



MACEDONIAN DENTAL REVIEW

I S S N | **3 43**
2545-4757 | **2020**

Macedonian Dental Review is publishing by the Faculty of Dentistry, University „Ss. Cyril and Methodius“,
Skopje, Republic of North Macedonia and Macedonian Dental Society

<http://stomfak.ukim.edu.mk/msp/>

Tips and advices when planning and conducting the prosthodontic treatment in pediatric patients. <i>Bajraktarova Valjakova E, Korunoska Stevkovska V, Sotirovska Ivkovska A, Bajraktarova Misevska C, Elenchevski S, Georgieva S, Ivanovski K.</i>	85
Bilateral enlargement of major salivary glands as an initial sign of acute myeloid leukemia: case report. <i>Popovski V., Benedeti A., Stamatovski A., Koneski F.</i>	89
Prevalence of oral candidiasis in complete dentures wearers. <i>Tmava-Dragusha A., Shala K., Ivanovski K., Dirjanska K., Ristoska S., Elenchevski S.</i>	94
Hyaluronic acid: A promising mediator for periodontal regeneration. <i>Toshevska S., Pandilova M., Redjep E., Janev E., Mindova S., Gorgieva-Trpevski D., Angelovski B., Omerov E.</i>	100
Coronectomy - an alternative to surgical extraction of deeply impacted mandibular third molar - a case report. <i>Kacarska M.</i>	110
Torus palatinus: clinical aspect and therapeutic strategy. <i>Kacarska M.</i>	117
Oral rehabilitation of a child with hypohidrotic ectodermal dysplasia: six years follow-up study. <i>Bajraktarova Valjakova E, Jovanovska M., Tofoski G., Bajraktarova Misevska C., Panchevska S., Mijoska A., Korunoska Stevkovska V.</i>	123

Macedonian Dental Review is publishing by the Faculty of Dentistry, University „Ss. Cyril and Methodius“, Skopje, Republic of North Macedonia and Macedonian dental society.

Editor in chief - Prof. Kjiro Ivanovski, PhD, e-mail: kiroivanovski@stomfak.ukim.edu.mk

Associate editor - Prof. Elizabeta Georgievska PhD, Department of Pediatric and Preventive Dentistry, e-mail: egjorgievska@stomfak.ukim.edu.mk

Secretary - Vlatko Kokalanski, MBA, e-mail: vkokalanski@stomfak.ukim.edu.mk

Adress - Macedonian Dental Review, str. Majka Tereza br. 43 Skopje, Republic of North Macedonia, <http://stomfak.ukim.edu.mk/msp/>

Editorial Board

Mira Jankulovska, Skopje, North Macedonia
 Sonja Apostolska, Skopje, North Macedonia
 Silvana Georgieva, Skopje, North Macedonia
 Aleksandar Grchev, Skopje, North Macedonia
 Lidija Kanurkova, Skopje, North Macedonia
 Maja Pandilova, Skopje, North Macedonia
 Vesna Stevkovska, Skopje, North Macedonia
 Boris Velichkovski, Skopje, North Macedonia
 Vasilka Rendzova, Skopje, North Macedonia
 Ivan Alajbeg, Zagreb, Croatia
 Ivan Anastasov, Sophia, Bulgaria
 Nikola Angelov, Houston, USA
 Gurhan Caglayan, Hacettepe, Turkey
 Domagoj Glavina, Zagreb, Croatia
 Peter Jevnikar, Ljubljana, Slovenia
 Hristo Kisov, Plovdiv, Bulgaria
 Darko Macan, Zagreb, Croatia
 Ljubo Marion, Ljubljana, Slovenia
 John Nicholson, London, UK
 Darije Planchak, Zagreb, Croatia
 Kristina Popova, Sophia, Bulgaria
 Sasha Stankovikj, Nish, Serbia
 Dragoslav Stamenkovikj, Belgrade, Serbia
 Zrinka Tarle, Zagreb, Croatia
 Ljiljana Tihachek, Belgrade, Serbia
 Georgi Tomov, Plovdiv, Bulgaria
 Radomir Ugrinov, Sophia, Bulgaria
 Ana Angelova-Volponi, London, UK
 Vaska Vandevska, Oslo, Norway
 Radosveta Vasileva, Sophia, Bulgaria
 Miroslav Vukadinovikj, Belgrade, Serbia

Advisory board

Alberto Benedeti, Skopje, North Macedonia
 Aleksandar Dimkov, Skopje, North Macedonia
 Ana Sotirovska Ivkovska, Skopje, North Macedonia
 Aneta Atanasovska Stojanovska, Skopje, North Macedonia
 Antonio Kirkov, Skopje, North Macedonia

Biljana Kapusevska, Skopje, North Macedonia
 Biljana Dzipunova, Skopje, North Macedonia
 Vera Radojkova Nikolovska, Skopje, North Macedonia
 Vladimir Popovski, Skopje, North Macedonia
 Gabriela Kurchieva Cuckova, Skopje, North Macedonia
 Goran Pancevski, Skopje, North Macedonia
 Gordana Kovacevska, Skopje, North Macedonia
 Daniela Veleska Stevkoska, Skopje, North Macedonia
 Danica Popovikj Monevska, Skopje, North Macedonia
 Evdokija Jankulovska, Skopje, North Macedonia
 Edvard Janev, Skopje, North Macedonia
 Emilija Bajraktarova Valjakova, Skopje, North Macedonia
 Emilija Stefanovska, Skopje, North Macedonia
 Zlatko Georgiev, Skopje, North Macedonia
 Ilijana Muratovska, Skopje, North Macedonia
 Jadranka Bundevska Josifovska, Skopje, North Macedonia
 Julijana Nikolovska, Skopje, North Macedonia
 Katarina Dirjanska, Skopje, North Macedonia
 Kristina Mitikj, Skopje, North Macedonia
 Lidija Popovska, Skopje, North Macedonia
 Ljuben Guguvcevski, Skopje, North Macedonia
 Marija Peeva Petreska, Skopje, North Macedonia
 Marija Stevanovikj, Skopje, North Macedonia
 Marina Eftimoska, Skopje, North Macedonia
 Marina Kacarska, Skopje, North Macedonia
 Meri Pavleska, Skopje, North Macedonia
 Mira Jankulovska, Skopje, North Macedonia
 Mirjana Popovska, Skopje, North Macedonia
 Natasa Toseska Spasova, Skopje, North Macedonia
 Nikola Gigovski, Skopje, North Macedonia
 Oliver Dimitrovski, Skopje, North Macedonia
 Sanja Pancevska, Skopje, North Macedonia
 Saso Elencevski, Skopje, North Macedonia
 Snezana Pesevska, Skopje, North Macedonia
 Stevica Ristoska, Skopje, North Macedonia
 Suzana Dvojakovska, Skopje, North Macedonia
 Cvetanka Bajraktarova Misevska, Skopje, North Macedonia

Препораки при планирањето и спроведувањето на протетички третман кај пациенти во детска возраст. <i>Бајраќијарова Валјакова Е., Коруноска Сџевковска В., Соџировска Ивковска А., Бајраќијарова Мисевска Ц., Еленчевски С., Георѓиева С., Ивановски К.</i>	85
Билатерално отекување на големите саливарни жлезди како иницијален симптом кај акутна миелоидна леукемија. <i>Пойовски В., Бенедети А., Сџамаџоски А., Конески Ф.</i>	89
Преваленца на орална кандидијаза кај носители на тотални протези. <i>Тмава-Драѓуша А., Шала К., Ивановски К., Дирјанска К., Ристоска С., Еленчевски С.</i>	94
Хијалуронска киселина-ветувачки медијатор за пародонтална регенерација. <i>Тошевска С., Пандилова М., Реџеј Е., Јанев Е., Миндова С., Горѓиева-Триевски Д., Ангеловски Б., Омеров Е.</i>	100
Коронектомија - алтернативен пристап на хируршка екстракција на длабоко импактирани мандибуларни трети молари - приказ на случај. <i>Каџарска М.</i>	110
Torus palatinus: клинички аспекти и терапевтска стратегија. <i>Каџарска М.</i>	117
Орална рехабилитација на дете со хипохидротична ектодермална дисплазија: шест годишно следење и третман. <i>Бајраќијарова Ваљакова Е., Јовановска М., Тофоски Г., Бајраќијарова Мисевска Ц., Панчевска С., Мијоска А., Коруноска Сџевковска В.</i>	123

Македонски стоматолошки преглед го издава Стоматолошкиот факултет при Универзитетот „Св. Кирил и Методиј“ Скопје, Република Северна Македонија и Македонското стоматолошко друштво.

Одговорен уредник: Проф. д-р **Киро Ивановски**, e-mail: kiroivanovski@stomfak.ukim.edu.mk

Заменик одговорен уредник: Проф. д-р **Елизабета Ѓоргиевска**, e-mail: egjorgievska@stomfak.ukim.edu.mk

Секретар на списанието: м-р **Влатко Коколански**, e-mail: vkokolanski@stomfak.ukim.edu.mk

Адреса - Македонски стоматолошки преглед, ул. Мајка Тереза бр. 43 Скопје, Република Северна Македонија

<http://stomfak.ukim.edu.mk/msp/>

Уредувачки одбор

Мира Јанкуловска, Скопје, Северна Македонија
Соња Апостолска, Скопје, Северна Македонија
Силвана Георѓиева, Скопје, Северна Македонија
Александар Ѓрчев, Скопје, Северна Македонија
Лидија Кануркова, Скопје, Северна Македонија
Маја Пандилова, Скопје, Северна Македонија
Весна Стевковска, Скопје, Северна Македонија
Борис Величковски, Скопје, Северна Македонија
Василка Ренцова, Скопје, Северна Македонија
Иван Алаѓеб, Загреб, Хрватска
Иван Анастасов, Софија, Бугарија
Никола Ангелов, Хјустон, САД
Гурхан Цаглајан, Хачетене, Турција
Домагој Главина, Загреб, Хрватска
Петер Јевникар, Љубљана, Словенија
Христо Кисов, Пловдив, Бугарија
Дарко Маџан, Загреб, Хрватска
Љубо Марион, Љубљана, Словенија
Џон Николсон, Лондон, В. Британија
Дарије Планчак, Загреб, Хрватска
Кристина Попова, Софија, Бугарија
Саша Станковиќ, Ниш, Србија
Драгослав Стаменковиќ, Белград, Србија
Зринка Тарле, Загреб, Хрватска
Љиљана Тихачек, Белград, Србија
Георѓи Томов, Пловдив, Бугарија
Радомир Угринов, Софија, Бугарија
Ана Ангелова Валони, Лондон, В. Британија
Васка Вандевска, Осло, Норвешка
Радосвета Васиљева, Софија, Бугарија
Мирослав Вукадиновиќ, Белград, Србија

Советодавен одбор

Алберто Бенедети, Скопје, Северна Македонија
Александар Димков, Скопје, Северна Македонија
Ана Сотировска Ивковска, Скопје, Северна Македонија

Анета Атанасовска Стојановска, Скопје, Северна Македонија
Антонио Кирков, Скопје, Северна Македонија
Билјана Капушевска, Скопје, Северна Македонија
Билјана Ципунова, Скопје, Северна Македонија
Вера Радојкова Николовска, Скопје, Северна Македонија
Владимир Поповски, Скопје, Северна Македонија
Габриела Курчиева Чучкова, Скопје, Северна Македонија
Горан Панчевски, Скопје, Северна Македонија
Гордана Ковачевска, Скопје, Северна Македонија
Даниела Велеска Стевковска, Скопје, Северна Македонија
Даница Поповиќ Монева, Скопје, Северна Македонија
Евдокија Јанкуловска, Скопје, Северна Македонија
Едвард Јанев, Скопје, Северна Македонија
Емилија Бајраќтарова Ваљакова, Скопје, Северна Македонија
Емилија Стефановска, Скопје, Северна Македонија
Златко Георѓиев, Скопје, Северна Македонија
Илијана Муратовска, Скопје, Северна Македонија
Јадранка Бундеска Јосифовска, Скопје, Северна Македонија
Јулијана Николовска, Скопје, Северна Македонија
Катарина Дирјанска, Скопје, Северна Македонија
Кристина Митиќ, Скопје, Северна Македонија
Лидија Поповска, Скопје, Северна Македонија
Љубен Гугувчевски, Скопје, Северна Македонија
Марија Пеева Петреска, Скопје, Северна Македонија
Марија Стевановиќ, Скопје, Северна Македонија
Марина Ефтимоска, Скопје, Северна Македонија
Марина Каџарска, Скопје, Северна Македонија
Мери Павлеска, Скопје, Северна Македонија
Мира Јанкуловска, Скопје, Северна Македонија
Мирјана Поповска, Скопје, Северна Македонија
Наташа Тошеска Спасова, Скопје, Северна Македонија
Никола Гиговски, Скопје, Северна Македонија
Оливер Димитровски, Скопје, Северна Македонија
Сања Панчевска, Скопје, Северна Македонија
Сашо Еленчевски, Скопје, Северна Македонија
Снежана Пешевска, Скопје, Северна Македонија
Стевица Ристоска, Скопје, Северна Македонија
Сузана Двојакоска Божовиќ, Скопје, Северна Македонија
Цветанка Бајраќтарова Мишевска, Скопје, Северна Македонија

*Letter to the editor***TIPS AND ADVICES WHEN PLANNING AND CONDUCTING THE PROSTHODONTIC TREATMENT IN PEDIATRIC PATIENTS****ПРЕПОРАКИ ПРИ ПЛАНИРАЊЕТО И СПРОВЕДУВАЊЕТО НА ПРОТЕТИЧКИ ТРЕТМАН КАЈ ПАЦИЕНТИ ВО ДЕТСКА ВОЗРАСТ**

Bajraktarova Valjakova E.^{1*}, Korunoska Stevkovska V.¹, Sotirovska Ivkovska A.², Bajraktarova Misevska C.³, Elenchevski S.¹, Georgieva S.⁴, Ivanovski K.⁴

¹Department of Prosthodontics, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, University Dental Clinical Center "St. Panteleimon", Skopje, ²Department of Pediatric and Preventive Dentistry, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, University Dental Clinical Center "St. Panteleimon", Skopje, ³Department of Orthodontics, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, University Dental Clinical Center "St. PanteleimonPanteleimon", Skopje, ⁴Department of Oral and Periodontal Diseases, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, University Dental Clinical Center "St. Panteleimon", Skopje

Respected Editor, respected colleagues,

Sometimes during the practice, the specialist for prosthodontics has a patient who is a child. There are several reasons for prosthetic treatment at this age group such as loss of a large amount of tooth substance or tooth extraction due to trauma or inadequate maintenance of oral hygiene, both in children with normal development and in those with developmental disabilities. Children with hypodontia or developmental anomalies of the teeth, and children with syndromes in whom the agenesis of some teeth is one of the symptoms are our patients as well. Considering the challenges we encounter when planning and implementing therapy in the youngest patients, in cooperation with colleagues from other specialties, the idea to share the gained experiences with you was imposed. We hope that the following tips and short advices will help you in providing prosthetic therapy in patients whose smile brings the greatest joy.

Почитуван уредник, почитувани колеги,

Во текот на работниот стаж на специјалистот по стоматолошка протетика, не ретко се случува пациентот да биде дете. Причини за протетички третман кај пациентите од оваа возрастна популација можат да бидат губење на голема количина на забна супстанца или предвремена екстракција на забите поради траума или несоодветно одржување на орална хигиена, како кај деца со нормален развој, така и кај оние со попреченост во развојот. Честопати наши пациенти се и деца со хиподонција или развојни аномалии на забите, како и оние со различни синдроми, кај кои агенезата на некои заби е една од карактеристиките. Тргувајќи од предизвиците со кои се среќаваме при планирањето и спроведувањето на терапијата кај најмладите пациенти, а во консултација со колегите од другите специјалности, се наметна идејата стекнатите искуства да ги споделиме со вас. Се надеваме дека овие кратки совети ќе ви помогнат при спроведувањето на протетичката терапија кај пациентите чија насмевка најмногу радува.

Tips and advices when planning and conducting the prosthodontic treatment in pediatric patients**Communication:**

1. Establish a friendly relationship with the pediatric patient based on mutual respect, trust, and love;

2. However, maintain your authority.
3. Assess the child's character and communicate accordingly.
4. Children's age, maturity, and developmental level matter!
 - with little children, try to be silly;
 - with school-age kids, find some common ground, like a cartoon character or TV show;

- when treating teenagers, you should talk with them with the same respect as with an adult person.
5. If they find you intimidating, remove the white coat and take a few steps back¹;
 6. Try to get close later on.
 7. Adjust the way you communicate, using terms the child will understand.
 8. When having an appointment with a pediatric patient, be positive, patient, and smile.

Planning the prosthodontics treatment:

1. Talk about the dental status with the child and explain the aim of the therapy, as follows:
 - what kind of prosthetic appliance should be manufactured,
 - the functions of the orofacial system which will be established.
2. Emphasize the aesthetic aspect of the appliance!
3. Explain the therapeutic procedures (without going into unnecessary details) and most of the materials you will use.
4. Be honest with the patient about the possible pain or other uncomfortable sensations that may occur during the therapy.

Appointment schedule and recommendations:

1. Assess the health status of the child for each appointment separately:
 - the patient needs to be in optimal health condition,
 - without symptoms of any acute and/or infectious diseases,
 - with passable upper respiratory tract,
 - without gastrointestinal disorders.
2. If there are two pediatric patients with the same or similar dental status requiring the same type of prosthetic appliance, do all the procedures on the older child first, in front of the younger child (you should gain a permission from the parents first).
3. Schedule the appointment in the morning, when the child is most rested, after a peaceful night with quality sleep².
4. The child should not have breakfast before the therapeutic phases in which the posterior parts of the oral cavity might be irritated (e.g. taking pre-

liminary or functional impressions).

5. Having an easily digestible meal is recommended before starting with all other treatment procedures.

Therapeutic procedure:

1. The therapeutic procedures should be carried out quickly, but carefully.
2. In cases when the procedure takes a longer period, and the child loses its attention and patience, give the child a short break or divide the procedure into two appointments (as long as it does not affect the quality of the prosthetic appliance).
3. If it is safe, allow the child to touch the instruments and materials you will work with.
4. Allow the child to choose the material you will use (e.g. the color of the impression material), but only if it does not disrupt the final quality of the prostheses.
5. Choose the materials that are most suitable for children²:
 - fast-setting irreversible hydrocolloid impression materials,
 - medium/high viscosity silicone impression materials,
 - thermoplastic materials that are optimally moldable when heated on a lower temperature.
6. Use a suitable technique while taking an impression to complete the procedure easier and safer:
 - select an impression tray according to the dental arch size;
 - fill the tray with an optimal amount of impression material, up to the tray borders;
 - put pressure over the posterior part of the tray, and after that over the frontal part, so the excess of the impression material, could flow in the vestibulum, not pharyngeal.
7. When making mobile dentures, just before taking the functional impressions, show all the movements with the lips, cheeks, and tongue to the child and ask him/her to imitate; practice the movements several times with an empty tray in the mouth only. During the impression-taking procedure, continue to show the required facial muscles' movements.
8. Verbally praise and symbolically reward the child at the end of each appointment, for his/hers patience and successfully completed working phase.

Pay attention please:

I. When making crowns³:

1. Crowns may be made for children of all ages.
2. However, if you are making a crown on the second primary molar:
 - pay attention to the convexity of the distal surface;
 - the artificial crown must not interfere with the normal eruption of the first permanent molar!
3. When preparing immature permanent teeth, remove as minimal of the tooth substance as possible to preserve the pulp vitality⁴ as:
 - the coronary pulp is voluminous,
 - the dentin canals are wide.

II. When making a dental bridge:

1. You may plan a dental bridge as a treatment of choice, after complete development of the jaws.
2. You are allowed to make a dental bridge at a younger age (not before 8 years of age), only if it is located in the frontal part of the mandible!
3. Conduct supragingival or paragingival tooth preparation in the cervical region.
4. Choose a veneering material or metal that will cause minimal attrition of the occlusal surfaces of the antagonistic teeth⁵.
5. Fixed prosthetic restorations should be luted on the supporting teeth with the glass ionomer luting cement, not with zinc phosphate cement.

After making the prosthetic appliance:

1. Show the child how to maintain the hygiene of the prosthetic appliance.

2. Teach the child how to take care of the longevity of the dentures.
3. Give instructions regarding the diet, the way of eating.
4. Monitor the child's adaptation to prosthetic appliances, and do everything in your power to make the adaptation period easier and faster.
5. Make timely corrections to prevent mucosal changes accompanied by pain (pressure ulcers).
6. During the night, the dentures should not be worn. Persuade the child to remove the prostheses to allow normal jaws' development, and to prevent the appearance of oral mucositis and palatal papillomatosis (papillary hyperplasia).
7. Schedule regular check-ups and make adjustments to enable eruption of the permanent teeth and to monitor jaws' growth and development.
8. Plan the manufacturing of new mobile prosthetic appliances after the phases of intensive child's body growth and development.

Reference

1. <https://medschool.ucla.edu/body.cfm?id=1158&action=detail&ref=806>
2. Bajraktarova Valjakova E, Miševska C, Korunoska Stevkovska V, Gigovski N, Sotirovska Ivkovska A, Bajraktarova B, Guguvcevski Lj. Prosthodontic management of Hypohidrotic Ectodermal Dysplasia: A case report. South Eur J Orthod Dentofac Res. 2015; 2(2):20-6.
3. Innes NP, Ricketts D, Chong LY, Keightley AJ, Lamont T, Santamaria RM. Performed crowns for decayed primary molar teeth. Cochrane Database Syst Rev. 2015(12):CD005512. DOI: 10.1002/14651858.cd005512.pub3.
4. Vulićević Z, Beloica M, Kosanović D, Radović I, Juloski J, Ivanović D. Prosthetics in Paediatric Dentistry. Balk J Dent Med. 2017;21:78-82.
5. Choi JW, Bae IH, Noh TH, Ju SW, Lee TK, Ahn JS, Jeong TS, Huh JB. Wear of primary teeth caused by opposed all-ceramic or stainless steel crowns. J Adv Prosthodont. 2016;8(1):43-52.

