonetheless, these enzymes end up destroying collagen fibers of the periodontal ligament and gingiva, leading to an apical migration of the junctional epithelium. Hence, pocket form atom the root surface, as the coronal portion of the gingiva separates from the root surface due to these inflammatory events.

3. TNH – ALPHA

TNF-alpha was first described in 1975 by *Carswell et al.* for its cytotoxic activity to tumor cells via immune cells and educed was named TF[18]. it is expressed as a type 2 trans membrane protein (mbTNF-alpha), but can be cut to its soluble forms (sTNF-alpha), with increased biological activity. the enzyme responsible for its cutting is TNF converting enzyme (TACE) or ADAM 17. the membrane bound mb TNF-alpha has a 233 amino acid sequence, Weights 26 K Da and forms homo trimers, the main supple of tNF-alpha are macrophages and many other cell such as neutofils and endothelial cells have been described to produce TNF-alpha. targets for TNF-alpha include two type 1 transmembrane receptors, TNF receptors1 and two TNF receptors 2 where's TNF 1 is expressed on every cell except erythrocytes TNF-2 is found only in endothelial animal cells. The clinical study including 34 patients with at least 20% burn surface area, it was shown that systemic TNF levels correlated with burn severity and predicated aspectability to infection. [20]. In general TNF-alpha surpasses osteoblast activity and some stage of differential and simulate osteoclast proliferation and differentiation. Similar to IL-6 tif alpha can regulated bone metabolism to the endocrine way.

Tumor necrosing factor (TNF-alpha), is involved in normal inflammatory and immune response. In both autocrine and paracrine inducer of other cytokines like IL-1, IL-6, IL-8, and plate let derived growth factor-B, eicosanoids platelet activating factors and granulocyte monocyte colony stimulating factor. TNF is secreted by macrophages, monocytes, neutrophils, T-cells, Natural-Killer–cells (NK-cells) following there stimulation by bacterial lipopolysaccharides. Cells that are expressing CD-4, secreted TNF-alpha, while CD-8+ve secreted little or no TNF-alpha. Besides the direct effect on the pathogenesis of periodontal diseases, TNF- alpha up regulates the production of other classic proinflamatory innate immune cytokines, such as IL-1B and IL-6 [20, 21].

TNF- alpha can synergized with RANK-L in promoting osteoclastogenesis. Further studies show that TNF-alpha activates C-Jun, NF-kB and calcium signaling leading to NFAT-CL-activation and thus osteoclast differentiation independent of RANKL in human macrophages [22]. TNF-alpha plays a central role in inflammatory reaction, alveolar bone resorption and loose of connective tissue attachment [23]. It is known to be associated in local and systemic inflammation involving bone loose. It is present at high levels in diseased periodontal tissues, where it is positively correlated with RANKL expression [23, 24].

Experimental models of periodontitis are primates demonstrate that local injection of TNF- alpha antagonist reduce the appearance of inflammatory cells in the alveolar bone and the formation of bone resorbing osteoclasts. There studies show spontaneous osteoclast formation and increased bone resorption from circulating PBMCs of periodontitis patients correlating with high levels of TNF-alpha and RANK-L [25, 26]. As a result of the innate immunity response, TNF- alpha is locally produced by neutrophils, which exhibits increased chemotaxis production of proinflammatory [27]. Macrophages represent an important source of TNF- alpha, that, under dysregulations contribute to host tissue destruction.After antigenic stimulation; naïve CD-4+T-cells activate, proliferate and differentiate into distinct effector cell subset characterized by their specific cytokine. This Th-1 lymphocytes subset is characterized by the secretion of TNF- alpha. TNF-alpha contributes to periodontal damage by its direct effect on osteoclastogenesis and by amplification of inflammatory immune reactions. Furthermore, in into data demonstrate and effect of TNF- alpha not only on osteoclasts, but also on osteoblasts by inhibiting differentiation and bone nodule formation [27]. TNF-beta is commonly known as a lymphotoxin. TNF and IL-1 have effects at three different levels: metabolic effects; vascular effect and endocrines pyrogens.