BILATERAL ENLARGEMENT OF MAJOR SALIVARY GLANDS AS AN INITIAL SIGN OF ACUTE MYELOID LEUKEMIA: CASE REPORT

БИЛАТЕРАЛНО ОТЕКУВАЊЕ НА ГОЛЕМИТЕ САЛИВАРНИ ЖЛЕЗДИ КАКО ИНИЦИЈАЛЕН СИМПТОМ КАЈ АКУТНА МИЕЛОИДНА ЛЕУКЕМИЈА

Popovski V.¹, Benedeti A.², Stamatovski A.³, Koneski F.⁴

¹University Clinic for Maxillofacial Surgery, ²Ss. Cyril and Methodius University in Skopje, ³Faculty of Dentistry, ⁴Department of Maxillofacial Surgery

Abstract

There is a wide spectrum of causes of bilateral enlargement of submandibular and parotid salivary glands. Usually, these enlargements may be due to viral, metabolic, systemic or medication nature. Part of these pathologic conditions may be easily diagnosed based on the clinical presentation and thorough anamnesis. The non-differentiated bilateral enlargements may be a huge challenge for the diagnostic process, where a deep knowledge of the possible etiology for such condition is required, as well as physician experience and aptitude for differential diagnostics. This case report is about the bilateral enlargement of submandibular and parotid glands, as initial sign in acute myeloid leukemia (AML). **Keywords:** salivary glands, acute myeloid leukemia, non-Hodgkin lymphoma, leukemia.

Апстракт

Постои широк спектар на причини за билатерално зголемување на субмандибуларните, односно на паротидните саливарни жлезди. Најчесто овие отекувања може да бидат од вирусна, метаболичка, системска или медикаментозна природа. Дел од ваквите патолошки состојби можат лесно да се дијагностицираат преку клиничка слика и добра анамнеза, додека за неиздиференцираните билатерални отекувања, поставувањето на дефинитивна дијагноза е голем предизвик и бара познавање на сета можна етиологија која би можела да доведе до ваква состојба, како и поседување на искуство и вештина на терапевтот во диференцијалната дијагностика. Овој приказ на случај се однесува на билатерално зголемување на субмандибуларните, односно паротидни жлезди, како иницијален знак за акутна миелоидна леукемија (АМЛ). **Клучни зборови:** саливарни жлезди, акутна миелоидна леукемија, нон-Хоџкин лимфом, леукемија.

Introduction

Acute myeloid leukemia (AML) in general is a disease that occurs in older-age patients; AML rarely appears in patients under the age of 4. The mean age of patients who suffer from this disease is 63. Although there is no known precise etiology, there are cases of AML occurring after radiotherapy, exposure to some chemical (genotoxic) factors or medication treatment (especially if it is associated with an existing hematological disease). In the basis of the pathogenesis of this disease lays malignant transformation of multipotent, hematopoietic stem cells, due to genomic alterations (mutations of genes and chromosomal inversions, as well as translocations). An enlargement of parotid and submandibular glands, with no other clinical symptoms,

is a rarity in the initial manifestation of AML. The physician should be prepared for this unusual presentation of the disease, because any postponement of the diagnostic process may be fatal. The aim of this case report is to emphasize the importance of correct and timely diagnostics of AML in a patient with unusual initial presentation.

Case report

A female 26-year-old patient, a physician, was referred to the Clinic for Maxillofacial Surgery in Skopje in September 2016, with bilateral enlargement of submandibular glands, which were painless and soft on palpation. The enlargement had persisted for 8 days. On the first examination she provided an already done ultra-

sonographic analysis, which was in favor of infective mononucleosis with enlarged lymph nodes bilaterally, in the submandibular area. Routine laboratory analyses were performed, a complete blood analysis and differential blood analysis, including CRP and sedimentation. They were in normal range (WBC : $6.9 \times 10^9/L$, RBC: $4.29 \times 10^{12}/L$ PLT $269 \times 10^9/L$). Serum analysis was also performed, for a potential virus infection (CMV, MUMPSs and EBV), all with negative outcome. In the peripheral blood smear analysis, the percentage of lymphocytes were 59,3% (22-35%). Non-segmented neutrophils were found to be 3,3% (2-5%), segmented 28,6% (58-68%) and monocytes 8,8% (4-8%). The patient was referred to the Clinic for Hematology, where she was advised to perform a fine-needle aspiration biopsy (FNAB) of the submandibular glands. The cytological analysis revealed a chronic inflammation, i.e. hyperplastic ductal epithelium, with no cytological atypia. She had been treated with proteolytic enzyme in the form of a supplement (Serrapeptase) and cephalosporine antibiotics – cefixime (Pancef), then with ciprofloxacin (Citeral), along with anti-swelling treatment (Chymoral forte). Two weeks later, the patient complained about strong pain in the submandibular area, and increased body temperature of $38^\circ C$ (intermittent, every 3-4 days). At the same time, the submandibular glands started to become palpable, on the right side with a dimension of a walnut, and on the left side with a dimension of an egg, tender and slightly painful. No other lymph nodes were palpable in the neck area. Following worsening of the symptoms, 50 days after the onset, the patient was hospitalized in the Clinic for maxillofacial surgery for a period of 6 days. Antibiotic and antiphlogistic treatment was given. The blood test results were within the normal ranges and did not correspond with the clinical presentation (WBC: $4.0 \times 10^9/L$, RBC : $5.39 \times 10^{12}/L$, PLT $180 \times 10^9 /L$). A stroboscopic examination was performed at the Clinic for otorhinolaryngology, with a normal appearance of the larynx (oropharyngoscopically the left tonsil was with cripts and detritus). Serologic tests were performed for a possible tularemia – with a negative finding. The findings from the Clinic for rheumatology were also negative and did not indicate a presence of lymphoepithelial lesion of the salivary glands (Sy, Sjogren, M. Mikulicz). HBsAgQ2 and Anti-HCV were also negative, after which she was referred to perform an MRI. The radiology report was as follows: in the projection of the left submandibular gland there is an encapsulated change with a dimension of 28x21 mm, with a signal in favor of a hemorrhage. This change might have been an inflammatory haematoma in phase of organization, taking into consideration the pointed inflammatory reaction of the surrounding deep fat tissue

in the submandibular area, as well as the presence of an increased number of reactive lymph nodes in the region. A smaller haematoma was observed in the right submandibular gland, with dimensions of 25x11 mm, with no presence of pathologically colored capsule. Both parotid and thyroid glands were with normal appearance. On the 51st day of the onset of symptoms, the serologic analysis revealed a positive value for EBV: (EBNA)IgM 0,57 (grey zone). The examination performed at the Institute for lung diseases and tuberculosis ruled out tuberculosis as a possible cause for the condition. After 3,5 months of the onset of symptoms, both parotid glands got enlarged. A serologic test for EBV presence was again performed, with negative values, but with present leukocytosis: Le $13.00 \times 10^9/L$ (4.0-11.0), [Lymf 48.80% (25-40 %) and Mon 34.40 % (3.0-7.0 %)]. Because of the bilateral enlargement of parotid glands, the patients was again referred to the Clinic for rheumatology, where all test results were negative. Two days after the confirmed leukocytosis, in the axillary area, a palpable painless lymph node was observed, associated with subjective feeling of excessive sweating. Tests were performed at the Clinic for infective diseases and febrile conditions with ELFA, and a positive value for EBV IgM-1,0 was found, with increasing value five days later (EBV IgM: 1,53). Four months after the onset of symptoms, a sternal puncture was performed and the following results were found: 88% of the cells were CD45, plus mononuclear cells with the following immunophenotype (Table 1):

Table 1. Results obtained from the sterna puncture biopsy.

Myeloid markers	Lymphoid markers	Rest
CD13 18,3 %	CD2 neg.	CD34 38,8 %
CD33 99%	CD7 29,1%	HLA-OR neg.
CD14 neg.	CD19 neg.	CD117 44,3 %
CD15 neg.	CD79a neg.	CD79a neg.
MPO 14,3 %	CD10 neg.	CD79a neg.
TcT neg., CD22 neg.		

The test results were in favor of AML with aberrant expression of CD7. At the same time, the EBV test was again performed, and it was negative (0,77). The control blood analysis revealed values for WBC of $34,6 \times 10^9/L$.

Blood analysis was regularly performed in the following two days. Leukocytosis was twice observed ($30,94 \times 10^9 / L$ and $36,99 \times 10^9 / L$). Five months after the onset of symptoms, a smear from a salivary gland was taken, with negative result. The comparative MRI revealed a reduction of the haematomas in both submandibular glands, which were almost completely resolved (there was a leftover of 10 mm). Both submandibular and parotid glands were enlarged, with homogenous appearance, edematous, with a restriction of the diffusion – a finding that indicates a persistent sialoadenitis. Focal pathological lesions were not observed, nor intraparenchymic, and locoregional pathologically changed lymph nodes. The major salivary glands' ducts were not dilated. There was a bilaterally present mastoiditis and otitis media with diffuse sinusitis, a finding that was not observed at the first examination. A blood test was again performed, and it alarmed about increased leucocytosis of $35,22 \times 10^9 / L$.

In February 2017, a pathological finding of the 2-cm bony part from iliac crest was obtained. The sections were stained with HE, Gimsa and immunohistochemistry for: CD20, CD3, CD10, CD235, Tdt, CD34, CD117, Myeloperoxidase, Neutrophil elastase, CD68, MAC 387 and CD15. Positive results were obtained for: CD235 (erythroid precursors 30-40%), CD34 (5-10%, with dispersed, interstitial arrangement), Myeloperoxidase (10%), CD68 (myeloid-histiocyte precursors 30-40%). The final conclusion from the pathology and immunohistochemistry was that, taking into consideration the immaturity of part of the cell population, with no signs of maturation and negative expression for CD20, CD3, CD1 and Tdt (positive CD34, myeloperoxidase, CD68 and CD235), and with ruled out lymphoid proliferation, as well as in accordance with the clinical picture, it was recommended to evaluate a possible AML. The analysis of mutation of genes NPM1, FLT3 and CEBPA (otherwise present in AML) showed negative results and no gene mutations were observed. The sternal puncture aspirate was in favor of acute leukemia, with high infiltration with blasts of 60-70%. The patient was then hospitalized at the Clinic for hematology, from February 10, 2017 to March 03, 2017. Chemotherapy was administered by protocol and transfusion: Tr mass 34 doses, Er 4 doses. The control sternal aspiration biopsy showed around 15% blasts. The patient was again hospitalized from March 13, 2017 to April 06, 2017, when a treatment according to FLAG-IDA protocol was given.

After the treatment, the bilateral enlargement of the parotid glands was completely resolved and the disease entered into a phase of remission. Her older sister was found to be HLA-DNA identical, after which a bone marrow transplantation was performed, with uneventful post-transplantation follow-up.

Discussion

There are several conditions whose clinical picture is characterized by bilateral enlargement of the salivary glands. Often there are two or more causes which present with a similar clinical picture, which may be challenging for the physician, and it might lead in the wrong direction while setting the final diagnosis. In our case, we did a "step by step" process of diagnosis, by ruling out sialectasis, as well as bacterial, medication-induced, immunological, congenital and tumor etiology of the bilateral enlargement of the salivary glands. What drew our attention the most, was the discontinuity of the results from serology analysis for EBV and the suspicion of possible lymphoproliferative malignant pathology. We received the first concrete result from the serologic analysis for EBV 3,5 months after the onset of symptoms, which was later confirmed twice, although always with different values, varying from "grey zone" to a positive result. However, the last serologic finding for EBV was negative. Infection with EBV usually occurs in early childhood, after which the virus remains to persist in a low number of B cells. EBV attacks B-lymphocytes, bonding to CD21 receptor and causing latent infection in vivo and in vitro¹. There is a wide spectrum of LPD (lymphoproliferative diseases) which are related to EBV and which occur in patients with primary immunodeficiency, in patients with AIDS or with iatrogenic post-transplantation immunosuppression, as well as in those who undergo other types of treatment, like methotrexate and tumor necrosis factor (TNF) alpha antagonists treatment. Recently it was proved that the presence of EBV might lead to the occurrence of EBV-positive LPDs in adult patients who do not show signs of immunodeficiency at all².

Co-infection with EBV may appear in Morbus Hodgkin, large cell lymphoma, and lymphoma in AIDS^{3,6}, but also in chronic lymphocytic leukemia in childhood⁷. Shlehofer et al.⁸ documented an increased number of EBV-VCA (viral capsid antigen) in a study performed on 121 children with ALL in Germany, without PCR test. The patients with EBV have been shown to have a higher frequency of relapses of the disease and mortality, compared with those who have EBV-ALL. Infection with EBV in patients with acute leukemia is more frequent in B-cells ALL, compared to T-cells ALL. EBV-positive patients show a worse prognosis compared to others. However, the recent literature points out the controversy of the role of EBV in leukemia in childhood^{9,10}. In literature, the association between LPDs and EBV infection in adults is mostly seen. In our case, the patient was 26-year old, with no history of lymphoproliferative disease. Lymphadenopathy of the head and neck may be

the result of lymphoma¹¹. Lymphomas of the salivary glands are very rare and mainly arise from B-cells¹². The extranodal lymphomas are mostly Non-Hodgkin (NHL) and represent 10-20% of all lymphomas¹³. Non-Hodgkin lymphoma of a salivary gland usually presents as a painless mass that progresses quickly and increases in dimensions¹⁴⁻¹⁷. MALT lymphomas are most common among NHL of the major salivary glands. Low-grade MALT lymphoma of the parotid gland is usually a result of BLL (benign lymphoepithelial lesion)¹⁸. The transformation of BLL into MALT lymphoma is thought to be a “multistep” process. The initiation might be a long-lasting stimulation (activation) of B-cells by an inflammatory stimulus¹⁹. According to Rosenstiel et al.²⁰, in patients with Sjogren syndrome, the risk of non-Hodgkin is increased 44 times and 80% of those lymphomas are so-called MALT subtypes. According to Anacak et al.²¹, MALT lymphomas of the salivary glands are more common in females. In their study the female:male ratio was 3:1. The cause of female predominance is unknown. In our case, all results from the examinations performed at the Clinic for rheumatology were negative (even when repeated). The bilateral enlargement of the salivary glands was limited (with no progression in dimensions since the initial examination), but they had become painful on palpation with time. Granulocytic sarcoma, or so-called myeloid sarcoma (MS) or “Chloroma” is a rare extramedullary neoplasm, which consists of mature and immature granulocytes or monocytes. It is extremely rare to occur MS in patients with no previous history of myeloid neoplasm. It is present in 2,5%-9,1% of patients with AML and five times less in patients with chronic myelogenous leukemia. It occurs equally in males and females, and 60% of the patients are younger than 15. The number of cases with MS immediately after transplantation with allogeneic stem cells is higher, and some authors suggest that MS is in fact a consequence of “graft versus leukemia” effect, that develops extramedullary²². MS also occurs in patients with AML and proven (8:21) cytogenetic abnormality (translocation) i.e. in AML with maturation (M2) according to FAB classification. After the fine needle biopsy of four cases with MS of the salivary glands, the cytological evaluation showed spread acini of salivary gland, mixed with dispersed atypical cells. The atypical cells were heterogeneous, medium and large in size, with wrinkled nucleolus with fine chromatin. In one case the cells showed homogeneity, with rounded nucleoli and fine chromatin²³. In our case, the fine needle aspiration biopsy showed hyperplasia of the ductal epithelium, with no cellular atypia.

Conclusion

The course of the diagnostics and treatment in the case reported in this study lead to a conclusion that there is no disease with whatever “benign” clinical presentation of longer enlargement of major salivary glands, which should not be underestimated. It should always be approached seriously and with no compromises. In our case, the initial impression of infective mononucleosis eventually led to a final diagnosis of AML. Bilateral enlargement of the major salivary glands is very rarely an initial symptom of AML, but the serious approach in line with interdisciplinarity allowed timely initiated and successfully performed treatment with long term remission of the disease.

Conflicts of interest

All authors confirm that there is no conflict of interest regarding this manuscript.

Reference

1. Hopwood PA, Thomas JA, Dorothy H. Crawford (2002). Expansion in scid mice of Epstein-Barr virus-associated post-transplantation lymphoproliferative disease biopsy material. *J Gen Virol* 1: 173-178.
2. Guan, Hongzai; Miao, Hongxia; Ma, Na; Lu, Wei; Luo, Bing. Correlation between Epstein-Barr virus and acute leukemia, *Journal of Medical Virology*, Vol. 9, Number 8, 1 August 2017, pp.1453-1460(8).
3. Jarrett RF. Risk factors for Hodgkin's lymphoma by EBV status and significance of detection of EBV genomes in serum of patients with EBV-associated Hodgkin's lymphoma. *Leuk Lymphoma* 2003;44:S27-32.
4. Anagnostopoulos I, Herbst H, Niedobitek G, Stein H. Demonstration of monoclonal EBV genome in Hodgkin's disease and KI-1 positive anaplastic large cell lymphoma by combined Southern blot and in situ hybridization. *Blood* 1989;74:810-6.
5. MacMahon EM, Glass JD, Hayward SD, Mann RB, Becker PS, Charache P, et al. Epstein Barr virus in AIDS related primary central nervous system lymphoma. *Lancet* 1991;338:969-73.
6. Pedersen C, Gerstoft J, Lundgren JD, Skinhøj P, Böttzauw J, Geisler C, et al. HIV associated lymphomas; histopathology and association with EBV genome: relation to clinical, immunological and prognostic features. *Eur J Cancer* 1991;27:1416-23.
7. Laytragoon-Lewin N, Chen F, Avila-Carino J, Zou JZ, Mellstedt H, Ernberg L et al. Epstein Barr virus (EBV) carrying cells of chronic lymphatic leukemia (CLL) subpopulation express EBNA 1 and LMPs but not ENBA2 in vivo. *Int J of Cancer* 1995;63:486-90.
8. Schlehofer B, Blettner M, Geletnek K, Haaf HG, Kaatsch P, Michaelis J et al. Sero-epidemiological analysis of the risk of virus infections for childhood leukemia. *Int J of Cancer* 1996;65:584-90.
9. Lehtinen M, Koskela P, Ogmundsdottir HM, Bloigu A, Dillner J, Gudnadottir M, et al. Maternal Herpes virus infection and risk of Acute Lymphoblastic Leukemia in the offspring. *Am J Epidemiol* 2003;158:207-13.
10. Loutfy SA, Alam El-Din HM, Ibrahim MF, Hafez MM. Herpes simplex type 1 and 2, Epstein Barr virus and cytomegalovirus in

-
- children with acute lymphoblastic leukemia in Egypt. *Saudi Med J* 2006;27:1139-45.
11. Urquhart A, Berg R. Hodgkin's and non-Hodgkin's lymphoma of the head and neck. *Laryngoscope*. 2001;111:1565-1569.
 12. Nadendla LK, Meduri V, Paramkusam G. Imaging characteristics of diffuse large cell extra nodal non-Hodgkin's lymphoma involving the palate and maxillary sinus: a case report. *Imaging Sci Dent*. 2012;42:111-114.
 13. Van der Waal RI, Huijgens PC, van der Valk P, van der Waal I. Characteristics of 40 primary extranodal non-Hodgkin lymphomas of the oral cavity in perspective of the new WHO classification and the International Prognostic Index. *Int J Oral Maxillofac Surg*. 2005;34:391-395.
 14. Gleeson MJ, Bennett MH, Cawson RA. Lymphomas of the salivary glands. *Cancer*. 1986;58:699-704. doi: 10.1002/1097-0142(19860801)58:3<699::AID-CNCR2820580317>3.0.CO;2-E.
 15. Hyman GA, Wolff M. Malignant lymphomas of the salivary glands. Review of the literature and report of 33 new cases, including four cases associated with the lymphoepithelial lesion. *Am J Clin Pathol*. 1976;65:421-438.
 16. Mehle ME, Kraus DH, Wood BG. et al. Lymphoma of the parotid glands. *Laryngoscope*. 1993;103:17-21.
 17. Schusterman MA, Granick MS, Erickson ER. et al. Lymphoma presenting as a salivary gland mass. *Head and Neck Surg*. 1988;10:411-415. doi: 10.1002/hed.2890100609.
 18. Diss TC, Wothersoon AC, Speight P. et al. B-cell monoclonality, Epstein Barr Virus, and t (14;18) in myoepithelial sialadenitis and low-grade B-cell MALT lymphoma of the parotid gland. *Am J Surg Pathol*. 1995;19(5):531-536. doi: 10.1097/00000478-199505000-00004.
 19. Marioni G, Marchese-Ragona R, Marino F. et al. MALT-type lymphoma and Warthin's tumour presenting in the same parotid gland. *Acta Otolaryngol*. 2004;124(3):318-323. doi: 10.1080/00016480310015263.
 20. Kalpadakis C, Pangalis GA, Vassilakopoulos TP. et al. Non-gastric extra-nodal marginal zone lymphomas: A single centre experience on 76 patients. *Leuk Lymphoma*. 2008;49:2308-2315. doi: 10.1080/10428190802510331.
 21. Anacak Y, Miller RC, Constantinou N, Mamusa AM, Epelbaum R, Li Y, Calduch AL, Kowalczyk A, Weber DC, Kadish SP, Bese N, Poortmans P, Kamer S, Ozsahin M. Primary Mucosa-Associated Lymphoid Tissue Lymphoma of the Salivary Glands: A Multicenter Rare Cancer Network Study. *Int J Radiat Oncol Biol Phys*. 2010. in press .
 22. Singhal S, Powles R, Kulkarni S, et al. Long-term follow-up of relapsed acute leukemia treated with immunotherapy after allogeneic transplantation: the inseparability of graft-versus-host disease and graft-versus-leukemia, and the problem of extramedullary relapse. *Leuk Lymphoma* 1999; 32: 505-512.
 23. Cai G, Levine P, Sen F. Diagnosis of myeloid sarcoma involving salivary glands by fine-needle aspiration cytology and flow cytometry: report of four cases. *Diagn Cytopathol*. 2008 Feb;36(2):124-7.

PREVALENCE OF ORAL CANDIDIASIS IN COMPLETE DENTURES WEARERS

ПРЕВАЛЕНЦА НА ОРАЛНА КАНДИДИЈАЗА КАЈ НОСИТЕЛИ НА ТОТАЛНИ ПРОТЕЗИ

Tmava-Dragusha A.¹, Shala K.¹, Ivanovski K.², Dirjanska K.², Ristoska S.², Elenchevski S.³

¹Department of Prosthetic Dentistry, Faculty of Medicine, School of Dentistry, Prishtina, Kosovo, ²Department of Oral pathology and Periodontology, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, ³Department of Prosthetic Dentistry, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje

Abstract

Objective: As the population age is growing the need for oral prosthetic rehabilitation is increasing accordingly. Oral candidiasis is a common opportunistic infection of the oral cavity caused by an overgrowth of *Candida* spp., the commonest being *Candida albicans*. **Materials and Methods:** To obtain the set objectives, 50 patients (from the experimental group EG), complete denture wearers, were included and sampled at the University Dentistry Clinical Center of Kosovo, Prishtina. Also, we designate a control group of 50 patients, older than 50 years of age. Clinical changes in the oral mucosa were assessed using thorough intra/oral examination with the emphasis on the eventual oral mucosal changes in contact with dentures. In both experimental and control group patients' swabs were obtained for testing the presence of *Candida albicans*. In the experimental group of patients along with oral mucosal swabs, denture swabs were taken as well. **Results:** In our study the highest percentage was found for *Candida albicans* - 26.0%, followed by *Candida tropicalis* - 12.0%, and *Candida crusei* - 6.0%, of the cases. There was a correlation between denture wearing and the occurrence of oral candidiasis. ($p < 0.05$) (Pearson Chi-square: 13.6364, $p = 0.00222$). While there was no correlation found between the duration of denture wearing and the occurrence of oral candidiasis. ($p > 0.05$) (Pearson Chi-square: 1.02339, $p = 0.311716$), however, there was a correlation noted between the years of denture wearing and the occurrence of *Candida* spp. on the patient denture base. **Conclusions:** The prevalence of Denture Stomatitis in complete denture wearers is high and no association with its risk factors was found. **Key words:** denture stomatitis, complete denture wearers, oral candidiasis, *Candida albicans*.

Апстракт

Цел на трудот: Како што се зголемува возраста на популацијата, соодветно се зголемува и потребата од орална протетска рехабилитација. Оралната кандидијаза е честа опортунистичка инфекција во усната празнина, којашто е предизвикана од прекумерен раст на *Candida* spp, од коишто најчесто станува збор за *Candida albicans*. **Материјали и Методи:** За да се постигнат поставените цели, 50 пациенти (од експерименталната група ЕГ), носители на тотални протези, беа вклучени и од нив беа земени примероци во Универзитетскиот Стоматолошки Клинички Центар во Косово, Приштина. Исто, оформивме контролна група од 50 пациенти, постари од 50 години. Клиничките промени на оралната мукоза беа оценети преку темелен интра/екстраорален преглед со акцентирање на евентуалните промени на мукозата којашто е во контакт со тоталната протеза. И во експерименталната и во контролната група, од пациентите беше земен брис за одредување на присуство на *Candida albicans*. Во експерименталната група на пациенти, покрај брисот од оралната мукоза, беше земен и брис од тоталната протеза. **Резултати:** Во нашето испитување, процентуално најголемо присуство беше одредено за *Candida albicans* – 26.0%, потоа *Candida tropicalis* – 12.0% и *Candida crusei* – 6.0% од случаите. Утврдивме корелација помеѓу носењето на тотална протеза и појавата на орална кандидијаза. ($p < 0.05$) (Pearson Chi-square: 13.6364, $p = 0.00222$). Не утврдивме корелација помеѓу времето на носење на протезата и појавата на орална кандидијаза ($p > 0.05$) (Pearson Chi-square: 1.02339, $p = 0.311716$), но, забележавме корелација помеѓу годините на носење на тоталната протеза и појавата на *Candida* spp. на базата на тоталната протеза. **Заклучоци:** Преваленцата на протетскиот стоматитис кај носителите на тотални протези е висока и не е во асоцијација со неговите ризик-фактори. **Клучни зборови:** протетски стоматитис, носители на тотални протези, орална кандидијаза, *Candida albicans*.

Introduction

As the population age is growing the need for oral prosthetic rehabilitation is increasing accordingly¹. Although, the number of treatment options for dentate and edentulous patients is staggering both in number and techniques, not every member of that population can benefit from all of the options, mainly due to the finan-

cial constraints². One of the most common and optimal options, both clinically and financially, is resin-based complete denture³.

Oral fungal infection is a common disease in complete denture wearers. Oral candidiasis is a common opportunistic infection of the oral cavity caused by an overgrowth of *Candida* spp., the most common being *Candida albicans*⁴. *C. albicans* is a dimorphic yeast

strongly gram-positive able to live as a normal commensal organism in the oral cavity of healthy people of 45–65%, but in denture wearers, the prevalence of *Candida* increases to 60–100% which increases the risk of infection^{5, 6, 7}.

The etiology of denture stomatitis is multifactorial, with factors including trauma caused by ill-fitting dentures, increased age of the patient and of the dentures, lack of denture hygiene, and a favorable environment for proliferation for *Candida albicans* in particular^{8, 9, 10}.

Patients with candidiasis may report varied symptoms such as painful sensations, local discomfort, difficulty swallowing, a burning sensation in the oral cavity, or an alteration in taste, but such infections are most often asymptomatic¹¹.

Candida species are frequently isolated from the oral cavity in healthy individuals of all ages, and it is therefore difficult to differentiate oral candidiasis from the commensal state by microbiological detection of the *Candida* species in the oral cavity. Therefore, additional microbiological criteria are required to diagnose oral *Candida* infection correctly. Various methods can be used to isolate *Candida* from the oral cavity, including smears, plain swabs, imprint cultures, whole saliva collection, concentrated oral rinses, and mucosal biopsies^{12, 13}. Clinical studies have shown that *C. albicans* is not only able to adhere to the mucous surfaces, but also to stick to the acrylic resins of the dental prostheses, where both the plaque accumulated on the dentures and the poor oral hygiene contribute to the virulence of *Candida*, offering a clinical picture of *Candida*-associated denture stomatitis¹⁴.

The purpose of this study was to determine changes in the oral environment occurring in denture-wearers by recording:

- Clinical expression in oral mucosa in close contact with complete dentures.
- Microbiological findings.

Material and Methods

To obtain the set objectives, 50 patients (from the experimental group EG), complete-denture wearers, were included and sampled at the University Dentistry Clinical Center of Kosovo, Department of Prosthodontics, Pristina. Inclusion criteria were as follows:-

- Patients that have worn their dentures for at least one year.
- The dentures should have been fabricated at the laboratory of UDCK from the same technician under the most similar conditions for denture fabrication for all groups, and

- The patients should be older than 50 years.

Also, we designate a control group (CG) of 50 patients, older than 50 years, without removable prosthodontic restorations, that attend the University Dentistry Clinical Center of Kosovo, Pristina, for other reasons.

History was recorded in the experimental and control group including:

- Medical and Medication History,
- Duration of Denture Wearing (Experimental Group),
- Subjective issues related to their dentures.

Denture hygiene habits were recorded using special questionnaire developed by **Peracini et al.** (2010)¹⁵.

Clinical changes in the oral mucosa were assessed by means of thorough intra/extra-oral examination with emphasis on the eventual oral mucosal changes in contact with dentures. These examinations included the control group as well.

From clinical aspect, all patient with denture related stomatitis are classified into three clinical types (Newton classification):

Newton's type I: pin-point hyperemic lesions (localized simple inflammation)

Newton's type II: diffuse erythema confined to the mucosa contacting the denture (generalized simple inflammation)

Newton's type III: granular surface (inflammatory papillary hyperplasia).

In addition, the dentures' stability was assessed.

In both experimental and control group, patients' swabs were obtained for testing the presence of *Candida albicans*. In the experimental group of patients along with oral mucosal swabs, denture swabs were taken as well.

Microbiology analysis was conducted at the Institute of Public Health, Department of Microbiology, Pristina. Oral and palatal mucosal samples were taken.

Results

In patients from the CG there was no candida infections recorded.

Candida infections were recorded in 24.0% of the patients in the EG. *Candida crusei* and *Candida albicans* was simultaneously found in two patients (4.0%). *Candida albicans* alone was found in 20.0% of patients, evidently *Candida albicans* is found in 24.0% of total patients. (Table 1, Graph 1).

Table 1. Patient distribution by *Candida* – mouth variable

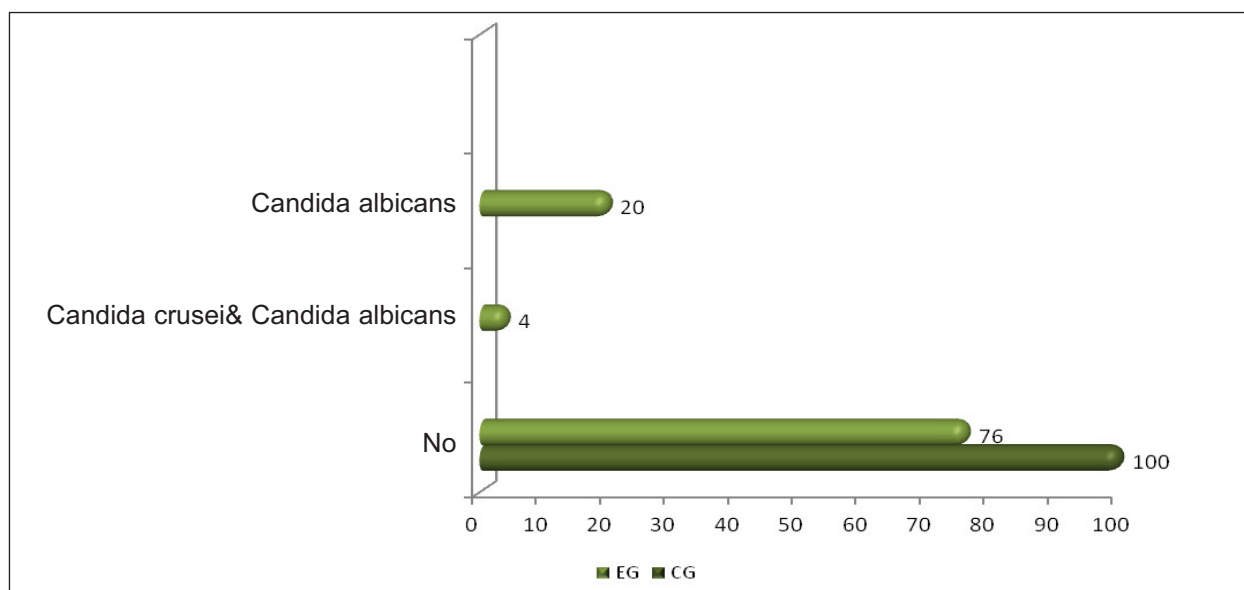
	CG		EG	
	Count	Percent	Count	Percent
No	50	100.0	38	76.0
<i>Candida crusei</i> & <i>Candida albicans</i>			2	4.0
<i>Candida albicans</i>			10	20.0
Total	50	100.0	50	100.0

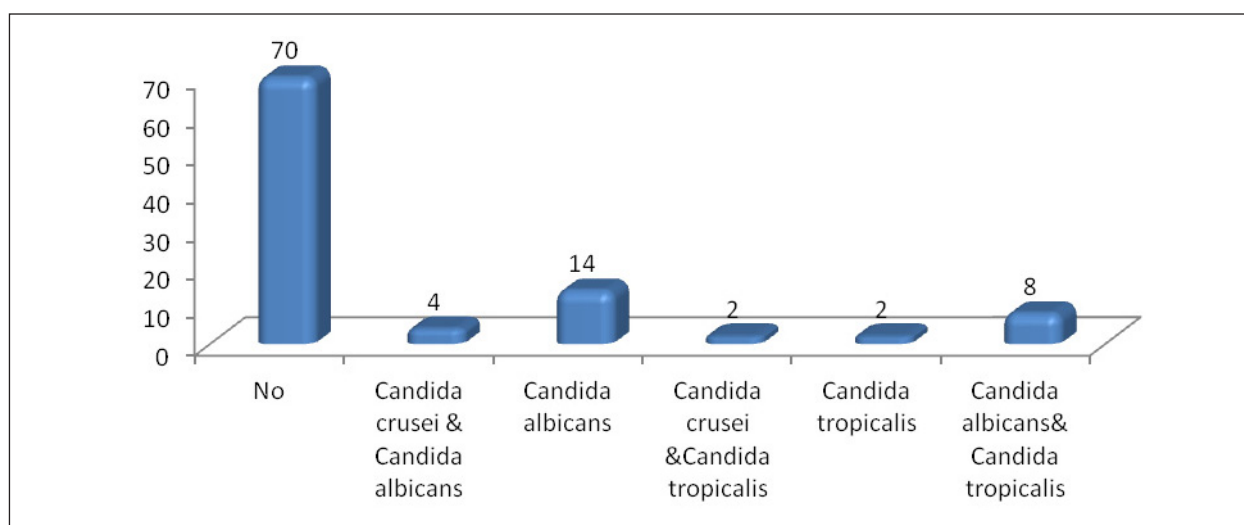
Table 2. Patient distribution by *Candida*-dentures variable in EG

	EG	
	Count	Percent
No	35	70.0
<i>Candida crusei</i> & <i>Candida albicans</i>	2	4.0
<i>Candida albicans</i>	7	14.0
<i>Candida crusei</i> & <i>Candida tropicalis</i>	1	2.0
<i>Candida tropicalis</i>	1	2.0
<i>Candida albicans</i> & <i>Candida tropicalis</i>	4	8.0
Total	50	100.0

In 30% of complete denture wearer patients, *Candida* spp. was isolated on the actual denture base. *Candida crusei* and *Candida albicans* were simultaneously found in two patients (4.0%). *Candida albicans* alone was found in 14.0% of the patients. *Candida crusei* and *Candida tropicalis* were simultaneously found in a single patient, (2.0%). *Candida tropicalis* alone was found in a single patient. *Candida albicans* and *Candida tropicalis* were simultaneously found in 8.0% of EG of patients (Table 2, Graph 2). In total, the highest percentage was found for *Candida albicans* - 26.0%, followed by *Candida tropicalis* - 12.0% and *Candida crusei* - 6.0%, of the cases.

There was a correlation between denture wearing and the occurrence of oral candidiasis. ($p < 0.05$) (Pearson Chi-square: 13.6364, $p = .000222$).

**Graph 1.** Patient distribution by *Candida* – mouth variable



Graph 2. Patient distribution by *Candida*-dentures variable in EG

During the study, there was no correlation found between the years of denture wearing and the occurrence of oral candidiasis. ($p > 0.05$) (Pearson Chi-square: 1.02339, $p = 0.311716$), however, there was a correlation noted between the years of denture wearing and the occurrence of *Candida* spp. on the patient denture base. ($p < 0.05$) (Pearson Chi-square: 13.7188, $p = 0.000212$). Similarly, a correlation between diabetes in denture-wearing patients and candida infections was confirmed. ($p < 0.05$) (Pearson Chi-square: 17.9107, $p = 0.000023$).

Discussion

The *Candida* species form the normal commensal fungi component, and its activity is regulated by many intrinsic and extrinsic factors. The pathogenic nature of *Candida* has been correlated with various systemic conditions, which in some manner affect the immunity of the patients¹⁶.

The *Candida* concentration associated with several clinical oral signs in the infected patients and may be closely related to the patient's current clinical status and prognosis¹⁷. In our research of patients from the CG there was no candida infections recorded. Our results agree with Al Tarawneh et al.¹⁸ who concluded that mucosal candidal counts and the presence of cytological hyphae did not show significant difference when comparing DS to healthy participants. Our results show that the highest percentage was found for *Candida albicans* in denture in EG patients (26.0%), followed by *Candida tropicalis* and *Candida crusei*, of the cases. Many authors have reported that *Candida albicans* is the most common species in denture users, making up 70% of all isolates¹⁹. Zomordian et

al.²⁰, investigated risk factors associated with progression to candida-related dentures stomatitis in patients using complete dentures, and they found that *C. albicans* was the most frequently recovered species, followed by *C. glabrata* and *C. tropicalis*. Therefore, according to Mizugai et al.²¹ in their study evaluate the association among age distribution and denture wearing status and *Candida* spp. detection rate. This study indicates that, although detection rate of single *Candida* spp. were rather high in the youngest group of non-dentures wearers, detection rates of single and multiple *Candida* spp. were significantly higher in denture wearers of all other age groups compared with non-denture wearers ($P < 0.05$). Many studies have also shown that denture hygiene practices are essential, because the porous material of the surface biofilm can serve as a reservoir of fungal microorganisms, and contribute to reinfection^{22,23}.

During the study there was no correlation found between the years of denture wearing and occurrence of oral candidiasis, however, there was a correlation between the years of denture wearing and occurrence of *Candida* spp. on the patient denture base. Our results agree with previous reports which indicate that DRS are in statistically significant continuous denture wearing^{24,25}. Due to the deterioration of dentures over time, such as the polished surfaces fit to the underlying tissues and the occlusion, dentures could become more irritant to the mucosa and more open to candida and bacterial colonization.

Our findings suggest that there is a significant difference between diabetes in denture wearing patients and candidiasis. The most frequent oral signs and symptoms observed in both controlled and uncontrolled diabetic

patients was hyposalivation, halitosis, periodontitis, taste alteration, aphthous stomatitis, and they found significant difference between the groups. Also, the most common lesion seen in both the groups were candidiasis, fibrous hyperplasia, aphthous ulcers and benign neoplasia where the chi-square test showed a significant difference between the groups $P < 0,05$ according to Shrimali et al.²⁶, Daniluk et al.²⁷. *Candida albicans*, statistically significantly, more frequently was isolated in denture wearers' patients with diabetes melitus and without diabetes, comparing to such groups of patients but without dentures.

Our results may differ due to our smaller number of participants, or due to other issues associated with their age and general health. Therefore it should be pointed out that older dentures are harder to clean due to a tendency for porosity in their bases, which can contribute for the emergence of the disease. It should be concentrated on patient information and motivation on hygiene, for prophylactic purposes. Future studies will be a series of clinical epidemiologic studies, already planned in our department, to investigate pathogenesis of Denture stomatitis.

Denture Wearers

Laura Lourenço Morel¹, Anna Paula da
FernandaFaot¹, Luciana de Rezende Pinto¹,

Laura Lourenço Morel¹, Anna Paula da
FernandaFaot¹, Luciana de Rezende Pinto¹

Conclusion

In conclusion, the prevalence of Denture Stomatitis in the total number of denture wearers is high and although no association with its risk factors was found.

Preventive and educational measures for oral health in the elderly, stimulating the correct hygiene of the denture and the oral cavity, should be a routine among professionals. Patients that use dentures must maintain their dentures in order to preserve their oral health.

Conflicts of interest

The authors confirm that this article content has no conflict of interest.

Reference

- Ageing WP. World Population Ageing 1950-2050. Popul English Ed [Internet]. 2002;26:5-9. Available from: <http://www.un.org/esa/population/publications/worldageing19502050/>
- Leles CR, Ferreira NP, Vieira AH, Campos AC V, Silva ET. Factors influencing edentulous patients' preferences for prosthodontic treatment. J. Oral Rehabil. 2011;38:333-9.
- McKenna G, Allen F, Woods N, O'Mahony D, Cronin M, Damata C, Normand C. Cost-effectiveness of tooth replacement strategies for partially dentate elderly: a randomized controlled clinical trial. Community Dent. Oral Epidemiol. [Internet]. 2013;1-9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2425138>
- Salerno C, Pascale M, Contaldo M, Esposito V, Petrucci M, Sercipo R. Candida-associated denture stomatitis. Med. Oral. Patol. Oral Cir. Bucal. 2011 Mar 1;16 (1):139-43.
- Loster BW, Loster J, Wiecezorek A, Ryniewicz W. Mycological analysis of the oral cavity of patients using acrylic removable dentures. Gastroenterol. Res. Pract. 2012. 2012: 951572. Published online 2012 Apr 8. doi: 10.1155/2012/951572.
- Loster JE, Wiecezorek A, Loster BW: correlation between age and gender in Candida species infections of complete denture wearers: a retrospective analysis. ClinInterv Aging. 2016;11:1707-1714.
- Zomorodian K, Haghighi NN, Rajaei N, et al. Assessment of Candida species colonization and denture-related stomatitis in complete denture wearers. Med. Mycol. 2011;49:208-211.
- Abaci O, Haliki-Uztan A. Investigation of the susceptibility of Candida species isolated from denture wearers to different antifungal antibiotics. Afr. J. Microbiol. Res. 2011;5:1398-1403.
- Wilson J. The aetiology, diagnosis and management of denture stomatitis. Br. Dent. J. 1998;185:380-384.
- Webb BC, Thomas CJ, Willcox MDP, et al. Candida-associated denture stomatitis: aetiology and management: a review: part I: factors influencing distribution of Candida species in the oral cavity. Aust. Dent. J. 1998;43:45-50.
- Hoshi N, Mori H, Taguchi H, et al. Management of oral candidiasis in denture wearers. J. Prosthodont. Res. 2011;55:48-52.
- Williams DW, Lewis MA. Isolation and identification of Candida from the oral cavity. Oral Dis. 2000;6:3-11.
- Byadarahally.Raju S, Rajappa S. Isolation and identification of candida from the oral cavity. ISRN Dent. 2011;2011:487921.doi:10.5402/2011/487921.
- Akpan A, Morgan R. Oral candidiasis. Postgrad. Med. J. 2002;78:455-459.
- Peracini A, de Andrade I. M., da Silva C. H. L., Paranhos H. de F. O. Behaviors and Hygiene Habits of Complete Denture Wearers. Braz. Dent. J. 2010;21(3): 247-252.
- Fenn SM, Narayanan M, Jacob M. Prevalence of oral Candida in saliva of uncontrolled and controlled type 2 diabetes mellitus patients – Beyond reasonable doubt? SRM J. Res..Dent. Sci.2019;10:1-6.
- Tooyama H, Matsumoto T, Hayashi K, Kurashina K, Kurita H, Uchida M, Kasuga E, Honda T. Candida concentrations determined following concentrated oral rinse culture reflect clinical oral signs. BMC Oral Health 2015; 15:150.
- Al Tarawneh S, Bencharit S, Mendoza L, Curran A, Barrow D, Barros S, Preisser , Loewy ZG, Gendreau L, Offenbacher S. Clinical and histological findings of denture stomatitis as related to intraoral colonization patterns of Candida albicans, salivary flow, and dry mouth. J. Prosthodont. 2013 Jan;22(1):13-22.
- D'aistan S, Aktas AE, Caglayan F, Ayyildiz A, Bilge M. Differential diagnosis of dentur-induced stomatitis, Candida, and their variations in patients using complete denture: a clinical and mycological study.Mycoses. 2009;52:266-271. doi:10.1111/j.1439-0507.2008.01592.
- Zomorodian K, Haghighi NN, Rajaei N, Pakshir K, Tarazooie B, VojdaniM, Sedaghat F, Vosoghi M. Assessment of Candida species colonization and denture-related stomatitis in complete denture wearers. Med. Mycol. 2011 Feb;49(2):208-11. doi: 10.3109/13693786.2010.507605. Epub 2010 Aug 26. PubMed PMID: 20795762.
- Mizugai, Hiroyuki; Isogai, Emiko; Hirose, Kimiharu; Chiba, Itsuo. 2007 Effect of denture wearing on occurrence of Candida

-
- species in the oral cavity. The Journal of Applied Research. 2007; Vol. 7, No. 3: 250-254.
22. Hoshing C, Dixit S, Mootha A, Diwan N. Role of *Candida albicans* in denture stomatitis. J. Indian Acad. Oral Med. Radiol. 2011;23:617-619.
23. Dantas APFM, Consani RLX, Sardi JCO, Mesquita MF, Silva MCVS, Sinhoreti MAC: biofilm formation in denture base acrylic resins and disinfection method using microwave. J. Res. Pract. Dent. 2014; Article ID 112424. doi:10.5171/2014.112424.
24. Fenlon MR, Sherriff M, Walter JD. Factors associated with the presence of denture related stomatitis in complete denture wearers: a preliminary investigation. Eur. J. Prosthodont. Restor. Dent. 1998; 6:145-147.
25. Jeganathan S, Payne JA, Thean HP. Denture stomatitis in an elderly edentulous Asian population. J. Oral Rehabil. 1997; 24:468-472.
26. Shrimali L, Astekar M, Sowmya GV. Correlation of Oral Manifestations in Controlled and Uncontrolled Diabetes Mellitus. International Journal of Oral & Maxillofacial Pathology. 2011;2(4):24-27.
27. Daniluk T, Tokajuk G, Stokowska W, Fiedoruk K, Sciepuk M, Zaremba ML, Rozkiewicz D, Cylwik-Rokicka D, Kedra BA, Anielska I, Górska M, Kedra BR. Occurrence rate of oral *Candida albicans* in denture wearer patients. Adv. Med. Sci. 2006;51Suppl 1:77-80.