Interleukin-6(IL-6)

IL-6 is shown to play important note in autoimmune decease bacterial infections and metabolic site effects have been observed also. interestingly, IL6 was first described for its effects on adaptive immunity, promoting cluster od differentiations CD-4+ t-cells IL-21 production, and promoting t cells differentiations toward helper 2 cells and t17 cells.

The reason for using IL-6 as a biomarker plays central role inactivating and maintaining inflammatory response. however, unfortunately it is inflammatory properties are so far neglected in clinical practice. while early inflammation is dominated by neutrophils, later stages of inflammations are dominated by monocytes. IL-6 along with IL-1 and TNF-alpha is a major immune inflammatory mediator. It is a pleiotropic cytokine influencing immune responses. One action of Il-6 and B-cells is the increased secretion of Ig M. It also induced T-cell proliferation.

Interleukin – 8 (IL-8)

Il-8 is known for its effects on neutrophils, specifically, its ability to act as a chemoattractant for them. Thus cytokine secreted by many cells, such as monocytes, lymphocytes, fibroblasts and endothelial cells. It induces the adhesion of PMN to endothelial cells and their transendothelial migration, as well as the release of granule enzymes from these cells.

Macrophage migration inhibitor factor (MIF)

MIF is usually efficiently involved in the adaptive immune response through favoring Th1 activation and differentiation. It plays crucial roles in the recruitment of activation of macrophages as well as in helping to kill bacteria. It is also know as a glycosylation inhibiting factor (GIF). MIF plays a major role in innate immunity against bacterial infections through enhancement of TNF-alpha secretion, toll-like receptor 4, (TLR4) expression phagocytosis and intracellular killing mechanisms and is equally efficiently involved in the adaptive immune response through favoring Th 1 activation and differentiation.

b. Cytokines with predominant immune-regulatory functions:

In this group of cytokine are: interferon, Interleukin 12 and interleukin 18.

Interferons:

Antiviral effects of interferons are not specific. Interferon alpha and interferon beta, are produced by leucocytes and fibroblast, after challenge with viruses. Interferon- gamma is a polypeptide with 166 amino acids. And it has a wide range of effects. IL-beta induced an increase in the expression of cyclic adenosine monophosphate on the cytoplasmic membrane of endothelial cells egress from the vascular bed. Large number of T-lymphocytes will thus exist in the

vascular bed in areas with hypersensitivity reactions. Interleukin N- gamma has most important effects to activation of monocytes.

Interleukin - 12

Interleukin 12 (Il 12) is an important regulatory cytokine, that has a function central to the initiation and regulation of cellular immune responses. IL-12 is produced by: macrophages, monocytes, dendritic cells and beta cells in response to bacterial products. He is responsible primarily for the production of IFN-gamma and TNF-alpha from both NK cells and helper T-cells [28, 29].

Interleukin -18

It is a recently discovered interleukin, reflecting is major biological role. In many respect it is similar to IL-1, IL-12, IL-18.

c. Cytokine that regulate lymphocyte growth, activation and differentiation.

In this category are: IL-2, IL-4, IL-5, IL-12, IL-15 and transformation growth factor B (TGF-B).

IL-2

It is important for the proliferation of T and B lymphocytes. The receptors of this cytokine are a heterotrimeric protein complex whose gamma chain is also shared by interleukin (IL4) and interleukin 7 (IL 7). IL 2 is also necessary during T-cell development in the thymus for the maturation of a unique subset of T-cells that are termed regulatory T-cells.[30]

IL-4

It is an important factor affecting both T and B cells. It is through IL-4, plays a major role in T-cell development. IL 4 can also act as a mast cells growth factor. IL 4 exerts different effects on B-cells at different stage in the cells cycle. On resting B-cells, IL 4 acts activating factor, inducing them to enlarge in size and increase class II MHC expression. Following activation by an antigen or mitogen<IL4 acts as a growth factor, driving DRNA replication in the B-cells [31].

IL-5

It is known for its activity on B-cells and eosinophiles. It is produced by T-helper-2 cells and mast-cells.

IL-12

It has the capacity to regulate the differentiation of naïve T-cells into TL1 cells. It is produced by macrophages, monocytes, dendritic cells and B-cells in response to bacterial products and intracellular parasites. IL-12 is responsible primary for the subsequent production of TNF-gamma and TNF-alpha from both Nk cells and helper T-cells [26].

IL-15

IL-15 regulates T-cells and NK-cell activation and proliferation. This cytokine and interleukin 2 share many biological activities. They are found to bind common hematopoietic receptors subunits and may compete for the some receptor, and thus negatively regulate each other's activity. The number of SD-8+memory cells, is shown to be controlled by a balance between this cytokine and IL-2.

d. Cytokines that help hematopoiesis

These include: granulocyte-monocyte colony-stimulating factor (GM-GSF),

Interleukin 1 (IL-1), Interleukin 3 (IL-3), Interleukin 6 (IL-6), Interleukin 7 (IL-7).

Thus cytokines stimulated production of new blood cells by acting of hematopoietic progenitor cells. It released by activated T lymphocytes, bone marrow, monocytes, fibroblasts, osteoblast and vascular endothelial cells.

T-Lymphocytes and monocytes

Alpha chemokines: Interleukin 8 (IL 8)

f. Chemokine are a broad and loose category of small proteins that are important of cell signaling. Chemokine can also be involved in autocrine signaling. There are released from lymphocytes and monocytes stimulated with TNF alpha or IL-1In function as a chemotactic and activating factor for granulocytes, the cell population with the highest

level of IL-8 receptor expression. IL-8 recruits granulocytes to areas of inflammation and increasing their phagocyte and pro-inflammatory abilities. It has also been demonstrated to be chemotactic for T- lymphocytes.

Beta chemokines;

In this group are included four major cytokines:

i. RANTES, released by T-cells

ii. Macrophage chemotactic proteins

iii. Eotaxin, chemokine induced by IL-4 that recruits eosinophils and TH 2, CD41 T cells to the sites of inflammation.

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THE MULTIDISCIPLINARY MANAGE`MENT OF CLEFT LIP AND PALATE PATIENTS- ORTHODONTIC POINT OF VIEW

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Abstract. *The management of patients with cleft lip and palate is complex and requires a multidisciplinary team with several interventions and long-term treatment. The regular timing of orthodontic and surgical treatment is important for a successful long-term outcome and for reducing the burden of caring for both the child and the family. This paper will focus on the orthodontic treatment of patients born with cleft lip and palate from an early age to skeletal maturity. Management of patients with cleft lip and cleft palate requires extended orthodontic treatment and interdisciplinary approach in providing these patients with optimal aesthetics, function and stability. Orthodontic therapy in infant phase, primary, mixed and permanent dentition and after the end of growth will be discussed with an appropriate interdisciplinary approach in the planning of treatment and its timing during each phase of orthodontic and surgical treatment.*

Keywords: *cleft; cleft lip; cleft palate; multidisciplinary team; orthodontics.*

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Consent*: All pictures are with a permission of the patients and from free internet library.*

1. INTRODUCTION

Clefts present the most often craniofacial anomaly (circa one newborn baby is born with cleft in a 1000 hundred live born babies). The number ranges higher in some countries. There are two types of clefts: complete or incomplete and unilateral or bilateral. A palatal cleft may occur as an isolated phenomenon. Patients may have a cleft on the primary palatum, secondary palatum or both of them, or their every possible combination. (Fig.1) Clefts are often a part of a congenital anomaly or some syndrome.[1]Complete unilateral or bilateral clefts of the lip have an arch that is collapsed into the transversal, especially on the side of the cleft. Treatment of the patients with clefts is a long and multidisciplinary process with the participation of many specialties which form "the cleft team". The orthodontist enters the team a few days after the baby is born with pre surgical orthodontic therapy in order to prepare it for a further surgical treatment. The first phase of the orthodontic treatment consist out a distraction of the maxillary segments. The second phase of the orthodontic treatment is being conducted in order to incite a normal occlusion or if a skeletal discrepancy exists, to prepare jaw arches for orthognathic surgery leading the patient with normal occlusion, anatomo - morphological and functional face expression, normal chewing, normal speech development, and development of the patient into a healthy person.