HYALURONIC ACID: A PROMISING MEDIATOR FOR PERIODONTAL REGENERATION

ХИЈАЛУРОНСКА КИСЕЛИНА-ВЕТУВАЧКИ МЕДИЈАТОР ЗА ПАРОДОНТАЛНА РЕГЕНЕРАЦИЈА

Toshevska S.¹, Pandilova M.², Redjep E.³, Janev E.⁴, Mindova S.², Gorgieva-Trpevski D.⁵, Angelovski B.⁵, Omerov E.⁶

¹PhD student at the Department of Oral Pathology and Periodontology, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, ²Department of Oral Pathology and Periodontology, Faculty of dentistry, University "Ss Cyril and Methodius" – Skopje, ³European University, Skopje, ⁴Department of Oral Surgery and Implantology, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, ⁵Resident at the Department of Pediatric Dentistry, Faculty of Dentistry, UKIM, Skopje, North Macedonia, ⁶Resident at the Department of Oral Pathology and Periodontology, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje

Abstract

The management of periodontal defects has been an ongoing challenge in clinical periodontics. This is mainly a result of the fact that tissues which comprise the periodontium, the periodontal ligament, and the cementum and alveolar bone, represent three unique tissues in their own right. Thus, reconstruction of the periodontium is not just a simple matter of regenerating one tissue but involves at least three quite diverse and unique tissues. Resective surgical therapy, with or without osseous recontouring, was considered the norm during the 1950s and the 1960s, in the belief that attainment of shallow pocket depths was a worthwhile goal. More recently, attention has been focused more on regenerative and reconstructive therapies, rather than on resective therapies. Among the many mediators used in periodontal regeneration is hyaluronic acid. In the field of dentistry, hyaluronic acid has shown anti-inflammatory and anti-bacterial effects in the treatment of periodontal diseases. The article reviews recent evidence of the effects of hyaluronic acid on periodontal tissue. **Keywords:** hyaluronic acid, bone regeneration, periodontal regeneration and reconstructive therapies.

Апстракт

Справувањето со пародонталните дефекти претставува постојан предизвик во клиничката пародонтологија. Предизвикот е поголем со согледување на фактот дека ткивата што го сочинуваат пародонтот, пародонталните лигаменти, цементот и алвеоларната коска претставуваат посебни уникатни ткива со свои специфички метаболна динамика и регенеративни потенцијали. Така, реконструкцијата на пародонтот не е само едноставна работа за регенерирање на едно ткиво, туку вклучува најмалку три прилично разновидни и уникатни ткива. Додека ресективната хируршка терапија се сметаше за норма во текот на 1950-тите и во 1960-тите години, во поново време вниманието е насочено повеќе кон регенеративните и реконструктивните терапии. Покрај многубројните материјали кои се користат, сепак не постојат доволно податоци за да се даде предност на одредени супстанции кои ќе доведат до подобра регенерација на ткивата. Во последните години хијалуронската киселина се повеќе се користи како медијатор, тоа е материјал кој се аплицира во пародонталниот дефект со цел да предизвика регенерација на коските. Во областа на стоматологијата, хијалуронска киселина апокажа анти-инфламаторно и антибактериско дејство во третманот на пародонталните болести. Иако подолго време се користи во различни области на стоматологијата, сепак до крај не е проследено влијанието на хијалуронската киселина врз ткивата на пародонтот. Токму затоа и одлучивме да направиме согледување на досегашните резултати во однос на примената и ефектите од хијалуронската киселина во пародонтологијата. **Клучни зборови:** хијалуронска киселина, коскена регенерација, пародонтална регенерација и реконструктивни терапии.

Introduction

Hyaluronic acid has been identified in all periodontal tissues in varying amounts and is more pronounced in non-mineralized tissues, such as the gingival and periodontal ligaments, compared with mineralized tissues such as cement and alveolar bone. In addition, due to the high levels of hyaluronic acid in the circulating blood serum, it is constantly present in the gingival blood flow fluid (GCF) which is a factor in serum overload¹. Natural

hyaluronic acid is an extremely hydrophilic polymer that exists, as viscous does not in itself have the structural features needed for use as a surgical product. Hyaluronic acid ester synthesized by esterification of a carboxyl group with benzyl alcohol is less soluble in water and is therefore more stable. Due to its unique molecular structure, hyaluronic acid can accumulate at different molecular weights such as lyophilized or esterified in different structural configurations such as membranes. The rate of biodegradation of these materials can be manipulated by

changing their degree of lyophilization or esterification. Thus, hyaluronic acid may be useful as a reproductive material in regenerative surgical procedures².

Hyaluronic acid is an anionic, glycosaminoglycanic acid widely distributed throughout connective, epithelial, and nerve tissues. It is unique among glycosaminoglycans in that it is non-sulfated and forms in the plasma membrane instead of in the Golgi apparatus. The human synovial hyaluronic acid averages about 7 million daltons per molecule, or about twenty thousand disaccharide monomers, while other sources mention 3-4 million daltons. One of the major components of the extracellular matrix, hyaluronic acid, contributes significantly to cell proliferation and migration, and may also be involved in the progression of some malignancies. The average 70 kg person has approximately 15 grams of hyaluronic acid in the body, of which one third is degraded and synthesized every day³. Hyaluronic acid is also a component of group A streptococcal extracellular capsule, and is believed to play an important role in virulence. Hyaluronic acid is one of the most well-known hygroscopic molecules known in nature. When HA is incorporated in aqueous solution, hydrogen bonding occurs between adjacent carboxyl and N-acetyl groups; this feature allows hyaluronic acid to maintain conformational stiffness and retain water. One gram of hyaluronic acid can bind up to 6 L of water. As a physical material, it has functions in spatial filling, lubrication, shock absorption, and protein exclusion⁴. The viscoelastic properties of the material can slow down the penetration of viruses and bacteria, a feature of particular interest in the treatment of periodontal disease. Hyaluronic acid as a viscoelastic substance helps in periodontal regenerative procedures by maintaining spaces and protecting surfaces⁴. By recognizing its hygroscopic and viscoelastic nature, hyaluronic acid can affect cell function by modifying surrounding cellular and extracellular micro and macro media. The hyaluronic acid has many structural and physiological functions within tissues, including extracellular and cellular interactions, the interaction between the growth factor and the regulation of osmotic pressure, and tissue lubrication, which helps maintain the structural and homeostatic integrity of tissues⁵.

Considering the various beneficial effects of hyaluronic acid, we focused our interest on the review of the effects of hyaluronic acid on periodontal tissue

Material and Methods

The purpose of this paper was to systematize available data on effects of hyaluronic acid on periodontal tissues. The survey was conducted through Pubmed-medicine

database using key words periodontal tissue, periodontal regeneration, and hyaluronic acid.

Results and discussion

In the early inflammatory phase of wound healing, HA is abundant as if it were a damaged tissue, probably a reflection of the increased synthesis. The HA acts as a promoter of early inflammation, which is crucial in the whole process of skin wound healing. In the model as a bag for air odors of carrageenan / IL-1-induced inflammation, HA has been observed to improve cell infiltration. (6,7) showed a dose-enhancing dose of proinflammatory cytokines TNF- α and IL-8 production from human stem fibroblasts at concentrations of HA from 10 μ g / ml to 1 mg / mL via a CD44-mediated mechanism. Endothelial cells, in response to inflammatory cytokines such as TNF- α and bacterial lipopolysaccharide, also synthesize hyaluron, which has been shown to facilitate primary adhesion to cytokine-activated lymphocytes, which express hyaluronic acid binding variants, and static flow⁸. HA has contradictory dual functions in the inflammatory process. Not only it can promote inflammation, as noted above, but it can also calm the inflammatory response, which can help stabilize the tissue matrix during granulation, as described in the next section. An integral part of the formation of granulation tissue, in order to proceed with normal tissue repair inflammation needs to be modelled. Initially, granulation tissue is highly inflammatory with high rate of tissue turnover mediated by enzymes that degrade matrices and reactive oxygen metabolites that are products of inflammatory cells⁶. Stabilization of the granulation tissue matrix can be achieved with moderate inflammation. HA functions as an important moderator in this process of moderation, in contrast to its role in inflammatory stimulation, as described above. HA can protect against free radical damage to cells⁹. This can be attributed to its property of free radical scavenging, a physicochemical characteristic shared by large polymer polymers. In the rat model of free radical scavenging, HA was shown to reduce granulation tissue damage¹⁰. In addition to the role of a free-radical task, HA can function in a negative feedback loop from inflammatory activation through specific biological interactions with the biological constituents of inflammation⁶. TNF- α , an important cytokine generated in inflammation, stimulates the expression of TSG-6 (TNF-stimulated gene 6) in fibroblasts and inflammatory cells. TSG-6, a protein binding to HA, also forms a stable complex with a serum proteinase inhibitor I α I (Inter- α -inhibitor) with a synergistic effect on the plasmin-inhibitory activity of the latter. Plasmin is involved in the activation of the proteolytic cascade of matrix

metalloproteinases and other proteinases that lead to inflammatory tissue damage. Therefore, the action of the TSG-6 / IαI complex, which can be further organized by binding HA into the cell matrix, can serve as a powerful link for negative feedback to moderate inflammation, and stabilize granulation tissue as healing progresses⁶.

Cell migration is necessary for the formation of granulation tissue⁶. The early stage of granulation tissue is dominated by extracellular matrix-rich hyaluronic acid, which is considered a suitable environment for cell migration in this transient wound matrix. The contribution of hyaluronic acid to cell migration can be attributed to its physicochemical properties as well as its direct interactions with cells. Hyaluronic acid provides an open hydrated matrix that facilitates cell migration, while the other role is aimed at migrating and controlling locomotive cell mechanisms that are mediated through specific interactions between HA and HA surface receptors. As previously discussed, the three major surface receptors for HA cells are CD44, RHAMM, and ICAM-1. RHAMM is more associated with cell migration. Forms bonds with several protein kinases associated with cell locomotion, for example, extracellular signal-regulated protein kinase (ERK), p125fak, and pp60c-src^{11,12,13}. During fetal development, the migratory pathway through which nerve cells migrate is rich in hyaluronic acid⁶. HA is closely related to the process of cell migration into the granulation tissue matrix, and studies have shown that cell movement can be inhibited, at least in part, by degrading HA or blocking HA receptor involvement¹⁴. By providing dynamic cell strength, HA synthesis has also been shown to be associated with cell migration¹⁵. In essence, HA is synthesized in the plasma membrane and released directly into the cell environment⁶. This may contribute to hydrated microecology at the sites of synthesis and is necessary for cell migration by facilitating cell separation.

HA is a key component of the periodontal ligament and plays a number of important roles in cell regeneration, migration, and differentiation mediated by various HA binding proteins and cell-surface receptors such as CD44. This CD44 antigen is expressed in periodontal tissues, and interaction with HA-CD44 has been associated with periodontal ligament (PDL) cell proliferation and mineralization activities¹⁶. CD44 is a single-chain molecule composed of: N-terminal extracellular domain containing ligand binding sites, proximal membrane membrane, transmembrane segment, and cytoplasmic portion¹⁷. The molecular size of CD44 ranges from 80 to 150 kDa depending on the variable fusion of at least 11 of the 21 exons encoding CD44. Specifically, periodontal ligament cells express the isoforms CD44 and CD44H^{16,18}. CD44 regulates proliferation and mineraliza-

tion of cells in the periodontal ligament. Zeinab Al-Rekabi and colleagues¹⁹ at In vivo study prove key scientific research, where recent results suggest strong evidence that HA affects contractility in periodontal ligament cells, which in turn causes these cells to move more slowly and migrate shorter distances. Given the full focus of this study, it states that CD44, hyaluronic acid, and T-lymphocytes stimulate feedback from cytokines, and suppressor T cells as well as B-growing cells, but most importantly activate the macrophage system. This would follow that hyaluronic acid has the role of a powerful anti-inflammatory mediator, which would show a better and faster reparative effect in soft and hard tissues. HA is a metabolite or diagnostic marker of inflammation in gingival puncture of the gingiva as well as an important factor in growth, development and repair of tissues. Based on current evidence in the literature, it is now known that along with mechanical therapy, the use of chemotherapeutic agents provide a better treatment strategy. The most common chemotherapeutic agents are antimicrobial and anti-inflammatory drugs. They are administered either systemically or locally. Topical antimicrobial agents for the treatment of periodontal disease include chlorhexidine, tetracyclines, and metronidazole.

Low molecular weight hyaluronic acid has a significant angiogenic effect, while, surprisingly, high molecular weight has the opposite effect. Hyaluronic acid is a major component of the extracellular matrix and plays a key role in tissue regeneration, inflammatory response, and angiogenesis, which are stages of skin wound repair. As of 2016, reviews evaluating the effect of promoting wound healing, however, show only limited evidence from clinical trials affecting burns, diabetic feet, or any skin surgery. In gel form, hyaluronic acid combines with water and swells, making it useful in skin treatments such as dermal filler for the treatment of facial wrinkles and lasting about 6 to 12 months, clinical treatment with regulatory approval²⁰.

Hyaluronic acid can be degraded by a family of enzymes called hyaluronidases. In humans, there are at least seven types of hyaluronidase-like enzymes, several of which are tumor suppressors. Degradation products of hyaluronic acid, oligosaccharides, and very low molecular weight hyaluronic acid show pro-angiogenic properties²¹. In addition, recent studies have shown that fragments of hyaluronic acid, rather than a high molecular weight parent molecule, can cause inflammatory reactions in macrophages and dendritic cells in tissue injury and skin transplantation. Hyaluronic acid can also be degraded by non-enzymatic reactions. These include acid and alkali hydrolysis, ultrasonic decomposition, thermal decomposition, and oxidant degradation²².

Recent studies of regenerative surgical procedures show that reducing the bacterial load on the wound site may improve the clinical outcome of regenerative therapy. High concentrations of medium and low molecular weight hyaluronic acid have the greatest bacteriostatic effect, especially on *Aggregatibacter actinomycetemcomitans*, species of *Prevotella oris* *phylococcus aureus* most commonly found in oral gingival lesions and periodontal wounds. Clinical application of hyaluronic acid membranes, gels, and sponges during surgical therapy may reduce bacterial contamination at the surgical wound site, reducing the risk of postoperative infection and promoting more predictable regeneration¹.

Hyaluronic acid has also been reported to be anti-adhesive and antimicrobial, which are two more beneficial characteristics for scaffold implantation at injury sites. As a hydrophilic natural polymer, its antimicrobial effects on common orthopedic pathogens such as *Staphylococcus*, β -hemolytic *Streptococcus*, *Pseudomonas aeruginosa*, *Enterococcus*, and others have been proven in various studies^{23, 24, 25}, although other research has presented contradictory results for specific bacteria such as *S. mutans*²⁶. The anti-adhesive and antibacterial properties of HA have also been studied, indicating a concentration-dependent anti-adhesive effect on *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The effect of hyaluronidase-producing bacteria was not considered, however, and the inhibition mechanisms behind the results are unclear. Thus, further investigation is needed, as noted by the authors. In fact, prior to any practical applications, the antibacterial effect on common pathogens present at surgical sites needs to be considered²⁶. In addition, employing the carrying ability of hyaluronic acid to load anti-septics is a better way to prevent infection.

A study by Yi Xu et al.²⁷ concluded that there was no clinical or microbiological improvement achieved by the adjunctive use of Hyaluronan 0.2% gel when compared to mechanical debridement. However in this study, Hyaluronan 0.2% gel was applied only once a week for six weeks, a total of seven applications over a six-week period, compared to the recommended application level of three times daily for at least four to eight weeks. The absence of observed clinical improvements, contrary to other published studies, may indicate that the Hyaluronan levels used in this study were well below the optimum levels required to achieve a significant clinical improvement. Vanden Bogaerde² in a recent clinical report evaluated the clinical efficacy of esterified hyaluronic acid in the treatment of infrabony periodontal defects. The author concluded that application of hyaluronic acid seems a promising method for the treatment of infrabony defects by inducing a significant

reduction in pocket depth and promoting gain in clinical attachment.

An interesting *in vivo* study with convincing evidence is provided by the report of Masako Fujioka-Kobayashi²⁸, together with his colleagues, who examines the effect of HA on the periodontal ligament cells - cell compatibility, proliferation, and differentiation. Both hyaluronic acid formations, necroslinked (HA ncl) and crosslinked (HA cl) HA showed high viability of periodontal ligament cells (greater than 90%) regardless of culture conditions. Furthermore, no significant difference was observed in mRNA levels and proteins in proinflammatory cytokines, including MMP2 and IL-1. Both, diluted HA_ncl and HA_cl, significantly increased cell numbers compared to the controlled TCP samples at 3 and 5 days. HA_ncl and HA_cl in standard cell growth media significantly reduced ALP staining, COL1 immunization, and early regulated early osteogenic differentiation, including Runx2, COL1, and OCN mRNA levels, compared with controls. When osteogenic differentiation medium (ODM) was added, interestingly, the expression of early osteogenic markers increased with demonstration of higher levels of COL1 and ALP expression; especially in HA 1:10 diluted state. Late-stage osteogenic markers remained inhibited. All of this led to the general conclusion that non-cross-linked and interconnected HAs maintained high periodontal ligament cell viability, increased proliferation, and early osteogenic differentiation. However, HA was consistently associated with a significant reduction in late osteogenic differentiation of primary human PDL cells.

Andrew L Raines et al.²⁹ in his study demonstrated that the enhanced neovascularization observed in ablated marrows treated with low MW NaHY + DBM is further increased when accounted for the volume occupied by the DBM, indicating that the neovascularization induced by NaHY is further stimulated by the presence of DBM. Also in his experiment in rat tibial marrow ablation model, both high MW HA with demineralized bone matrix (DBM), and low MW HA with DBM, induced a significant increase in the blood vessel volume fraction when compared with empty defects, suggesting that HA promotes neovascularization.

Palatal and gingival fibroblasts play an important role in oral wound healing. The use of bioactive substances that influence their behavior and thus support oral soft tissue wound healing/regeneration is of major clinical interest. Therefore, the aim of the study on Maria B Asparuhova and her associates³⁰ was to investigate the specific role of two commercially available HA formulations in affecting oral fibroblast cell behavior including proliferation, migration, and wound healing-related gene expression. All these processes affect soft tissue wound

healing/ regeneration following reconstructive periodontal surgery. Our data demonstrates that both formulations of HA (a) are fully biocompatible and exert no negative effects on the viability of HPFs and HGFs; (b) are able to increase the proliferative and migratory abilities of both cell types; (c) trigger expression of COL3A1 and TGFβ3 genes characterizing scarless fetal wound healing; (d) upregulate the expression of genes encoding the growth factors PDGFB, FGF-2, and EGF, which are essential for the wound healing process; (e) induce pro-inflammatory cytokine gene expression, thus potentially initiating a cellular inflammatory response; and (f) affect MMP gene expression either directly (MMP1 and 8) or indirectly (MMP2 and 3), potentially through induction of proinflammatory cytokines, thus influencing ECM remodeling. Finally, (g) our data point on Akt, Erk1/2, and p38 as the signaling molecules by which the two HA preparations exert their effects on oral fibroblasts. Understanding the mechanisms whereby these HAs function may reveal how to intervene in the dynamic process of oral soft tissue regeneration with the aim to improve it. They concluded that, both HA formulations investigated in the current study, exert diverse positive effects on human palatal and gingival fibroblasts, two cell types involved in soft tissue regeneration following periodontal reconstructive therapies that utilize palatal connective tissue or free gingival grafts. The observed pro-proliferative, pro-migratory and pro-wound healing properties of the two HAs speak in favor of their clinical potential. However, both HA formulations are biocompatible and enhance the proliferative, migratory and wound healing properties of cell types involved in soft tissue wound healing, following regenerative periodontal surgery.

Jung-Ju Kim and his associates (31), in one experimental study on dogs, filled the sockets with mineralized bone ($47.80\% \pm 6.60\%$) and bone marrow ($50.47\% \pm 6.38\%$) in the control group, whereas corresponding values were $63.29\% \pm 9.78\%$ and $34.73\% \pm 8.97\%$ for the test group, respectively. There was a statistically significant difference between the groups. Reversal lines and a copious lineup of osteoblasts were observed in the middle and apical parts of the sockets in the test group. An infected socket shows delayed healing of the socket wound, and HA, because of its osteo-inductive, bacteriostatic, and anti-inflammatory properties, may improve bone formation and accelerate wound healing in infected sockets. In the end they concluded and suggested that the application of HA with ACS in compromised extraction sockets provides enhanced regenerative efficacy for bone healing compared with rhBMP-2.