Figure 1. Different types of clefts

2. MULTIDISCIPLINARY CLEFT TEAM

Cleft patients need continual special care over a period of almost 20 years. This is why these children should be taken care by a multidisciplinary team (MDT) made of professional's trained to treat cleft patients. The team usually consist of:

- Genetical advising specialist
- Gynecologist ultrasonography specialist
- Micropediatrician
- Nurse specialized in nursing cleft babies
- Maxillofacial surgeon
- Orthodontist
- Otorhinolaryngologist
- Speech therapist
- Doctor of child dentistry
- Prosthodontist
- Psychologist

MDT includes an orthodontist, who is present at all team meetings, and who has the proper education, training, and experience that enable him/her to diagnose and treat patients afflicted by clefts on the lips and/or palate. Modern orthodontics includes treatment of severe deviations of the lip and palate, which are just examples of extreme cases of the normal biological variety amongst people.[8]

3. PREOPERATIVE ORTHODONIC THERAPY OF CLEFTS

Preoperative orthodontic treatment aims at successful surgical intervention, which has the goal to avoid relapse of all maxillary segments included in the cleft. Our country, as well as all other countries around the world, uses preoperative orthodontic therapy in almost all cleft cases.

It is used only with patients afflicted by the following cleft types:

1. Unilateral cleft of the primary and secondary palate
2. Bilateral complete cleft of the primary and secondary palate
3. Bilateral complete cleft of the primary palate

The deformities that occur in the maxillary arch of these clefts are most severe; the distance among maxillary segments is the greatest, thus there is a necessity to perform an early preoperative orthodontic treatment. Patients with unilateral complete cleft of the primary palate, incomplete cleft of the primary and secondary palate, isolated clefts of the palate and uvula, partial clefts of the lip, as well as all microclefts DO NOT exhibit any indications for preoperative orthodontic treatment, since the deformity of the maxillary arch is mild as well as the distance among maxillary segments.

3.1. Main Reasons for Early Orthodontic Treatment of Newborns with Cleft

Necessity to correct the deformed maxillary segments and provide a good skeletal basis for surgical treatment of cleft lips and a goal to avoid a postsurgical collapse of the maxillary arch, Improvement of the surgical results, Better feeding of children with complete clefts and achieving a better psychological effect on the parents and ensuring their future collaboration.[5] The preoperative orthodontic treatment should be performed as soon as possible, 2-3 days after birth, especially in cases of newborns with complete bilateral clefts and end when the children reach the age of 6 – 8 months, since this is when tissues in this area develop the fastest. (Fig.2)

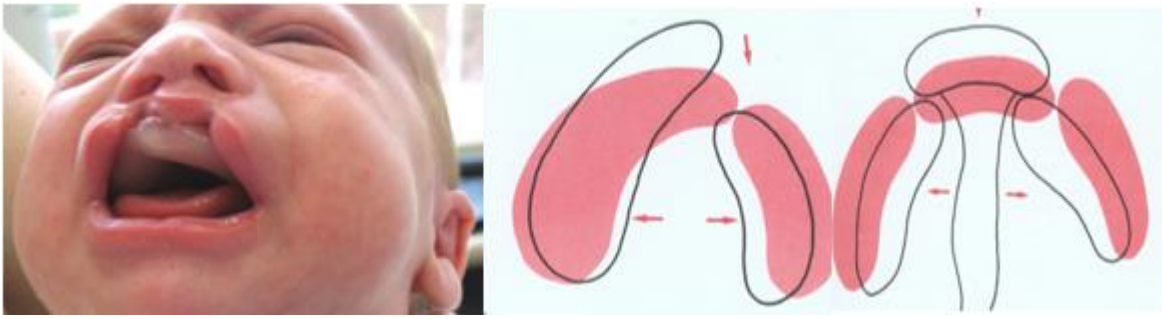

Figure 2. Obturator in unilateral and bilateral cleft

The McNeil treatment, which was the first preoperative orthodontic treatment, is most often executed. Preoperative orthodontic treatment aims at successful surgical intervention, which has the goal to avoid relapse of all maxillary segments included in the cleft.6