Peisong Zhai³² and associates, in their study concluded that HA derivatives incorporated composite scaffolds

have shown excellent potential for improving osteogenesis and mineralization, and also HA should be a promising tool in bone regeneration.

Alcântara and his colleagues³³, gave a clear message with their study which contains: after each tooth extraction, the empty alveola must be filled with 1% of hyaluronic acid in the form of a gel, which would accelerate the process of bone formation significantly faster, relative to leaving the alveola empty. This study evaluated the effects of hyaluronic acid (HA) on bone repair of human dental sockets. Thirty-two lower first premolars were extracted from 16 patients (2 per patient) for orthodontic reasons. Following the extractions, one socket was randomly filled with 1% HA gel, while the other was allowed to naturally fill with blood clot. After 30 and 90 days of surgery, patients underwent cone beam computed tomography. Five central orthoradial slices were captured from each socket. The gray intensity was measured in each image and results were reported as mean percentage of bone formation. The buccolingual alveolar ridge width was measured, and dimensional changes were compared between the postoperative intervals. The pattern of alveolar trabecular bone was evaluated through the fractal dimension. Treated sockets showed a higher percentage of bone formation and fractal dimension values (58.17% and 1.098 , respectively) compared with controls (48.97% and 1.074 , respectively) in the 30-day postoperative period ($p < 0.05$). After 90 days, there was no significant difference between groups; it was performed on patients in whom the treated alveoli with HA and without 90 days were measured with CBCT where the measured bone parts were proven.

Kumar and his colleagues³⁴, have focused their research on the effects of hyaluronic acid on root canal procedures in addition to the coronary artery bypass graft (CAF) procedure. In this study design, 10 patients with 20 sites of Miller I recession were treated and monitored for a period of 6 months. Experimental sites were treated with 0.2% HA gel and CAF while control sites were treated with CAF only. There is a significant change in the outer surface of the root (RD), no probing bleeding (PPD), clinical attachment level (CAL), and percentage of root coverage in the two groups compared to baseline, but there is no statistically significant difference between the parts of the root. HA and control points in relation to RD, PPD and CAL. Although there is no statistically significant difference, root coverage at HA sites appears to be clinically more stable than the CAF-treated control site after 24 weeks.

Engström et al.³⁵ investigated the anti inflammatory effect and the effect on bone regeneration of Hyaluronan in surgical and non surgical groups. No statistical difference was found on radiographs in the non surgical

group, whereas the decrease in bone height was found for both groups after scaling. Probing depth (PD) reduced after the surgical treatment as well as after scaling and root planning (SRP). Hyaluronan in contact with bone and soft tissues had no influence on the immune system.

The esthetic area is defined as the visible area during functioning and includes the anterior maxillary and mandibular teeth. Interdental “black triangles” were considered as the third most disliked and less attractive esthetic problem after caries and crown margins. The loss of gingival papillary height results in open gingival embrasures which leads to several problems in phonetics, esthetic concerns, and food impaction. This loss of interdental papillae (IDP) commonly known as “black holes” or “black triangles”. The gingival black space is the distance from the cervical black space to the interproximal contact. Different surgical and nonsurgical approaches are proposed in the periodontal literature to provide satisfactory IDP reconstruction. Several non-surgical and surgical techniques for the reconstruction of lost IDP remain elusive. The compromised blood supply, scarring, and trauma in thin gingival biotypes increase the failure risk. Interdental papillae have always been of interest for research, especially its reconstruction in the event of its collapse, so a clinical study by Shivani Singh and Kharidi Laxman Vandana³⁶ shows that the application of hyaluronic acid 5% at the base of the papilla and other clinical points is significantly good because it completely fills the interdental space for up to 8 months. The dependence of the duration of hyaluronic acid in the soft tissue primarily depends on the fitness of the surrounding soft and hard tissue. The use of modified stent for clinical improvement assessment of IDP is recommended. Further, long-term studies would throw more insight with this regard. Further histologic studies are required to assess the mechanism of hyaluronic action.

Araújo Nobre and his colleagues⁹ compared the health status of the peri-implantitis complex during the period of osseointegration of implants for immediate function, using HA gels or chlorhexidine (CHX). The purpose of this study was to compare the health status of the peri-implant complex (hard and soft tissues surrounding the implant) during the healing period of immediate function implants, using HA or CHX gels in the patient's maintenance protocol. Both groups were followed up for 6 months, with clinical observations on the 10th day, 2 months, 4 months and 6 months post-surgically. During the course of the study, HA and CHX produced good results in maintaining a healthy peri-implant complex in immediate function implants for complete rehabilitations in the edentulous mandible. Statistically significant differences were found in favor

of the HA group in the modified bleeding index on the second observation ($P = 0.003$). The difference was more marked in the axial implants placed in the fifth sextant ($P = 0.05$). Correlation coefficient between plaque and bleeding index revealed a potentially better result for CHX at 6 months. They found a statistically significant lower modified bleeding index in group HA in combination with the control group treated with CHX. It can be said with certainty that it is good to use a combination treatment with the use of HA 0.2% gel in the first 2 months and 0.2% CHX from 2 to 6 months.

After thorough examination and evaluation of the persisting data we can summarize that there is an evidence of multifunctional benefits of hyaluronic acid in periodontology.

Hyaluronic acid and multifunctional roles in periodontics:

Topical application of subgingival hyaluronic acid gel can be used as an antimicrobial agent as an adjunct to scaling and root planning. These data suggest that a hyaluronan containing gel has a beneficial effect in the treatment of plaque-induced gingivitis³⁷. Johannsen et al.³⁸, in their study evaluated the adjunctive effect of the local application of a hyaluronan gel to scaling and root planning in the treatment of chronic periodontitis. Twelve patients with chronic periodontitis were recruited to participate in a study with a split-mouth design and provided informed consent. Plaque formation and bleeding on probing were evaluated pre-treatment (baseline) and at 1, 4, and 12 weeks post-treatment. Probing depths and attachment levels were evaluated at baseline and at 12 weeks. The patients received full-mouth scaling and root planning. A hyaluronan gel was administered subgingivally in the test sites at baseline and after 1 week. The results show a significant reduction in bleeding on probing scores and probing depths were observed in both groups at 12 weeks ($P < 0.05$). Significantly lower bleeding on probing scores were observed in the hyaluronan group compared to control at 12 weeks ($P < 0.05$). Mean probing depth reductions between baseline and 12 weeks were 1.0 ± 0.3 mm and 0.8 ± 0.2 mm for the hyaluronan and control groups, respectively. The difference between the groups was statistically significant ($P < 0.05$). The conclusion of the author and his colleges is that the local application of hyaluronan gel in conjunction with scaling and root planning may have a beneficial effect on the periodontal health in patients with chronic periodontitis. The clinical application of hyaluronic acid in gingivitis therapy, the author Alexander Pistorius⁶ in his study with sixty non-smoking outpatients in good general condition, with

clinical signs of gingivitis, were included. Forty patients (HA group, 20 men, 20 women; age: 32.8 +/- 11.3 years) used a spray containing HA 5 times daily over a period of 1 week. The control group consisted of 20 patients (10 men, 10 women; age: 31.3 +/- 9.3 years). The clinical parameters DMF-T (decayed, missing, filled teeth) index, approximal plaque index, sulcus bleeding index, papilla bleeding index, and gingival crevicular fluid were measured at baseline (T₁), after 3 days (T₂), and after 7 days (T₃). The results show a reduction in the sulcus bleeding index of the HA group (T₁: 72.9 +/- 19.5%) to 50.3 +/- 21.1% was noted at T₂, and at T₃ the sulcus bleeding index was 40.7 +/- 23.0%. The papilla bleeding index values of the HA group were 1.6 at T₁, 1.0 at T₂, and 0.7 at T₃. The gingival crevicular fluid showed significant reductions in the HA group. At T₁ the recorded mean value was 16.3, at T₂ it was 11.8, and at T₃ it was 7.9. Only insignificant changes were observed in the respective indices of the control group. There were no significant alterations in the plaque values of either group throughout the study period. Conclusion: the results obtained by this study demonstrate that the topical application of an HA-containing preparation represents a potentially useful adjunct in the therapy of gingivitis, although its use does not diminish the need for plaque reduction as a primary therapeutic measure.

Bone regeneration in periodontal bone defects.

More recently, cross-linked HA products were used as gel barriers to cover the osseous defects around the implants and implant recipient sites and thereby promoting GBR². Claar performed a lateral coverage of the augmentation followed by use of cross-linked HA in gel form, which was developed especially for GBR³⁹. The principles of GBR applications^{40, 41} are as follows:

- **Cell exclusion:** Creating a barrier to prevent forming fibrous connective tissue by epithelial cells.
- **Tenting:** New wound space beneath the membrane must be regenerated solely around soft tissues so that high quality of new tissue can be gained.
- **Scaffolding:** At first, a fibrin clot is seen in this space which is a scaffold for progenitor cells. Adjacent hard tissues serve as storage for stem cells.
- **Stabilization:** To gain successful healing, the defective area must be protected from environmental effects such as flap movement, bacterial invasion, exposure of region, etc. by fixing the membrane into position.

Non-surgical treatment of peri-implant pockets.

The results obtained in this study favor the adoption of non-surgical protocols. The fact that no significant dif-

ferences were found between both groups supports the research hypothesis in the use of HA in the treatment of pockets up to 5 mm, and of CHX for the treatment of pockets up to 6 mm. this conclusion means that it is possible that the use of non-surgical therapy is effective, making it possible either to treat peri-implant pathologies with a simple protocol, or to prepare the site for surgical therapy in case of an unsuccessful treatment⁸.

Peri-implant maintenance of immediate function implants. The objective of this study was to compare the health status of the peri-implant complex (hard and soft tissues surrounding the implant) during the healing period of immediate function implants, using HA or CHX gels in the patient's maintenance protocol. Thirty complete edentulous patients, with four immediate function Brånemark System implants placed in the mandible (total of 120 implants), were randomly assigned to two groups (HA and CHX) using only these two chemicals in their daily implant self-care. Both groups were followed up for 6 months, with clinical observations on the 10th day, 2 months, 4 months and 6 months post-surgically. In the course of the study, HA and CHX produced good results in maintaining a healthy peri-implant complex in immediate function implants for complete rehabilitations in the edentulous mandible. Statistically significant differences were found in favor of the HA group in the modified bleeding index on the second observation ($P = 0.003$). The difference was more marked in the axial implants placed in the fifth sextant ($P = 0.05$). Correlation coefficient between plaque and bleeding index revealed a potentially better result for CHX at 6 months. The findings point out the importance of a maintenance protocol in immediate function implants. Both chemicals are valid tools for implant maintenance. The authors suggest that it might be advantageous to administer HA in the first 2 months and CHX between 2 and 6 months (9).

As autologous cell hyaluronic acid graft gingival augmentation in mucogingival surgery. Seven sites from 6 patients were used in this study. Five patients (5 sites) needed gingival augmentation prior to prosthetic rehabilitation, and one patient (2 sites) needed augmentation because of pain during daily tooth brushing. Full-mouth plaque score (FMPS), full-mouth bleeding score (FMBS), probing depth (PD), and clinical attachment level (CAL) were recorded for the sites at baseline and 3 months after surgery. The amount of keratinized tissue (KT) was measured in the mesial, middle, and distal sites of each involved tooth. A small 2 x 1 x 1 mm portion of gingiva (epithelium and connective tissue) was removed from each patient, placed in a nutritional medium, and sent to the laboratory. The gingival tissue was processed: keratinocytes and fibroblasts were separated and only

fibroblasts were cultivated. They were cultured on a scaffold of fully esterified benzyl ester hyaluronic acid (HA) and returned to the periodontal office under sterile conditions. During the gingival augmentation procedure, the periosteum of the selected teeth was exposed, and the membrane containing cultivated fibroblasts was adapted to, and positioned on the site. Three months after surgery, an increased amount of gingiva was obtained, and the histological examination revealed a fully keratinized tissue on all the treated sites. Prato and his colleagues (10) concluded that tissue engineering technology using an autologous cell hyaluronic acid graft was applied in gingival augmentation procedures, and provides an increase of gingiva in a very short time without any discomfort for the patient.

As a carrier for newer molecules in various regenerative procedures. In one study, the osteoinductive effect of the hyaluronic acid (HA) by using an esterified low-molecular HA preparation (EHA) as a coadjuvant in the grafting processes to produce bone-like tissue in the presence of employing autologous bone obtained from intra-oral sites, to treat infra-bone defects without covering membrane, was examined. The report on 9 patients with periodontal defects treated by EHA and autologous grafting (4 males and 5 females, all non smokers, with a mean age of 43.8 years for females, 40.0 years for males and 42 years for the group, in good health) with a mean depth of 8.3 mm of the infra-bone defects, as revealed by intra-operative probes. Data were obtained at baseline before treatment and after 10 days, and subsequently at 6, 9, and 24 months after treatment. Clinical results showed a mean gain in clinical attachment (gCAL) of 2.6mm of the treated sites, confirmed by radiographic evaluation. Such results, the author Andrea Ballini⁴² suggested, that autologous bone combined with EHA seems to have good capabilities in accelerating new bone formation in the infra-bone defects.

As a biomaterial scaffold in tissue engineering research.

Hyaluronic acid is biocompatible and intrinsically safe to use, with no evidence of cytotoxicity found¹¹. Hyaluronic acid gel, injections or oral (by mouth), should not be used in patients with allergies.

Recent studies on regenerative surgical procedures indicate that reduction of bacterial burden at the wound site may improve the clinical outcome of regenerative therapy. The high concentration of medium and lower molecular weight hyaluronic acid has the greatest bacteriostatic effect, particularly on *Aggregatibacter actinomycetemcomitans*, *Prevotella oris*, *Phylococcus aureus* strains commonly found in oral gingival lesions and periodontal wounds. Clinical application of hyaluronic

acid membranes, gels and sponges during surgical therapy may reduce the bacterial contamination of surgical wound site, thereby, lessening the risk of postsurgical infection and promoting more predictable regeneration. Also, Hyaluronic acid may act as biomaterial scaffold for other molecules, such as BMP-2 and PDGF-BB, used in guided bone regeneration techniques and tissue engineering research⁴³.

Conclusion

Today HA is widely used in many branches of medicine with interesting potential applications in dentistry for the treatment of acute and chronic inflammatory disease. Data obtained from the present review of 20 clinical studies demonstrates that, due to its positive action on tissue repair and wound healing, topical administration of HA could play a role not only in postoperative dental surgery, but also in the treatment of patients affected by gingivitis and periodontitis, with a significant improvement in their quality of life. Further, laboratory-based research and large-scale randomized controlled clinical trials on a larger scale are advisable to confirm these promising results. From the perspective of current research, hyaluronic acid-based bone regenerative scaffolds are more biocompatible and bioactive with biomimetic strategies. As a matrix component, hyaluronic acid, especially sulfated HA, may trigger cell behavior modulation via several signaling pathways, leading to faster and more desirable bone formation. Scaffolds and carriers based on HA are shaped into either rigid forms or colloids. As a rigid scaffold material, when incorporated with other materials, HA may alter the scaffold morphology and improve mineralization, making it more desirable and more functional for bone regeneration. Moreover, hyaluronic acid is chemically versatile, with its properties changed via simple chemical modification and crosslinking. The viscosity, rheological properties, pH, and charge properties of hyaluronic acid can be modulated into states suitable for gelation or delivery. This leads us to the carrier hyaluronic acid. Either by mixing, or by chemically or electrostatically encapsulating a diverse range of growth factors, drugs, mineralized components, or cells in HA-based carriers, bone formation can be markedly enhanced and accelerated. New bone formation could more closely resemble that of the original tissue. Some strategies can also perform superbly in Osseo integration for implantation. HA-based hydrogels and micro particles can covalently bind to metal implant surfaces and release bioactive components, resulting in better osteogenesis and Osseo integration. However, the specific mechanisms behind the effects of HA on osteogenesis still require proper investigation. We urge that more attention should be paid to

controlled delivery as well as biomimetic scaffold and carrier designs, not just HA-based forms. In conclusion, hyaluronic acid has overwhelmingly proven its potential for use in bone regeneration and should be considered as a useful option in future applications.

Conflicts of interest

The authors confirm that this article content has no conflict of interest.

Reference

- Embery G, Waddington RJ, Hall RC, Last KS. Connective tissue elements as diagnostic aids in periodontology. *Periodontol* 2000. 2000 Oct;24:193-214.
- Vanden Bogaerde L. Treatment of infrabony periodontal defects with esterified hyaluronic acid: clinical report of 19 consecutive lesions. *Int. J. Periodontics Restorative Dent*. 2009;29:315-23.
- Neumayer T, Prinz A, Findl O. Effect of a new cohesive ophthalmic viscosurgical device on corneal protection and intraocular pressure in small-incision cataract surgery. *J. Cataract. Refract. Surg*. 2008;34:1362-6.
- Laurent TC (ed.). In: *The Chemistry, Biology and Medical Applications of Hyaluronan and its Derivatives*. Portland Press, London, U.K. 1998.
- Weigel PH, Frost SJ, McGary CT, LeBoeuf RD. The role of hyaluronic acid in inflammation and wound healing. *Int. J. Tissue React*. 1988;10(6):355-65.
- Pistorius A, Martin M, Willershausen B, Rockmann P. The clinical application of hyaluronic acid in gingivitis therapy. *Quintessence Int*. 2005;36:531-8.
- Park JK, Yeom J, Oh EJ, Reddy M, Kim JY, Cho DW, et al. Guided bone regeneration by poly (lactic-co-glycolic acid) grafted hyaluronic acid bi-layer films for periodontal barrier applications. *Acta Biomater*. 2009;5:339-403.
- Miguel De Araújo Nobre M, Carvalho R, Malo P. Non surgical treatment of peri-implant pockets: an exploratory study comparing 0.2% chlorhexidine and 0.8% hyaluronic acid. *Can. J. Dent. Hygiene* 2009;43:25-30.
- Miguel De Araújo Nobre M, Cintra N, Maló P. Peri-implant maintenance of immediate function implants: a pilot study comparing hyaluronic acid and chlorhexidine. *Int. J. Dent. Hyg*. 2007;5:87-94.
- Prato GP, Rotundo R, Magnani C, Soranzo C, Muzzi L, Cairo F. An autologous cell hyaluronic acid graft technique for gingival augmentation: A case series. *J. Periodontol*. 2003;74:262-7.
- Campoccia D, Doherty P, Radice M, Brun P, Abatangelo G, Williams DF. Semisynthetic resorbable materials from hyaluronan esterification. *Biomaterials* 1998;19:2101-27.
- Benedetti L, Cortivo R, Berti T, Berti A, Pea F, Mazzo M, et al. Biocompatibility and biodegradation of different hyaluronan derivatives (HYAFF) implanted in rats. *Biomaterials* 1993;14:1154-60.
- Wisniewski HG, Hua JC, Poppers DM, Naime D, Vilcek J, Cronstein BN. TNF/IL-1-inducible protein TSG-6 potentiates plasmin inhibition by inter-alpha-inhibitor and exerts a strong anti-inflammatory effect in vivo. *J. Immunol*. 1996; 156 (4): 1609-15.
- Mohamadzadeh M, DeGrendele H, Arizpe H, Estess P, Siegelman M. Proinflammatory stimuli regulate endothelial hyaluronan expression and CD44/HA-dependent primary adhesion. *J. Clin. Invest*. 1998; 101 (1):97-108.
- Tammi R, Ripellino JA, Margolis RU, Tammi M. Localization of epidermal hyaluronic acid using the hyaluronate binding region of cartilage proteoglycan as a specific probe. *J. Invest. Dermatol*. 1988;90 (3):412-4.
- Yeh Y, Yang Y, Yuan K. Importance of CD44 in the proliferation and mineralization of periodontal ligament cells. *J. Periodontal Res*. 2014;49(6):827-835.
- Ponta H, Sherman L, Herrlich PA. CD44: from adhesion molecules to signalling regulators. *Nat Rev Mol Cell Biol*. 2003 Jan;4(1):33-45.
- Leonardi R, Loreto C, Caltabiano R, et al. Immunolocalization of CD44s in human teeth. *Acta Histochem*. 2006;108(6):425-429.
- Zeinab Al-Rekabia, Adriane M. Furab, Ilsa Juhlina, Alaa Yassinc, Tracy E. Popowicsd, and Nathan J. Sniadecki. Hyaluronan-CD44 interactions mediate contractility and migration in periodontal ligament cells. *Cell Adh. Migr*. 2019 12 8;13(1):138-150.
- Mendes RM, Silva GA, Lima MF, Calliari MV, Almeida AP, Alves JB, et al. Sodium hyaluronate accelerates the healing process in tooth sockets of rats. *Arch. Oral Biol*. 2008;53:1155-62.
- Matou-Nasri S, Gaffney J, Kumar S, Slevin M. Oligosaccharides of hyaluronan induce angiogenesis through distinct CD44 and RHAMM-mediated signaling pathways involving Cdc2 and gamma-adducin. *Int. J. Oncol*. 2009; 35 (4): 761-773.
- Yung S, Chan TM. Pathophysiology of the peritoneal membrane during peritoneal dialysis: the role of hyaluronan. *J. Biomed. Biotechnol*. 2011; 2011:180594. Published online 2011 Dec 12. doi: 10.1155/2011/180594
- C.L. Romanò, E. De Vecchi, M. Bortolin, I. Morelli, L. Drago. Hyaluronic acid and its composites as a local antimicrobial / antiadhesive barrier. *J. Bone Jt. Infect.*, 2 (2017), pp. 63-72, 10.7150/jbji.17705
- A. Ardizzoni, R.G. Neglia, M.C. Baschieri, C. Cermelli, M. Caratozzolo, E. Righi, B. Palmieri, E. Blasi. Influence of hyaluronic acid on bacterial and fungal species, including clinically relevant opportunistic pathogens, *J. Mater. Sci. Mater. Med*. 2011; 22 :2329-2338.
- G.A. Carlson, J.L. Dragoo, B. Samimi, D.A. Bruckner, G.W. Bernard, M. Hedrick, P. Benhaim. Bacteriostatic properties of biomatrices against common orthopaedic pathogens. *Biochem. Biophys. Res. Commun*. 2004 Aug 20;321(2):472-8.
- L. Wolinsky, G.W. Bernard, S. Haake, P. Pirnazar, S. Nachnani, A. Pilloni. Bacteriostatic effects of hyaluronic acid. *J. Periodontol*. 1999;70:370-374.
- Xu Y, Höfling K, Fimmers R, Frentzen M, Jervoe-Storm PM. Clinical and microbiological effects of topical subgingival application of hyaluronic acid gel adjunctive to scaling and root planing in the treatment of chronic periodontitis. *J. Periodontol* 2004;75:1114-8.
- Masako Fujioka-Kobayashi et al. In vitro effects of hyaluronic acid on human periodontal ligament cells. *BMC Oral Health*. 2017; 44.
- Andrew L Raines et al. Hyaluronic acid stimulates neovascularization during the regeneration of bone marrow after ablation. *J. Biomed. Mater. Res*. 2011 Mar 1;96(3):575-83.
- Maria B Asparuhova, Deniz Kiryak, Meizi Eliezer, Deyan Mihov, Anton Sculean. Activity of Two Hyaluronan Preparations on Primary Human Oral Fibroblasts. *J. Periodontal Res*. 2019 Feb;54(1):33-45.
- Jung-Ju Kim et al. Biomodification of Compromised Extraction Sockets Using Hyaluronic Acid and rhBMP-2: An Experimental Study in Dogs. *J. Periodontol*. 2019 Apr;90(4):416-424.
- Peisong Zhaia, Xiaoxing Pengb, Baoquan Lia, Yiping Liua, Hongchen Suna, Xiangwei Li. The application of hyaluronic acid