Figure 3. Preoperative orthodontic treatment aims at successful surgical intervention, which has the goal to avoid relapse of all maxillary segments included in the cleft

4. SURGICAL RECONSTRUCTION OF THE UPPER LIP * CHIELOPLASTICA * AND * PROCESSUS ALVEOLARIS*

The upper lip consists of several important anatomical elements: philtrum, its edges, and the vermilion with its vividly emphasized arches. (Fig,4)

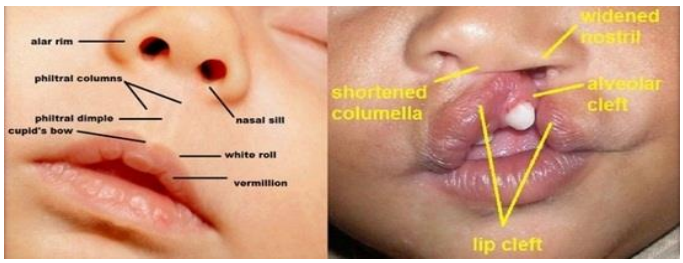

Figure 4. Normal lip versus cleft lip

Lip correction is of great importance since m.orbicularis oris allows facial expressions. This muscle enables nursing, whistling, speech, etc. The permanent pressure that this muscle exerts allows for proper development of the maxilla and alveolar segments along with the dental arches. (Fig 5)

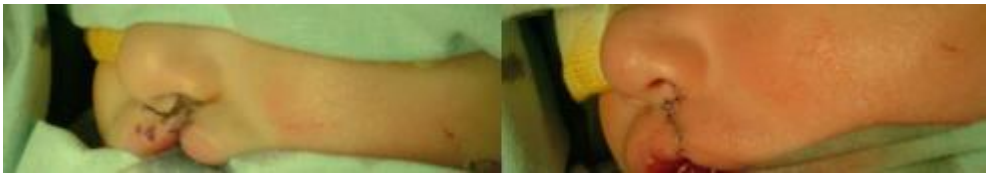

Figure 5.

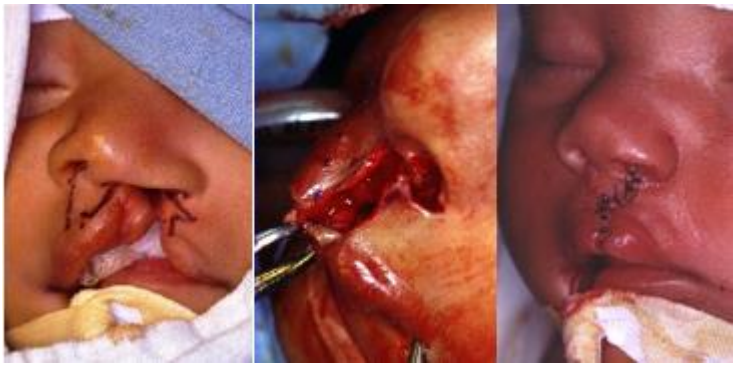

Figure 6. If the cleft affects only the soft tissue, surgical closure is linear. (Kilner & Peet linear method)

But, if the cleft includes clefting of the primary and/or secondary palate, the maxillary segments and premaxilla of unilateral and bilateral clefts needs maxillary segment leveling in order to acquire tension free lip closure and avoid large discrepancies in future development of the maxilla and dental occlusion. Good preoperative preparations lead to good final results. Most surgeons prefer to postpone surgical treatment of the lip until the age of three months, since the infant, as well as its lip, are bigger at this period. This time period allows the orthodontist to complete the preoperative treatment, which significantly enhances the end results.

5. SURGICAL RECONSTRUCTION OF THE SOFT AND HARD PALATE - PALATOPLASTICA

Primary palate clefts are usually closed simultaneously with the lip closure. Secondary palate clefts, which may spread from the foramen incisivum to the uvula, is usually made in one step when the patient is 24 months old or in the period of complete deciduous dentition. The aim of this surgery is to provide an intact oral arch, mobility of the soft palate, and a complete contact with the posterior wall of the pharynx, accompanied by a sufficient velopharyngeal closure, which will in return provide for speech development or avoid rhinolalia; a normal upper and lower jaw ration and occlusion; normal anatomical, morphological and functional appearance of the face; normal mastication; normal breathing; normal hearing; normal swallowing; and, development of the patient into a healthy socialized person. (Fig.7) Dissection of palatal flaps can be achieved by Von Langenbeack method or along the palate arteries, i.e. using the Veau Wadil – Kilner Push Back method.[7]

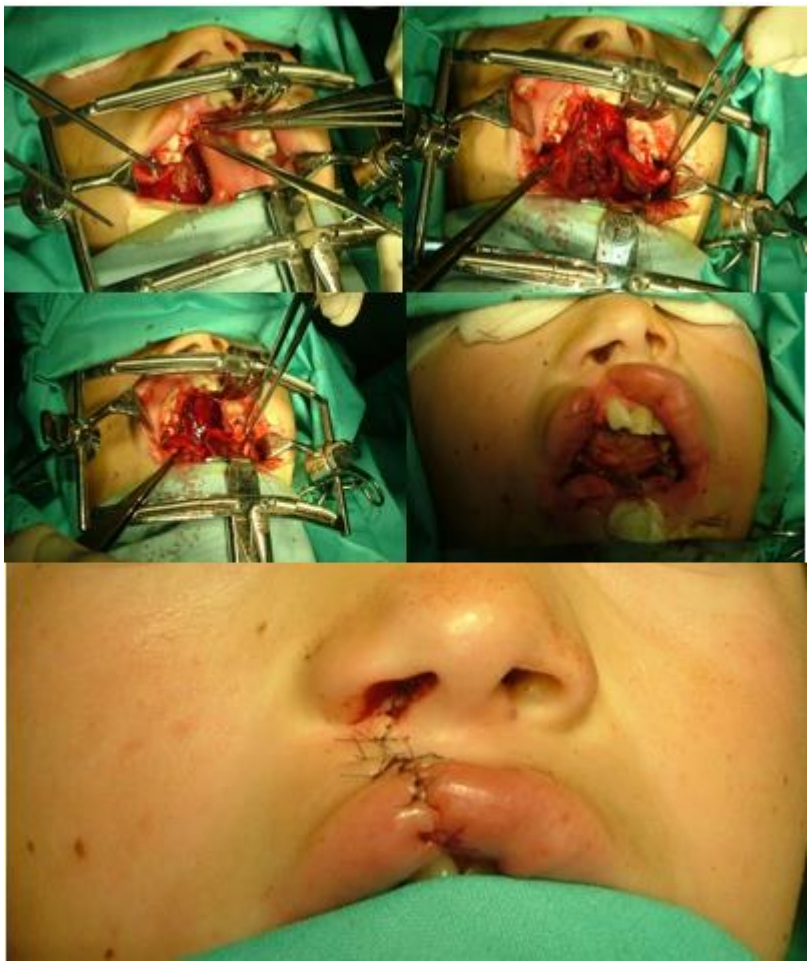

Figure 7.