-
- in bone regeneration. *Int. J. Biol. Macromol.* 2020 May 15;151:1224-1239.
33. Alcântara Carlos Eduardo Pinto, Castro Mauricio Augusto Aquino, Noronha Mariana Saturnino de, Martins-Junior Paulo Antônio, Mendes Renato de Melo, Caliaro Marcelo Vidigal et al. Hyaluronic acid accelerates bone repair in human dental sockets: a randomized triple-blind clinical trial. *Braz. oral res.* [Internet]. 2018 [cited 2020 Nov 26] ; 32: e84. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-83242018000100265&lng=en. Epub Sep 13, 2018. <https://doi.org/10.1590/1807-3107bor-2018.vol32.0084>.
34. Kumar R, Srinivas M, Pai J, et al. Efficacy of hyaluronic acid (hyaluronan) in root coverage procedures as an adjunct to coronally advanced flap in Millers Class I recession: A clinical study. *Journal of Indian Society of Periodontology* 2014; 18: 746–750.
35. Engström PE, Shi XQ, Tronje G, Larsson A, Welander U, Frithiof L, et al. The effect of hyaluronan on bone and soft tissue and immune response in wound healing. *J. Periodontol.* 2001;72:1192-200.
36. Shivani Singh and Kharidi Laxman Vandana. Use of different concentrations of hyaluronic acid in interdental papillary deficiency treatment: A clinical study. *J Indian Soc Periodontol.* 2019 Jan-Feb; 23(1): 35–41.
37. Jentsch H, Pomowski R, Kundt G, Göcke R. Treatment of gingivitis with hyaluronan. *J. Clin. Periodontol.* 2003;30:159-64.
38. Johannsen A, Tellefsen M, Wikesjö U, Johannsen G. Local delivery of hyaluronan as an adjunct to scaling and root planing in the treatment of chronic periodontitis. *J. Periodontol.* 2009;80:1493-7.
39. Claar M: Hyaluronic acid in oral implantology. *EDI Case Studies.* 2013; 4: 64-68.
40. Wang HL, Carroll MJ: Guided bone regeneration using bone grafts and collagen membranes. *Quintessence Int.* 2001; 32: 504-515.
41. Hitti RA, Kerns DG: Guided bone regeneration in the oral cavity: a review. *Open Pathol. J.* 2011; 5: 33-45.
42. Ballini A, Cantore S, Capodiferro S, Grassi FR. Esterified hyaluronic acid and autologous bone in the surgical correction of the infra-bone defects. *Int. J. Med. Sci.* 2009;6:65-71.
43. Hunt DR, Jovanovic SA, Wikesjö UM, Wozney JM, Bernard GW. Hyaluronan supports recombinant human bone morphogenetic protein-2 induced bone reconstruction of advanced alveolar ridge defects in dogs. A pilot study. *J. Periodontol.* 2001;72:651-8.

CORONECTOMY - AN ALTERNATIVE TO SURGICAL EXTRACTION OF DEEPLY IMPACTED MANDIBULAR THIRD MOLAR - A CASE REPORT

КОРОНЕКТОМИЈА - АЛТЕРНАТИВЕН ПРИСТАП НА ХИРУРШКА ЕКСТРАКЦИЈА НА ДЛАБОКО ИМПАКТИРАНИ МАНДИБУЛАРНИ ТРЕТИ МОЛАРИ - ПРИКАЗ НА СЛУЧАЈ

Kacarska M.

Department of oral surgery, Faculty of Dentistry, University, Ss. Cyril and Methodius", Skopje

Abstract

Deeply impacted mandibular third molars in close proximity to the inferior alveolar canal pose a therapeutic challenge. Difficult surgical removal may lead to temporary or permanent damage to the inferior alveolar nerve (IAN) resulting in paresthesia, hypoesthesia or dysesthesia of the lower lip, teeth, gingiva and skin over the chin, which significantly affects the patient's quality of life. Besides (also), the need to prevent these kinds of injuries is especially important since current treatment modalities of neurosensory deficit management show only limited improvement in sensation. Coronectomy is the oldest and the best researched of the IAN injury-risk reducing procedures. This procedure is designed to remove only the crown portion of the tooth, leaving the roots in situ, thus damage to the inferior alveolar nerve is minimized. The aim of this paper is to depict a case of coronectomy performed as an alternative approach to complex surgical removal of a deeply impacted mandibular third molar with inferior alveolar nerve involvement. Careful perioperative radiological assessment of root morphology and detection of radiological signs for mandibular canal involvement preceded the treatment decision. With number of roots vaguely established to four, apically dilacerated, superimposed and extended beyond the lower rim of the mandibular canal the assumption of complex surgical removal of the impacted third molar with abundant bone loss, root fractures and inferior alveolar nerve injury was made. Coronectomy was considered to avoid major surgical trauma and to minimize the risk of inferior alveolar nerve injury. Under local infiltrative anesthesia, triangular flap was raised and pericoronar osteotomy was made, followed by transversal section of the crown at the cement-enamel junction. The crown was detached and removed, and the residual surface was trimmed. The wound was thoroughly cleaned and sutured. The postoperative period was uneventful. No signs of sensitive disturbances in the left mandibular side were noted. **Key words:** impacted mandibular third molar, coronectomy

Апстракт

Мандибуларните трети молари кои се длабоко импактирани и во непосредна близина на инфериорниот алвеоларен канал претставуваат терапевтски предизвик. Тешкото хируршко отстранување може да доведе до привремено или трајно оштетување на инфериорниот алвеоларен нерв (ИАН), резултирајќи со парестезија, хипоестезија или дизестезија на долната усна, забите, гингивата и кожата на брадата, состојби кои значајно влијаат на квалитетот на животот. Покрај тоа, потребата од превенција на овој вид на повреда е исто така особено важна бидејќи актуелните терапевтски модалитети на неуросензитивен дефицит покажуваат само делумно подобрување во осетливоста. Коронектомијата претставува најстара и најдобро проучена процедура за намалување на ризикот од оштетување на инфериорниот алвеоларен нерв. Оваа процедура е дизајнирана така да се отстранува само коронарниот дел на забот, додека корените се оставаат in situ, со што се намалува ризикот од повреда на инфериорниот алвеоларен нерв. Целта на овој труд беше да прикаже случај на коронектомија изведена како алтернатива на комплексната хируршка екстракција на мандибуларен трет молар импактиран длабоко и во непосредна близина на инфериорниот алвеоларен нерв. На одлуката за видот на третманот и претходеше внимателна предоперативна рентгенолошка проценка на коренската морфологија и детекција на рентгенолошките знаци за инволвираност на мандибуларниот канал. По провизорно утврдување на бројот на корените на четири, апикилно повиени, совпаднати и протегнати под долната ивица на мандибуларниот канал, се претпостави комплексно хируршко отстранување на импактираниот трет молар со обемен коскен губиток, фрактура на корените и повреда на инфериорниот алвеоларен нерв. Коронектомија беше земена предвид со цел да се избегне значителна хируршка траума и да се намали ризикот од повреда на инфериорниот алвеоларен нерв. Под локална инфилтративна анестезија и формиран триаглест флап, се направи перикоронарна остеотомија и попречна секција на коронката на ниво на емајлово-цементната граница. По ослободување, коронката се отстрани, а останатата површина се израмни. Раната се исчисти и сутурира. Постоперативниот период беше спокоен. Не беа забележани знаци на сетилно нарушување на левата мандибуларна страна. **Клучни зборови:** импактиран мандибуларен трет молар, коронектомија.

Introduction

Mandibular third molars are the most frequently impacted permanent teeth. Newly published evidence suggested that 72,2% of the entire world's population has at least one impacted tooth (usually lower third molar)^{1,2,3,4}. Those associated with insufficient eruption space, recurrent pericoronitis, or advanced dental caries are deemed to be removed. Removal of impacted third molars is the most frequently performed surgery, compromising 30% of all operations⁵. Postoperative complications are highly related with the depth and position of impaction (i.e., mesio-angular, horizontal, vertical, and disto-angular), and the proximity to important anatomical structures such as the inferior alveolar nerve (IAN) canal⁶.

However, the most concerning postoperative complication is temporary or permanent damage to the inferior alveolar nerve (IAN) resulting in paresthesia, hypoesthesia or dysesthesia of the lower lip, teeth, gingiva and skin over the chin, which significantly affects the quality of life of the patient³. Ahmed C et al., reports that the common risk factors for the IAN damage includes advanced age and difficult impaction, but the most important one is the proximity of the root to the IAN canal⁷. The incidence of IAN damage varies from temporary paresthesia up to 8.1% and permanent discomfort up to 3.6%⁸. The risk of injury increases manifold, when the third molar root overlaps the nerve canal as identified by the radiographic imaging⁹.

The need to prevent these kinds of injuries is especially important since current treatment modalities of neurosensory deficit management show only limited improvement in sensation¹⁰. According to studies, complete recovery is uncommon with all types of available treatments^{10, 5}.

Therefore, prevention instead of cure. Various approaches have been proposed to decrease damage to the IAN in high risk cases, which comprise coronectomy and leaving the roots behind, staged surgical removal of the third molar¹¹, modified coronectomy and grafting¹², orthodontic aided extrusion¹³ and pericoronal osteotomy¹⁴.

Coronectomy is the oldest and the best researched of the IAN injury-risk reducing procedures¹⁵⁻²³. First described in 1984 by Ecuyer and Debien²³, this procedure is designed to reduce the risk of IAN injury by removing the crown portion of the tooth only, leaving the root in situ¹⁰. It has been listed as a standard treatment option for surgical management of third molars by the American association of oral and maxillofacial surgeons (AAOMS)²⁴. In spite of numerous studies supporting the effectiveness of coronectomy, the procedure

remains controversial due to the possibilities of infection and other odontogenic pathology arising from the roots left behind⁹.

The aim of this paper is to depict a case of coronectomy as an alternative approach to complex surgical removal of deeply impacted mandibular third molar with mandibular inferior alveolar nerve involvement.

Clinical report

A 42-year-old female patient was referred to the University department of oral surgery for removal of an unerupted tooth in the lower jaw due to the need for lower denture. She didn't have any complaints regarding the tooth in question. The patient was in good general health, without any co-morbidities. Clinical examination revealed continued mandibular front, from right premolar to left first molar. In the most posterior aspect of the left mandibular quadrant, a semilunar split in the attached gingiva was evident (figure 1).



Figure 1. Intraoral view of the left posterior mandibular quadrant with semilunar split in the crestal aspect of attached gingiva with normal color.

On probing, the hard enamel of the mandibular left third molar was reached. Patient's orthopantomogram depicted a deeply impacted mandibular third molar (class C according to Pell and Gregory's classification), with mesioangular angulation according to Winter's classification. Careful perioperative radiological assessment of root morphology and detection of radiological signs for mandibular canal involvement preceded the treatment decision. The number of roots was vaguely established to four: two mesial and two distal, apically dilacerated, superimposed and extended beyond the lower rim of the inferior alveolar canal. Even more important is that the radiopaque superior border of the canal was interrupted in the bifurcation area (figure 2).



Figure 2. Patient's orthopantomogram depicted deeply impacted left mandibular third molar with multipart root complex superimposed and extended beyond the lower rim of the mandibular canal



Figure 5. Peri coronary bone removed to the cemento-enamel junction



Figure 3. Triangular flap extended medially



Figure 6. Transversal section of the crown

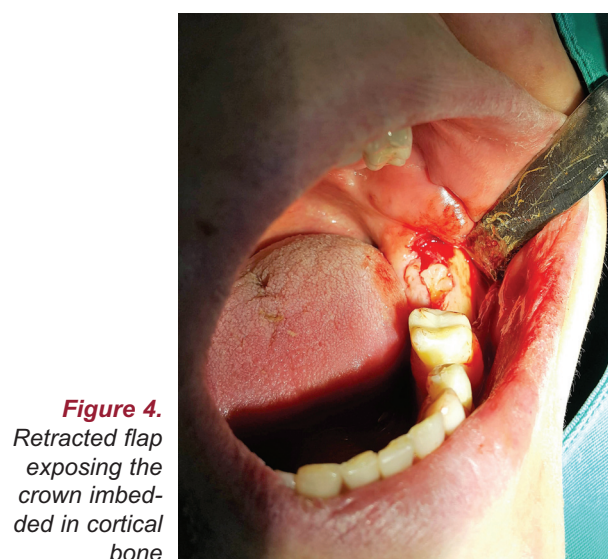


Figure 4. Retracted flap exposing the crown imbedded in cortical bone

After root morphology proximately established, and radiological signs of interest detected, the assumption of complex surgical removal with abundant bone loss, root fractures and inferior alveolar nerve injury was made. To avoid significant surgical trauma and to minimize the risk of inferior alveolar nerve injury, coronectomy was taken into consideration.

With the patient's concurrence, the coronectomy was planned in the following manner. Under local infiltrative block anesthesia of n.alveolaris inferior, n.lingualis and n.buccalis with 2% mepivacaine cum epinephrine (Scandonest 2% with epinephrine, Septodont – France) a triangular flap was positioned (figure 3) with a scalpel No.15 (Aesculap, Tuttingen Tuttlingen, Germany).



Figure 7. Detached crown on the surgical table



Figure 8.
Surgical
wound with
sutures

Peri coronary osteotomy with carbide round bur was executed, down to the cement-enamel junction, followed by transversal sectioning of the crown with carbide fissure bur under copious irrigation (figures 5 and 6). The crown was then detached (figure 7) and the remaining surface trimmed.

The wound was thoroughly cleaned from any debris. Finally, the wound's margins were reapproximated with interspersed sutures (figure 8).

The patient was advised to follow standard post-surgery recommendations. On the following day the patient was asymptomatic, without pain, swelling or discoloration (figures 9 and 10). Sutures were removed seven days post-op, and the extraoral and intraoral appearance remained as usual.



Figure 9. Postoperative extraoral appearance without swelling and skin discoloration



Figure 10. Wound
healing by secondary
intention

Discussion and conclusion

Surgery of impacted mandibular third molars depends on the pre-operative findings. Pre-operative assessment

must be carried out radiologically in an effort to identify the proximity of the impacted tooth to the inferior alveolar canal²⁵. Usually, surgical extractions of impacted teeth are planned in accordance with panoramic findings. Especially, when treatment of deep impactions lays ahead, it is vital to know that panoramic radiographs are reliable in assessing the proximity of impacted mandibular third molars to inferior alveolar canal²⁶. Certain radiological aspects are to be detected in order to predict whether a certain clinical situation poses a risk for IAN damage. Rood and Shehab tested the predictive ability of IAN injury according to panoramic radiography with seven radiological parameters²⁵. In their study, they considered four radiological parameters to be root-related, such as: root darkening, root diversion (deflection), root narrowing and root splitting. The additional three radiological parameters they considered to be canal-associated, such as: loss of continuity of the upper border of the mandibular canal, canal deflection and narrowing of the canal. Their research pointed out a significant correlation between the following radiological parameters and the possibility of a nerve damage following surgical treatment in lower third molars: canal deflection, root darkening and loss of continuity of canal borders. They concluded that other parameters are of no significance. Mesioangular impactions are closer to inferior alveolar canal and interruption of the white line is the most reliable risk predictor sign on the panoramic radiographs⁹.

The meticulous pre-operative radiological examination in the presented case showed medially angulated and deeply impacted left third molar, with complex root morphology, likely four split and diverse roots that superimposed and extended beyond the lower rim of the mandibular canal. Those are very strong radiological risk predictors per se. As mentioned before, the risk of injury increases manifold, when the third molar root overlaps the nerve canal as identified by the radiographic imaging⁹. Additionally, there was loss of the radiopaque superior border of the mandibular canal in the vicinity of the bifurcation area of the third molar. Such radiological parameters were indicative of alveolar nerve injury if surgical extraction was undertaken. Other radiological diagnostic methods might be beneficial in case of surgical extraction, such as cone beam computer tomography (CBCT). However, with the immensity of bone loss remaining the same during the surgical extraction with CBCT, such investigation was deemed unnecessary, expensive and was not pursued. Bone preservation is an essential surgical principal in all oral surgery procedures. In the presented case, the stabilization of the lower denture relied solely on the firm bony fundament. Therefore, the objective was to avoid significant surgical trauma and to minimize the risk of inferior alveolar

nerve injury. There are certain ways to perform a coronectomy. Landi L et al. recommends coronectomy to be done 2mm-3mm from the occlusal surface without involving the pulp after considering the pulpal anatomy of the impacted third molar tooth and the distance between the third molar crown and the second molar¹¹. In case of accidental pulpal exposure, pulpal dressing or pulpotomy was advised. In the presented case, the crown was sectioned at the level of cemento enamel junction, and the remaining enamel was grinded off 2-3 mm below the alveolar crest. It was described that the enamel is inert, and soft tissue cannot attach to its surface therefore the socket does not heal²⁷. It acts as a foreign body, so chances of infection of the unhealed socket are higher. Root fragment at least 3 mm inferior to the crest of bone seems appropriate and appears to encourage bone formation over the retained root fragment²⁸⁻³⁰. The roots were to be left behind and aim for osseocementum formation over the retained root, in contrast to migration and staged removal protocol of Landi L et al¹¹. After the coronectomy, the pulp was exposed without visible bleeding. Treatment attempts were not considered in concurrence with O'Riordan et al⁸. Coronectomy decompresses the pulp chamber, thus it will not be a significant contributing factor for post-operative pain. Histological evaluation of the retrieved lower third molar roots stated that symptoms after coronectomy do not result from the loss of pulp vitality or subsequent periradicular inflammation. It was refined that these pulpal tissues blend with overlying connective tissue when the mucosa heals successfully and the opening of the canal heals with osteocementum²⁷. As a curiosity, it was described that pulpal treatment of the retained root has resulted in high rate of infection and the subsequent need for removal³¹. Retention of root after coronectomy is based on the idea that broken fragments of vital teeth generally heal without complications^{32,33}, and³⁴. This procedure attracted special attention in the last decade, because of the reported benefits and success rate of this technique, in contrast to the contemporary belief that the roots left behind will be source of problems^{11,35}, and³⁶. Not all third molars are suitable for coronectomy. Those with infection and mobility should be excluded, because remnants of those teeth may act as foreign bodies. In addition, teeth that are horizontally impacted along the course of the inferior alveolar canal may be unsuitable, because the sectioning of a tooth could endanger the nerve¹⁵.

Although some authors used preoperative prophylactic antibiotic therapy or suggested post-operative use¹⁷, no such protocol was followed in this case and no infection emerged. The coronectomy performed on an intact third molar in a healthy individual was not an indication for

antibiotic prophylaxis of local inflammation. It is the author's firm belief that prudent antibiotic use is indispensable to fight antibiotic resistance.

In spite of the reported advantages, patients are very anxious about leaving the root behind in the bone and are not willing to take a chance for infection or a second surgical intervention. The surgeon is responsible for informing the patient to her/his best abilities concerning the proposed treatment, and to gain their trust.

The disadvantages of coronectomy include deep periodontal pockets on the distal of the second molars (similar to those after extractions in comparable circumstances), root migration with the possible need of a second procedure, dry sockets, local post-operative infections, post-operative pain and inadvertent root removal, or root walk-out during surgery which may increase the risk of IAN injury, also known as a failed coronectomy^{15, 16, 8, 37}. The second molar was absent so there was no reason for periodontal concern. Post-operative period was uneventful, without pain, or infection. And last, but not least, no signs of sensitive disturbances in the left mandibular side were noted. It is not necessary to recall the patient after 6 months, unless the patient becomes symptomatic¹⁵, which was not the case.

Conclusion

Coronectomy may be a suitable alternative to complex surgical extraction of impacted mandibular molars with no infection and in close proximity to the mandibular canal, as shown on the panoramic radiograph. Every patient is unique, every situation is special and in carefully selected cases the most conservative surgical approach is the appropriate one.

Reference

1. Motamedi K, Hosein M. A Textbook of Advanced Oral and Maxillofacial Surgery Complications Following Surgery of Impacted Teeth and Their Management. 2013
2. Divya T, Themozhi MS. Third molar impaction- a review. J Pharm Sci Res. 2014;6(11):363–367.
3. Juodzbalsys G, Daugela P. Mandibular third molar impaction: review of literature and a proposal of a classification. J Oral Maxillofac Res. 2013;4(2):1–12.
4. Popli G, Kiran D.N, Iyer N, Sethi S, Bansal V, Bansal A. Influence of Pederson score and its constitutional anatomical parameters to predict the postoperative morbidity after Lower Third Molar Removal: a prospective cohort study. Am J Oral Maxillofac Surg. 2014;2(1):7–14.
5. Alantar A, Roisin-Chausson MH, Commissionat Y, et al. Retention of third molar roots to prevent damage to the inferior alveolar nerve. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology 1995;80(2):p126.
6. Vafaei N, Ferretti C. Coronectomy: an alternative therapy for the symptomatic, impacted third molar report of 9 cases. Scientific. 2008;22:34:6–12.
7. Ahmed C, Wafae el W, Bouchra T. Coronectomy of third molar: a reduced risk technique for inferior alveolar nerve damage. Dent Update. 2011;38:267–76.
8. O'riordan BC. Coronectomy (intentional partial odontectomy of lower third molars) Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98(3):274–280.
9. Mukherjee S, Vikram B, Sankar D, Veerabahu MS. Evaluation of outcome following coronectomy for the management of mandibular third molars in close proximity to the inferior alveolar nerve. J.Clinical Diagnosis Res. 2016 Aug; 10(8):57–62.
10. Leung YY, Fung PPL, Cheung LK. Treatment modalities of neurosensory deficit after lower third molar surgery: a systematic review. Journal of Oral and Maxillofacial Surgery. 2012;70(4):768–778.
11. Landi L, Manicone PF, Piccinelli S, Raia A, Raia R. A novel surgical approach to impacted mandibular third molars to reduce the risk of paresthesia. J Oral Maxillofac Surg. 2010;68:969–74.
12. Leizerovitz M, Leizerovitz O. Modified and grafted coronectomy: A new technique and a case report with twoyear followup. Case Rep Dent. 2013.
13. Alessandri Bonetti G, Bendandi M, Laino L, Checchi V, Checchi L. Orthodontic extraction: Riskless extraction of impacted lower third molars close to the mandibular canal. J Oral Maxillofac Surg. 2007;65(12):2580–86.
14. Tolstunov L. Pericoronectomy as alternative treatment option for extraction of impacted mandibular third molars in proximity to inferior alveolar nerve. J Oral Maxillofac Surg. 2010;68(1):231–32.
15. Pogrel MA, Lee JS, Muff DF. Coronectomy: a technique to protect the inferior alveolar nerve. Journal of Oral and Maxillofacial Surgery. 2004;62(12):1447–1452.
16. Renton T, Hankins M, Sproate C, McGurk M. A randomised controlled clinical trial to compare the incidence of injury to the inferior alveolar nerve as a result of coronectomy and removal of mandibular third molars. British Journal of Oral and Maxillofacial Surgery. 2005;43(1):7–12.
17. Pogrel MA. An update on coronectomy. Journal of Oral and Maxillofacial Surgery. 2009;67(8):1782–1783.
18. Leung YY, Cheung LK. Safety of coronectomy versus excision of wisdom teeth: a randomized controlled trial. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 2009;108(6):821–827.
19. Hatano Y, Kurita K, Kuroiwa Y, Yuasa H, Aji E. clinical evaluations of coronectomy (intentional partial odontectomy) for mandibular third molars using dental computed tomography: a case-control study. Journal of Oral and Maxillofacial Surgery. 2009;67(9):1806–1814.
20. Dolanmaz D, Yildirim G, Isik K, Kucuk K, Ozturk A. A preferable technique for protecting the inferior alveolar nerve: coronectomy. Journal of Oral and Maxillofacial Surgery. 2009;67(6):1234–1238.
21. Cilasun U, Yildirim T, Guzeldemir E, Pektas ZO. Coronectomy in patients with high risk of inferior alveolar nerve injury diagnosed by computed tomography. Journal of Oral and Maxillofacial Surgery. 2011;69(6):1557–1561.
22. Leung YY, Cheung LK. Coronectomy of the lower third molar is safe within the first 3 years. Journal of Oral and Maxillofacial Surgery. 2012;70(7):1515–1522.
23. Ecuyer J, Debieu J. Surgical deductions. Actualites Odonto Stomatologiques. 1984;38(148):695–702.
24. Lieblisch SE, Kleiman MA, Zak MJ J. Parameters of care: clinical practice. Guidelines for oral and maxillofacial surgery. (AAOMS Par Care 2012) Journal of Oral and Maxillofacial Surgery. 2012;70 (e50).
25. Rood JP, Shehab BA (1990) The radiological prediction of inferior alveolar nerve injury during third molar surgery. Br J Oral

-
- Maxillofac Surg 28(1): 20–25.
26. Deshpande P, Guledgud M, Patil K. Proximity of impacted mandibular third molars to the inferior alveolar canal and its radiographic predictors: A panoramic radiographic study. *J. Maxillofacial surgery*. 2013;Jan; 12(2): 145-151.
 27. Patel V, Sproat C, Kwok J, Beneng K, Thavaraj S, McGurk M. Histological evaluation of mandibular third molar roots retrieved after coronectomy. *Br J Oral Maxillofac Surg*. 2014;52:415–19.
 28. Johnson DL, Kelly JF, Flinton RJ, Cornell MT. Histological evaluation of vital root retention. *J Oral Surg*. 1974;32(11):829–33.
 29. Whitaker DD, Shankle RJ. A study of the histologic reaction of submerged root segments. *Oral Surg Oral Med Oral Pathol*. 1974;37:919–35.
 30. Plata R L, Kelln E E, Linda L. Intentional retention of vital submerged roots in dogs. *Oral Surg Oral Med Oral Pathol*. 1976;42:100–08.
 31. Sencimen M, Ortakoglu K, Aydin C, Aydintug YS, Ozyigit A, Ozen T, et al. Is endodontic treatment necessary during coronectomy procedure? *J Oral Maxillofac Surg*. 2010;68:2385–90.
 32. Fareed K, Khayat R, Salins P. Vital root retention: A clinical procedure. *J Prosthet Dent*. 1989;62(4):430–34.
 33. Knutsson K, Lysell L, Rohlin M. Post-operative status after partial removal of the mandibular third molar. *Swed Dent J*. 1989;13(1-2):15–22.
 34. Velickovski B, Peeva M, Velevska D, Kacarska M: Coronectomy-prevention from the injury of the Inferior alveolar nerve (n.alveolaris inferior). *International Journal of case reports*, vol.5, 2015, No 14.
 35. Umar G, Obisesan O, Bryant C, Rood JP. Elimination of permanent injuries to the inferior alveolar nerve following surgical intervention of the "high risk" third molar. *Br J Oral Maxillofac Surg*. 2013;51(4):353–57.
 36. Goto S, Kurita K, Kuroiwa Y, Hatano Y, Kohara K, Izumi M, et al. Clinical and dental computed tomographic evaluation 1year after coronectomy. *J Oral Maxillofac Surg*. 2012;70:1023–29.
 37. Tolstunov L, Javid B, Keyes L, Nattestad A. Pericoronar osteotomy: an alternative surgical technique for management of mandibular third molars in close proximity to the inferior alveolar nerve. *Journal of Oral and Maxillofacial Surgery*. 2011;69(7):1858–1866.

TORUS PALATINUS: CLINICAL ASPECT AND THERAPEUTIC STRATEGY

TORUS PALATINUS: КЛИНИЧКИ АСПЕКТИ И ТЕРАПЕВТСКА СТРАТЕГИЈА

Kacarska M.

University department of oral surgery, University „Sts Cyril and Methodius“

Abstract

Torus palatinus is an exostosis of the hard palate located along the median palatine suture. With slow growth and usually asymptomatic, torus is usually diagnosed by accident. Surgical treatment is necessary when it presents an obstacle for prosthetic stabilization. This article presents clinical and therapeutical aspects of torus palatinus. The clinical manifestation of palatal torus was oval in shape with longer sagittal projection and normal gingival appearance. The surgical approach depended on its size and morphology. Local infiltrative anesthesia was used. After palatal Y incision and mobilization, the torus was sectioned in smaller fractions and removed. The rough bone surface was remodeled, and the primary closure was reached with simple sutures. The sutures were removed seven days after the procedure showing signs of wound dehiscence. The wound healing was postponed and follow ups were scheduled to facilitate the healing by secondary intention. **Key words:** torus palatinus, surgical removal, prosthetic stabilization

Апстракт

Torus palatinus претставува екзостоза на тврдото непце која е поставена долж sutura mediana. Поради својот бавен раст и отсуство на тегоби, многу често случајно се открива. Хируршка терапија е потребна кога торусот ја попречува стабилизацијата на протезата. Во овој труд се презентирани клинички и терапевтски аспекти на torus palatinus. Клинички палатиналниот торус се манифестираше со овална форма, подолга сагитална димензија и пингива со нормален изглед. Хируршкиот приод зависеше од неговата големина и морфологија. Операцијата беше изведена со локална инфилтративна анестезија. Хируршкиот приод беше овозможен со палатинална Y инцизија, а торусот беше поделен на помали делови и отстранет. Нерамната коскена површина беше замазнета и оперативното поле затворено per primam со поединечни сутури. Сутурите беа отстранети по седум дена со видливи знаци на дехисценција на раната. Поради одложување на заздравувањето, беа предвидени повеќе контроли за да се олесни заздравувањето по секундарен пат. **Клучни зборови:** torus palatinus, хируршко отстранување, стабилизација на протеза

Introduction

Torus palatinus may be defined as an exostosis of the hard palate located along the median palatine suture, involving both the processus palatini and the os palatinum¹. Hitherto no exact etiology has been identified for the presence of tori. The most widely accepted theory today is that this condition has a multifactorial etiology, which includes mainly genetics and environmental factors. According to the shape, torus palatinus can be classified as flat, spindle-shaped, nodular, and lobular². The size is highly variable, varying from that of a small pea to an enormous enlargement that may cover the entire palate to the extent of occlusal plane. Reichart et al have classified TP, based on their size, as small (less than 3 mm), medium (3–6 mm), and large (more than 6 mm) tori³. It is composed of a dense cortical bony structure and minimal amount of bone marrow covered with a

fragile and limited vascularized mucosa. Larger specimens can have a center of cancellous bone and the only difference between the palatal torus and other exostoses is in its being developed at characteristic sites and in a symmetrical manner⁴. Diagnosis is frequently in occasional way because those pathologies are asymptomatic⁵. Palatal tori are characterized by slow growth and the torus can reach a large size that requires surgical removal, for example, when representing an obstacle to prosthetic treatment^{6,4}.

This article presents clinical and therapeutical aspects of torus palatinus.

Aim of the paper

A 72 years old female was referred to the University department of oral surgery for pre prosthetic teeth removal. During anamnesis, the patient confirmed to be

diabetic and hypertensive. Clinically, gangrenous teeth in the maxilla and a prominence in the midline of the hard palate were visible. The oval shaped prominence had longer sagittal projection and normal gingival appearance (figure 1).



Figure 1. Clinical appearance of torus palatinus. Note the mid palate oval symmetrical protuberance, with longer sagittal projection and normal gingival appearance

It was firm and painless on palpation. Hence a diagnosis of torus palatinus was made. The patient was not aware and she didn't have any complaints or issues with the palatal protuberant. But in order to achieve prosthetic stabilization, it was obvious that torus palatinus had to be removed. The surgical removal was performed with

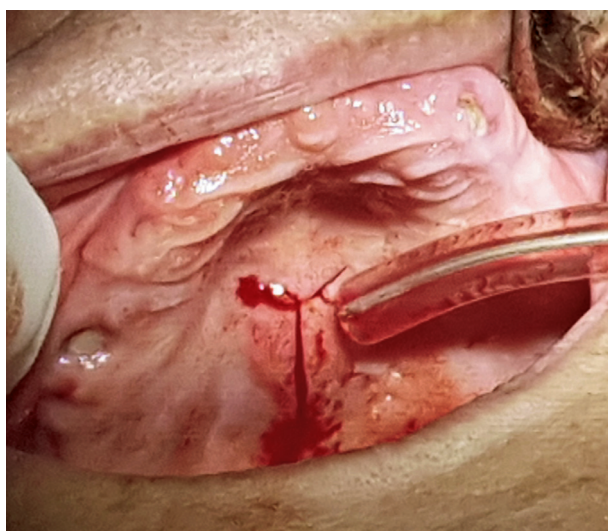


Figure 2. Y midpalate incision

local infiltrative anesthesia (3% mepivacaine, Scandonest). Bilateral terminal anesthesia was administered in premolar and molar region on vestibular as well as palatal side. Sagittal Y incision was positioned across the mid palate using scalpel No.15. (figure 2). Subsequently, mucosal tissue and the underlying periosteum were detached in order to expose the subjacent lesion to the largest possible extent (figure 3).

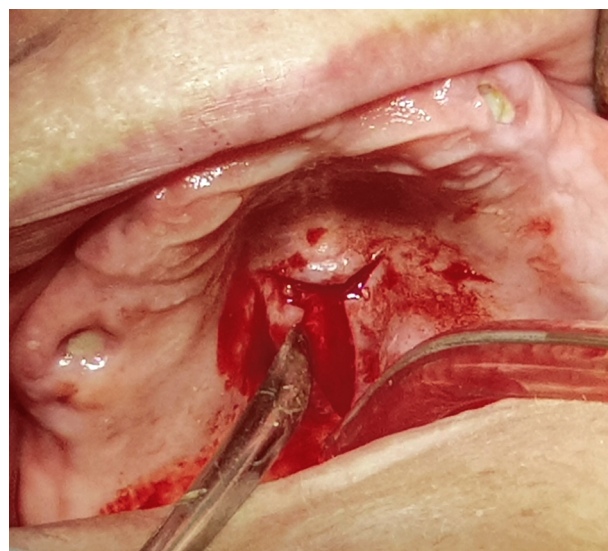


Figure 3. Mobilized Y incision

The surgical technique itself was based on the sectioning of the torus in smaller fractions and their removal. At first a sagittal groove with a fissure bur and a straight hand

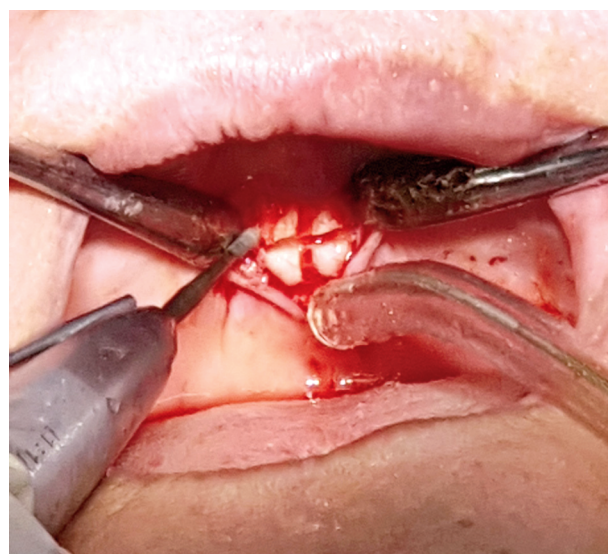


Figure 4. Four squares outlined with sagittal and transverse grooves

piece was made under abundant irrigation with 0.9% saline solution followed by transversal, thus four squares were outlined (figure 4).



Figure 5.

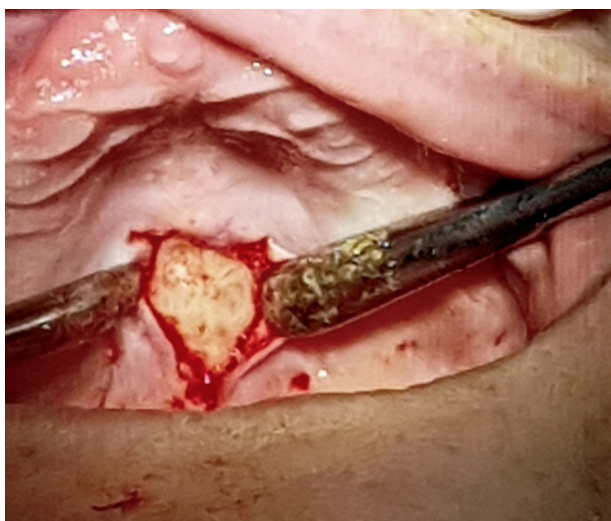


Figure 6.

Figure 5, 6 Remolding of the bone surface

Primary closure of the surgical bed was reached with simple sutures, tension free (figure 7). In the immediate postoperative period analgesic therapy was advised and the patient was advised to consume only cold liquids. At the first follow up palatal edema was evident (figure 8). The sutures were removed seven days after the procedure with visible wound dehiscence (figure 9). The wound healing was postponed and follow ups were scheduled to facilitate the healing by secondary intention (figure 10).



Figure 7. Surgical wound sutured, tension free

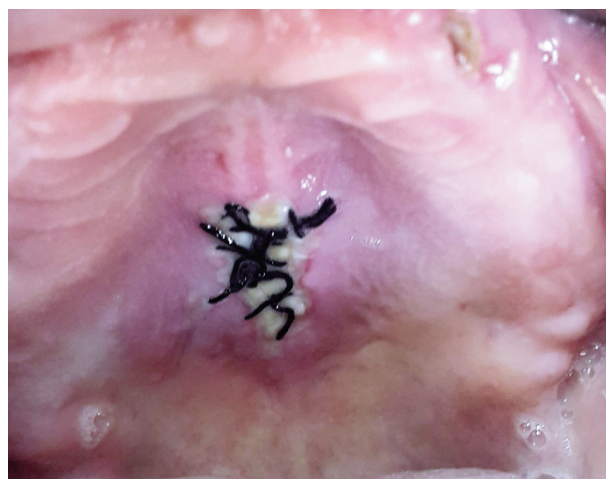


Figure 8. First postoperative follow up. Note the palatal edema



Figure 9. Wound dehiscence after suture removal



Figure 10. Wound healing by secondary intention

Discussion

According to the literature, palatal tori are the most common oral exostoses, more common than mandibular tori. The average prevalence of palatal tori seems to be 20–40% with significant topographical disparities. Most authors have observed a predominance of palatal tori in women as well as a larger average size⁷⁻¹⁰. Epidemiological data differs. Some studies have reported the appearance and growth to occur in people aged 10–30 years, with a subsequent decline. Others believe that tori growth may continue beyond the age of 30, in the 40–60 age group, with a variable incidence peak, depending on the population^{9,11} as was the case with the 72-year female patient. The exact etiology of tori has not been clearly established. Genetic theory attributes a preponderant role to certain genetic factors in the occurrence of palatal tori. Several authors have cited that environmental factors are likely to promote oral exostoses. Although not clearly identified, masticatory hyperactivity and para-functions appear to be the main factors, with diet (unsaturated fatty acids and calcium) to a lesser extent^{7,10,12}. Torus palatinus has been described as an anatomical variation rather than a pathological condition, which more frequently affects the female gender and young population^{13,14}. Palatal tori are mostly asymptomatic as was demonstrated in this case, which is why they usually go unnoticed, and characterized by a fortuitous discovery during a routine examination by the practitioner as presented in this case. The diagnosis of palatal torus is clinical, but radiographic and pathological examinations may sometimes be useful^{7,8}. For correct clinical diagnosis it is important to remember that torus palatinus is always symmetrical and located in the middle of the hard palate. Asymmetrical formations

must be differentially diagnosed as other benign or malignant lesions. If a suspected torus is not midline a biopsy is needed to rule out this potentially fatal adenoid cystic carcinoma¹⁵. A diverse morphological variation can be seen such as flat, nodular, lobular and spindle shaped, the prevalence of which depend on the epidemiological profile of each population¹⁶. The size of the tori may fluctuate throughout life and, when they interfere with function or partial/full denture placement, surgery is a necessity^{17,18}. The torus palatinus reported in this case was medium sized, spindle shaped with wide base, located in the middle palate of edentulous maxilla. Palatal tori are benign maxillary bone tumors that are most often asymptomatic, slow growing and do not require any specific management. However, surgical management may be necessary in case of prosthetic instability or pre-prosthetic surgery¹⁹. Local anesthesia is indicated in most cases, with large palatal and nasopalatal nerve blocks allowing complete analgesia in the intervention area. However, in cases of large palatal tori or a very posterior localization, general anesthesia may be considered⁷⁻²⁴. Various techniques have been used in the conventional surgical treatment of these lesions^{25,26,27,17,18,28,29}, since the technique will depend on the extent and location of the lesion, and the epidemiological profile of the patient. Conventional surgical treatment, in exception of chisel and hammers that involve possible risks of traumatic injuries, request to perform excision via bony burs once the flap has been anchored by different methodologies or simply elevated and maintained via suture needle or any other conventional means. The procedure has two essential phases: mucosal phase and bone phase. Four main types of incisions can be made depending on the location and morphology of the palatal torus: simple linear incision, Y incision, double Y incision, and double curvilinear incision with a long antero posterior axis delimiting an elliptical mucosal surface that will need to be excised⁷. In the presented case a Y incision was used to enable anterior flap mobilization. At the time of mucoperiosteal detachment, there is a risk of tearing of the adherent palatal mucosa and damage to the large palatal vessels, most often located at the borders of the palatal torus¹⁹. The palatal mucosa was thin, and submucosa was obscured, rigid, so flap mobilization was delicate, but not compromised. The surgery of torus palatinus reported in this case could be done in the few manners: torus removal by slicing or cutting with burs or pyzosurgery, wearing away the torus with surgical burs, pyezo or peeling/smoothing with Er:YAG laser. The cleavage of the bony torus can be accomplished using rotating instruments, followed by curved bone scissors. Alternatively, piezo surgery can be performed by continuously monitoring the direction of the cleavage plane to prevent any traumatic oral–nasal communication or radiating fractures.

Large palatal tori may fragment before removal. After cleavage, bone regularization is performed^{7,30,31}. The shape and the extent of torus influenced the treatment plan. Its spindle shape covered the anterior region of the palatal vault without extension to the alveolar process, thus torus was removed by sectioning. Before closing the mucosal tissue, it is essential to ensure that the mucous membrane has correctly adapted to the new palatal environment and to perform a mucosal resection if it has not been performed or if it was insufficient during the incisions at the beginning of the procedure¹⁹ which was not the case. The suturing was delicate, and a steady hand was required to not tear the gingiva while suturing. The per primam wound healing was disrupted as in a reported case of removal of giantiforme torus palatines, with sutures being removed 15 days post op³². It is the author's opinion that due the postoperative edema the wound dehiscence became apparent. A preoperatively prepared resin palatal plate or a removable prosthesis in cases of partial or total tooth loss can be put in place at the end of the procedure to provide local compression; this would prevent postoperative hemorrhaging, protect the mucosal wound, and decrease postoperative sensitivities. According to some authors, this may reduce the risk of recurrence. Similarly, a surgical resection guide can be performed, thereby reducing the risk of under-correction or over-correction with the proximity of peripheral anatomical structures^{7,23}. A palatal plate could restrain postoperative swelling and prevent wound dehiscence, so it is advisable to use it in palatal torus surgery.