6. POSTOPERATIVE ORTHODONIC CLEFT THERAPY: DECIDUOUS DENTITITION

Orthodontic treatment of malocclusions in children with clefts in deciduous dentition does not actually have distinct indications. The treatment is most often utilised in children with complete bilateral clefts of the primary and secondary palate. Their early treatment influences the dental arches development and aids towards elimination of many possible future orthodontic problems. There are emphasized treatment indications in this period in children with bilateral cleft, protruded premaxilla, and collapsed lateral segments. In these cases anterior parts of the lateral segments lean on the posterior part of the premaxilla and obstruct its shift oral. A simple mobile orthodontic plate with an extension screw, which is highly successful in treating lateral crossbite, is most often used. In case of bilateral clefts, this plate is cut along the medial line, while in cases of unilateral clefts, the cut is made on site of the cleft. Lateral bite ridges may also be added. The screw is activated each two to three days. The shift of the lateral segments provides for a more acceptable occlusion, thus permanent teeth erupt in a position that is better for future treatment of the patient. Also, the expansion of the maxillary arch provides more space for the tongue, thus enhancing the speech as well. In order to have a successful treatment it is most important that in this period the orthodontist establishes excellent communication with the patient's parents. Not one control check-up must be missed and the appliance must be worn at all times, since the results achieved by a three month treatment may be easily lost within several days. This is the reason why the appliance should be taken out of the child's mouth only for hygiene purposes. Deciduous dentition orthodontic treatment has the aim to maintain most favorable oral conditions, which serve as basis for good orthodontic treatment in mixed and permanent dentition.

6.1. Mixed Dentition

Treatment becomes necessary in this period as soon the first upper permanent incision teeth erupt. Rotated and inclined teeth are corrected by mobile plates in combination with labial arch and rails in palatal position. Fixed appliances are used in more severe cases. The use of orthopedic facial mask is especially emphasized in this period and the results are almost spectacular. The appliance for rapid palatal expansion is often combined with the orthopedic facial mask. (Fig.8 and 9) Depending on its usage, traction is combined with two elastic bands on each side, depending on the collapse. In this case, the elastic force exerted by hooks on the prelabial arch of the mask is the same as in maxillary 81andibular81cies. Traction intensity depends on the case. In order to lateralize and direct fragments anteriorly, an appliance for fast palate adhesion is used in cases where patients are older than 10, who have suffered a total collapse of fragments, and have not been subjected to orthodontic therapy. After sagittal and transversal contact of the mandibular and maxillar alveolar ridges has been acquired, the appliance remains in use for the purpose of retention within a period of 6 – 9 months. The appliance for fast palatal adhesion is often combined with the facial mask. Depending of the usage traction is combined with two elastic bands on each side, depending on the cleft. In this case, the elastic force is applied on hooks on the prelabial arch of the mask .Traction intensity depends on the case. When desired results in all three directions are achieved, stabilization is acquired by use of fixed techniques and the final solution is reached by prosthetic rehabilitation.

During treatment patients must always wear orthodontic devices.

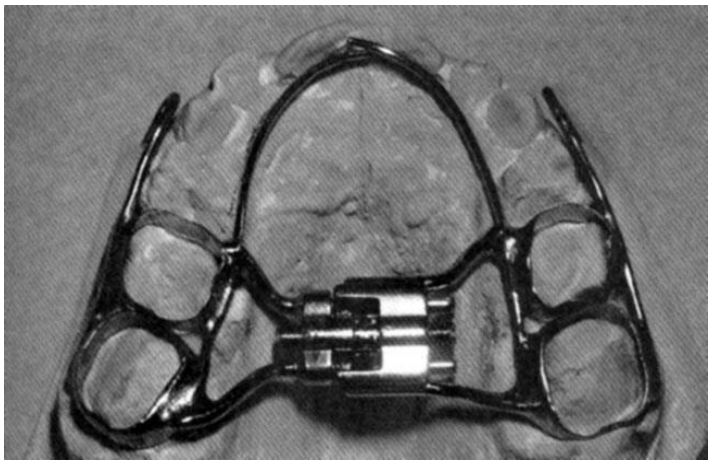

Figure 8. Rapid Palatal Expander

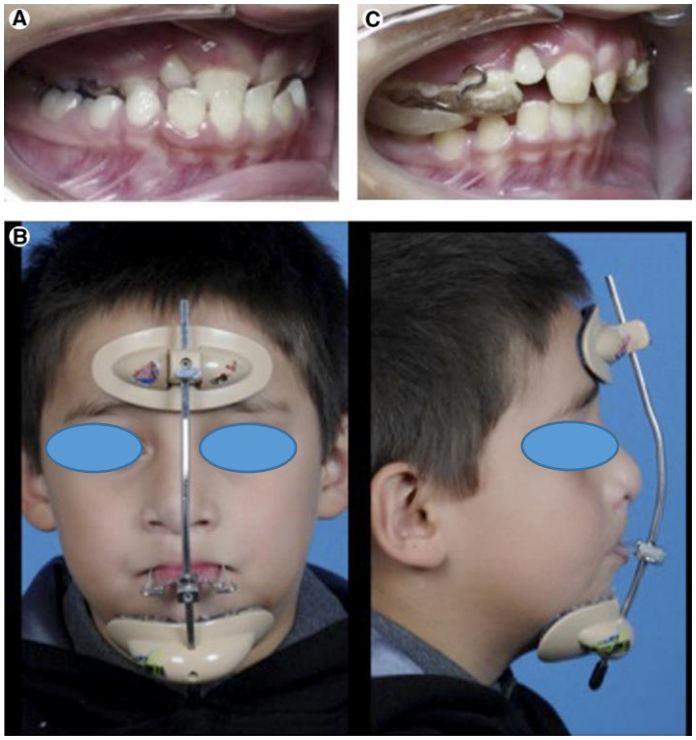

Figure 9. Orthopedic facial mask – Delaire type

6.2. Permanent Dentition

As soon as permanent dentition emerges, time comes to start fixed orthodontic treatments of clefts and all of their special characteristics. (Fig.10) Most often these defects are related to certain teeth and maxillary segments position. Provided there is no satisfactory result, orthognatic surgery is used as well.

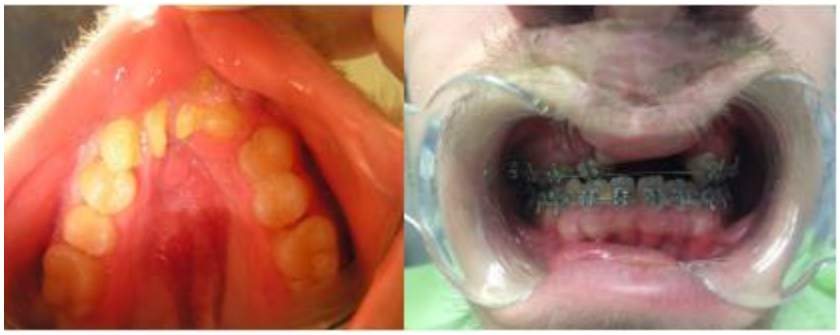

Figure 10.

7. RETENTION

Compared to routine cases, the retention treatment period is much longer here. Patients whose maxillary arches have been widened need a lifelong retention, which may be orthodontic or prosthetic. Orthodontic retention is in fact a very simple plate that must be fitted immediately after the removal of the fixed appliance, since recidivism is highly possible. If necessary, the appliance is corrected on site, by a self-adhesive acrylic. Prosthetic retention appliances may be mobile and fixed. Missing teeth are often replaced after maxillary arch correction. This is achieved by bridges or partial prosthesis that serve as retention as well.

8. CONCLUSION

- The orthodontist's role in the multidisciplinary team is of primary importance and starts almost at the birth of patients with cleft lips and/or palates.
- Preoperative orthodontic therapy should be carried out continuously since birth until the first surgical procedure (cheiloplasty), i.e. the age of three months and later until palatoplasty, i.e. the age of 24 months, when deciduous dentition is complete.
- Preoperative orthodontic treatment of cleft palates as part of complete unilateral and bilateral clefts, as well as their subtypes, is compulsory and carried out with the help of an obturator until time comes for surgical intervention, i.e. palatoplasty at the age of 24 months.
- Preoperative orthodontic treatment of complete, i.e. bilateral clefts, as well as their subtypes, which always exhibit cleft lips, is compulsory in order to draw the upper lip segments together and give them direction, and allow for tension free cheiloplasty. Thus, the upper lip acquires continuity and proper form.
- The postoperative orthodontic treatment starts immediately after rehabilitation from palatoplasty and uses mobile and fixed therapy and follows the growth and development of the maxilla, until the adult period.

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