Conclusion

Torus palatinus is an asymptomatic bone formation that has to be surgically removed as a prerequisite for prosthetic stabilization. The surgical approach depends on its size and morphology. Asymmetrical palatal formations must be differentially diagnosed from palatal torus as other benign or malignant lesions.

Reference

1. Sisman Y, Ertas ET, Gokce C, Akgunlu F. Prevalence of torus palatinus in Cappadocia region population of Turkey. *Eur J Dent*. 2008;2:269–275.
2. Simunković SK, Bozić M, Alajbeg IZ, Dulčić N, Boras VV. Prevalence of torus palatinus and torus mandibularis in the Split-Dalmatian County, Croatia. *Coll Antropol*. 2011;35:637–641.
3. Reichart PA, Neuhaus F, Sookasem M. Prevalence of torus palatinus and torus mandibularis in Germans and Thais. *Commun Dent Oral Epidemiol*. 1988;16:61–64.
4. Cawson RA, Odell EW – editors. *Cawson's essentials of oral pathology and oral medicine*. London: Churchill Livingstone; 2008.
5. J. P. Rocca, H. Raybaud, E. Merigo, P. Vescovi, C. Fornaini. Er:YAG Laser: A New Technical Approach to Remove Torus Palatinus and Torus Mandibularis. *Case Rep Dent*. 2012, 1-4.
6. Gorsky M, Raviv M, Kfir E, Moskona D. Prevalence of torus palatinus in a population of young and adult Israelis. *Arch Oral Biol*. 1996. Jun;41(6):623–5.
7. Tamba B, Dia Tine S, Barry BCG, Kounta A, Niang PD, Ba A et al. Exostoses buccales: revue de la littérature. *Med Buccale Chir Buccale* 2012;18:129–141.
8. Hascoet E, Vaillant PY, Tempescul A, Darbin C, Lansonneur C, Boisramé S. Tori et exostoses multiples: présentation d'un cas et revue de la littérature. *Med Buccale Chir Buccale* 2015;21:19–24.
9. Jankittivong A, Langlais RP. Buccal and palatal exostoses: prevalence and concurrence with tori. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;90 (1):48–53.
10. Al Quran FAM, Al-Dwairi ZN. Torus palatinus and torus mandibularis in edentulous patients. *J Contemp Dent Pract* 2006;7:112–119.
11. Sonnier KE, Horning GM, Cohen ME. Palatal tubercles, palatal tori, and mandibular tori: prevalence and anatomical features in a U.S. population. *J Periodontol*. 1999;70:329–336.
12. Kerdpon D, Sirirungrojying S. A clinical study of oral tori in southern Thailand: prevalence and the relation to parafunctional activity. *Eur J Oral Sci*. 1999;107:9–13.
13. Telang L.A, Telang A., Nerali J., Pradeep P. Tori in a Malaysian population: morphological and ethnic variations. *J. Forensic Dent. Sci*. 2019;11:107.
14. Pei-Ching C. Torus palatinus in Taiwan patients receiving peritoneal dialysis and hemodialysis: a prospective observational study. *J. Multidiscip. Healthc*. 2020;13:373.
15. R P. Usatine, M A. Smith, H S. Chumley, E.J. Mayeaux Jr. *A color atlas of family medicine*. Second edition: www.accessmedicine.com
16. MacInnis E.L., Hardie J., Baig M., Al-Sanea R. A Gigantiform torus palatinus: review of the literature and report of a case. *Int. Dent. J*. 1998;48:40–43.
17. Seah YH. Torus palatinus and torus mandibularis: a review of the literature. *Australian dental journal*. 1995;40(5):318–321.
18. Bruce I, Ndanu TA, Addo ME. Epidemiological aspects of oral tori in a Ghanaian community. *International Dental Journal*. 2004;54(2):78–82.
19. J Bouchet, G Hervé, G Lescaille, V Descroix, A

- Guyon. Palatal torus: etiology, clinical aspect, and therapeutic strategy. Up-to Date Review And Case Report. *J. Oral Med Oral Surg* 2019;18-25
20. Hiss J, Taddei C, Wolfram-Gabel R, Féki A. Le torus palatin. Etude réalisée sur 723 crânes humains et comparaison avec les données de la littérature. *Médecine Buccale Chirurgie Buccale* 2005;11:205–213.
 - Jainkittivong A, Apinhasmit W, Swasdison S. Prevalence and clinical characteristics of oral tori in 1, 520 Chulalongkorn University Dental School patients. *Surg Radiol Anat* 2007;29:125–131.
 21. Jainkittivong A, Apinhasmit W, Swasdison S. Prevalence and clinical characteristics of oral tori in 1, 520 Chulalongkorn University Dental School patients. *Surg Radiol Anat* 2007;29:125–131.
 22. El Achkar VNR, Lopes SLP de C, Pinto ASB, do Prado RF, Kaminagakura E. Imaging aspects of palatal torus in cone beam computed tomography and magnetic resonance: case report. *Acta Stomatol Croat* 2016;50:359–364.
 23. Regragui A, Sefrioui A, Merzouk N, Berrada S. Hypertrophie osseuse buccale chez l'édenté complet: une fatalité à contourner! *Actualités Odonto-Stomatologiques*. 2016;275:2.
 24. García-García AS, Martínez-González J-M, Gómez-Font R, Soto-Rivadeneira A, Oviedo-Roldán L. Current status of the torus palatinus and torus mandibularis. *Med Oral Patol Oral Cir Bucal* 2010;15:e353–e360.
 25. Garcia-Garcia AS, Martinez-Gonzalez JM, Gomez-Font R, Soto-Rivadeneira A, Oviedo-Roldan L. Current status of the torus palatinus and torus mandibularis. *Medicina Oral, Patologia Oral y Cirugia Bucal*. 2010;15(2):e353–e360.
 26. Antoniadis DZ, Belazi M, Papanayiotou P. Concurrence of torus palatinus with palatal and buccal exostoses: case report and review of the literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 1998;85(5):552–557.
 27. Haugen LK. Palatine and mandibular tori. A morphologic study in the current Norwegian population. *Acta Odontologica Scandinavica*. 1992;50(2):65–77.
 28. Sirirungrojying S, Kerdpon D. Relationship between oral tori and temporomandibular disorders. *International Dental Journal*. 1999;49(2):101–104.
 29. Jainkittivong A, Langlais RP. Buccal and palatal exostoses: prevalence and concurrence with tori. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2000;90(1):48–53.
 30. Princ G, Toledo R, Dichamp J. Chirurgie préprothétique. *Encyclopédie Médico-Chirurgicale Chirurgie orale et maxillo-faciale*. Paris: Elsevier, 1999:22-320-A-10.
 31. Fragiskos FD. Torus palatinus. *Oral Surgery*. Springer Science+Business Media, 2007:253–256.
 32. W. Bernaola-Paredes, A MPereira, T.A.Luiz, I. S Martins, F F. Lima, K. A. Vallejo-Rosero. An atypical presentation of gigantiform torus palatinus: A case report *Int J Surg Case Rep*. 2020; 75: 66–70.

ORAL REHABILITATION OF A CHILD WITH HYPOHIDROTIC ECTODERMAL DYSPLASIA: SIX YEARS FOLLOW-UP STUDY

ОРАЛНА РЕХАБИЛИТАЦИЈА НА ДЕТЕ СО ХИПОХИДРОТИЧНА ЕКТОДЕРМАЛНА ДИСПЛАЗИЈА: ШЕСТ ГОДИШНО СЛЕДЕЊЕ И ТРЕТМАН

Bajraktarova Valjakova E¹, Jovanovska M.², Tofoski G.³, Bajraktarova Misevska C.⁴, Panchevska S.¹, Mijoska A.¹, Korunoska Stevkovska V.¹.

¹Department of Prosthodontics, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, University Dental Clinical Center "St. Panteleimon", Skopje, ²Department of Pediatric and Preventive Dentistry, University Dental Clinical Center "St. Panteleimon", Skopje,

³Faculty of Medicine, University "Ss Cyril and Methodius" – Skopje, University Clinic of Gynecology and Obstetrics, Skopje, ⁴Department of Orthodontics, Faculty of Dentistry, University "Ss Cyril and Methodius" – Skopje, University Dental Clinical Center "St. Panteleimon", Skopje

Abstract

Introduction: Hypohidrotic ectodermal dysplasia (HED) is a congenital disorder affecting the tissues of ectodermal embryonic origin. Hypohidrosis, hypotrichosis, and hypodontia or anodontia represent a clinical triad of the syndrome. The ED individuals have typical facial features, while teeth agenesis in both dentitions, underdeveloped alveolar ridges, and improper maxillo-mandibular relations are the main characteristics of the oro-facial system. **Case report:** The manifestation of symptoms, way of communication, and the dental management of a patient with Hypohidrotic ectodermal dysplasia were described, following the patient from his 2.5 years until his 8.5 years of age. Removable acrylic dentures – complete denture in the mandible and maxillary teeth-supported overdenture, or mandibular complete denture and maxillary denture fenestrated in the anterior region, at 5.5 and 8.5 years of age respectively, have been produced, while the deciduous teeth have been reshaped using a composite material. **Conclusion:** When deciding on a dental treatment choice for a HED person, all the factors affecting the final success of the appliances should be considered, of which child's age and skeletal developmental stage are the most important factors. Production of a removable acrylic dentures seems to be the most reasonable, non-invasive and, cost-effective treatment solution in the growing ED patient with severe teeth agenesis. **Keywords:** Hypohidrotic ectodermal dysplasia, treatment choice, removable dentures.

Апстракт

Вовед: Хипохидротичната ектодермална дисплазија (ХЕД) е вродено нарушување на ткивата од ектодермално ембрионално потекло. Хипохидроза, хипотрихоза, и хиподонција или анодонција претставуваат клинички тријаз на синдромот. Лицата со ЕД имаат типичен изглед на лицето, додека пак агенезата на забите во двете дентитии, неразвиените алвеоларни гребени и нарушените меѓувилнички односи се главни карактеристики на оро-фацијалниот систем. **Приказ на случајот:** Во овој труд се прикажани симптомите, терапевтскиот пристап и денталниот третман кај пациент со Хипохидротична ектодермална дисплазија, и неговото следење од две и пол годишна, до осум и пол годишна возраст. Во зависност од возраста изработени се различни видови на подвижни акриллатни протези – мандибуларна тотална протеза и максиларна покривна протеза на пет и пол годишна возраст, односно мандибуларна тотална и максиларна протеза фенестрирана во фронталната регија на осум и пол годишна возраст, кога млечните заби се преобликувани со помош на композитен материјал. **Заклучок:** При изборот на дентален третман кај лица со ХЕД, треба да се земат предвид сите фактори кои влијаат на крајниот успех на терапијата, од кои возраста на детето и скелетниот развоен стадиум се најзначајните фактори. Подвижните акриллатни протези се најразумен, неинвазивен, и најевтин избор кај децата во развој со Ектодермална дисплазија и изразен недостаток на забите. **Клучни зборови:** Хипохидротична ектодермална дисплазија, избор на третман, мобилни протези.

Introduction

Ectodermal dysplasia (ED) is a congenital disorder characterized by abnormal development of two or several tissues or structures of ectodermal embryonic origin,

such as skin, hair, nails, teeth, sweat glands, mammary gland, eye lenses, parts of the inner ear, nerves. This syndrome was first described by Thurman in 1848¹, and until today several classification systems have been made. The most widely known one was introduced by

Freire-Maia, published in 1971², and upgraded several times afterwards. While initial classification systems were based on phenotypic features (clinical aspects) and mode of inheritance, the latest one, published in 2019 by an international advisory group, comprises of information from multiple domains including phenotype, mode of inheritance, genetic alteration, the components of complex molecular structures and the Online Mendelian Inheritance in Man number³.

ED syndrome includes approximately 200 clinically different conditions which differ from each other according to tissues and structures that are not properly developed⁴. All these conditions can be grouped in two major categories depending on the functionality and number of the sweat glands: Hidrotic and Hypohidrotic or Anhidrotic type.

Hidrotic ectodermal dysplasia, known as Clouston syndrome, is characterized by the clinical triad consisting of nail dystrophy, hypotrichosis, and palmoplantar hyperkeratosis. It is inherited as an autosomal dominant disorder, although *de novo* gene mutations have also been reported⁵. The main difference between Hidrotic and Hypohidrotic type of ED is that in the Hypohidrotic type the number of sweat glands is reduced and some of them do not function properly^{6,7}. This condition is characterized with heat-intolerance particularly in the summer or high ambient temperatures, and during exercise⁸, as the body cannot cool itself by evaporating sweat. HED is especially dangerous in infants, during infection diseases, which, if not timely recognized, may cause febrile seizures (hyperthermic episodes) with brain damage⁹, and consequent developmental retardation, and eventually lethal outcome. Other tissues and structures of ectodermal origin are also affected, making a triad of symptoms: hypohidrosis, hypotrichosis (skin- and scalp-hair anomalies accompanied by sparse and fine eyebrows and eyelashes) as well as anodontia or hypodontia (associated with small and conical incisors)^{6,10}. It may be inherited as an autosomal recessive or autosomal dominant disorder affecting both sexes equally, or as X-linked recessive disorder, in which males are severely affected, while female carriers can be asymptomatic or have a milder phenotype⁷. The key symptom of rare subtype of HED, Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID), is reduction in immune system function. It is characterized by low levels of immunoglobulins, while immune system T- and B- cells have a decreased ability to recognize and respond to bacteria, viruses, and yeast with glycan antigens attached to their surface. This is a reason for frequent and recurrent infections such as sinusitis, bronchitis, pneumonia, otitis and lymphadenitis^{11,12}.

HED is associated with nail abnormalities, low-set, sticking-out ears and typical facial features such as pro-

truding forehead, wrinkled eyelids, characteristic periorbital hyperpigmentation, saddle-bridged nose, protruding lips and hypoplasia of the mandible. Anodontia or hypodontia does not affect the development of the maxillary and mandibular alveolar ridges only, but has a negative impact on the masticatory efficiency and body growth overall, speech intelligibility, and facial appearance and aesthetic as well; the latest one having an impact over the mental development, self-confidence, and social life of the affected person¹⁰.

The treatment of the individuals with HED is very complex, engaging several specialists: neonatologist, pediatrician, otolaryngologist, pulmonologist, ophthalmologist, dermatologist, plastic surgeon, speech therapist, and psychologist. Regarding the teeth disorders, pedodontist, orthodontist, oral surgeon and prosthodontist should be engaged, as well as maxillo-facial surgeon in the cases of skeletal malocclusions, and cleft lip and/or palate¹³.

In this article, an oral rehabilitation of a child with Hypohidrotic ectodermal dysplasia and severe maxillary oligodontia and mandibular anodontia is presented, starting from his first visit to a dental office, until the production of the second pair of dentures.

Case report

A 8.5-year-old boy with Hypohidrotic ectodermal dysplasia (HED) and normal intellectual development came at the Department of Prosthodontics, University Dental Clinical Center, needing a new pair of acrylic dentures. The previous one, the maxillary overdenture and mandibular complete denture, had been successfully used for three years. Significant growth of the body and facial bones, especially mandible, has been noticed since his last visit - 6 months ago, the period when he barely wore the prosthesis because of discomfort and impossibility of adjustment as a result of the COVID 19 pandemic.

Case history: The boy had visited the Clinic for the first time when he was 2.5 years old, together with his parents and his 6.5-year-old brother having the same diagnosis and needing a new pair of acrylic dentures, as the previous ones didn't function well¹⁰. At that time, the prosthodontist couldn't get close to the younger boy, and was not able to do any kind of examination. The following recommendation was given: the parents should bring the younger son with them, during all appointments in which the older son's prosthesis were made. The idea was that the younger boy would get used to the Clinic's environment, to all the procedures of producing the prosthesis, and to make a connection with the prosthodontist. He was also present on the appointments that followed,

when the control examination or adjustment of the brother's prosthesis have been conducted. He realized that acrylic dentures can help during mastication, speaking, and can help eliminate the difference between his brother and his friends regarding the appearance of a lower face. The final decision of producing the first pair of maxillary and mandibular prosthesis was made when the boy reached the age of 5.

Family history: Parents denied any hereditary origin of the syndrome; mother, having agenesis of the upper lateral incisors only, stated that there were no differences between the pregnancies with the boys and the girls (14-years- and 2-years- old at the period of production of the second pair of dentures), born healthy, without ED. The older brother, having typical signs of ED, had been hospitalized several times because of bronchopneumonia, wheezing and asthmatic attacks, and has been diagnosed with Methicillin-resistant *Staphylococcus Aureus* (MRSA) in the nasal and pharyngeal mucosa recently.

Extraoral examination: The young patient had dry, warm, rough, thin and shiny skin (as a result of hypohidrosis), with several scratches, and pigmented areas as some wounds have healed. Hypohidrosis - reduced sweating is the reason for disability in the regulation of the body temperature as well, a condition especially problematic in the summer period (the boy usually lays down on the kitchen floor and has cold showers all the time), and during acute diseases followed by increased body temperature. The lacrimation, according to the mother's statement, was reduced, unlike his brother, who had no tears at all. Finger and toe nails were thick, slightly striated with white spots. The hair was sparse, very thin, soft and blond (hypotrichosis), including the eyebrows and eyelashes. The ears were prominent and pointed. Other signs of ED could be observed as well: square and bossing forehead, and prominent supraorbital ridges giving the dominant part of the upper third of the face; expressively wrinkled and slightly pigmented eyelids; short nose with anteverted nostrils, wide base and depressed nasal bridge contributing to the concave appearance of the middle third of the face; large philtrum, protruded upper lip, and indented lower lip, pointed chin with deep mentolabial and nasolabial folds, and reduced lower facial height (without first pair of dentures in child's mouth) giving a senile facial appearance (Fig.1; Fig. 11).

Intraoral examination revealed normal color and appearance of the oral mucosa and gingiva, and atrophic (knife-looking) alveolar ridges. In the period of producing the first pair of dentures (at the age of 5), underdeveloped maxilla and flat palatal vault with slightly prominent palatal tori, and presence of primary central incisors were detected only, while the edentulous

mandible had poorly expressed tubers. In the following period, the maxillary deciduous canines have erupted and took their final position; the deciduous teeth were spaced and conically shaped (Fig.12a). Expressed growth of the mandible with prominent tubers has been noticed (Fig. 12b) several months after the COVID 19 pandemic had started.

Radiographic evaluation of the maxilla and mandible: Undeveloped alveolar ridges were confirmed by an orthopantomogram taken at the age of 5 (Fig.2), revealing four deciduous maxillary teeth, two of them - central incisors present in the mouth, and two deciduous canines still positioned in the maxillary bone; there were only two developing permanent teeth (the crown stage), in the frontal region of the maxilla, in the position of the permanent central incisors, without flat incisal line, but with cusp instead. There were no deciduous or permanent teeth in the mandible.

A retroalveolar radiography (Fig.13), taken right before starting the production of the second pair of dentures, revealed lowered position of the permanent teeth with partially developed radices, and radices resorption of the deciduous incisors.

Treatment procedure

Production of the teeth-supported overdenture in the maxilla and complete denture in the mandible was the treatment of choice at the age of 5 (Fig.8), considering the patient's age and the presence of the maxillary deciduous central incisors in the mouth only. Three and a half years later, it was decided that a maxillary denture fenestrated in the anterior region and a mandibular complete denture should be manufactured (Fig. 18), while deciduous teeth have been reshaped using composite material (Tetric EvoCeram, Ivoclar Vivadent, Liechtenstein).

The following routine procedures for making dentures were carried out:

Preliminary impressions (Fig.3; Fig.14) were taken with appropriate stock trays using fast setting irreversible hydrocolloid material (Alliget, Kulzer, Germany). Casts, made of dental stone (Fig. 4; Fig. 15), were used for production of custom trays (Fig.5a) (Hoffmann's Ultra Violet Base Plates for Individual Custom Tray, light cure; Hoffmann, Dental Manufaktur GmbH, Berlin, Germany). Thermoplastic material (Hoffmann's Impression Compound green, Germany) was used for border molding, while the final (functional) impressions were taken with condensation silicone impression material Stomaflex Light, Pentron, Spofa Dental, Czech Republic (Fig.16); when producing the first pair of prosthesis, functional impressions had been made using polysiloxane impression material -

Xantopren, L blue, Kulzer, Germany (Fig.5b). Final casts were prepared using hard dental stone, followed by production of temporary bases (Hoffmann's Shellac Base Plates, Germany), with wax rim (Modeling wax, summer/winter, Morsa Dental, Germany) (Fig.6). Vertical dimension of occlusion and centric relation were recorded. After that, casts were mounted on a semi-adjustable articulator and artificial teeth (Eray acrylic teeth, Eraylar, Turkey), the smallest size, were arranged according to a balanced occlusion (Fig. 17). In the absence of children's artificial teeth acrylic teeth for adults have been used, but when making the first pair of dentures at the age of 5 the same were reshaped considering the child's age (Fig. 7). Final trial was made to check vertical and centric relations, occlusion, phonetics, and aesthetics. Conventional heat cure acrylic resin, SR Triplex Hot (Ivoclar Vivadent, Schaan Liechtenstein) was used for production of the first pair of dentures (Fig. 8), while Meliodent (Kulzer, Germany) was used for production of the second pair of prosthesis (Fig. 18).

After the final processing and polishing, the dentures were inserted in the patient's mouth followed by a careful adjustment of the bases, as well as occlusion, and articulation. Improvement of the facial frontal and profile appearance was evident (Fig. 9), which satisfied the patient (Fig. 10). The boy was given instructions for maintaining the dentures' hygiene although he was already familiar with all of the procedures. Finally, he was suggested to wear the dentures during the day only, thus enabling further jaw development.

First control visit was done after 24 hours and the necessary corrections were conducted few days later. The patient accepted the dentures within the first week, without any problems during the mastication process, and talking. Subsequent visits were scheduled at 2-months interval.

Discussion

All of the patients with ED have similar tissue disorders, and as is in all the cases of different syndromes, they have similar phenotype and resemble each other. Besides typical facial appearance, hypodontia or anodontia is one of the main characteristic of this congenital disorder. Early prosthodontic treatment of those children is important not only for the efficiency of the mastication process itself, but for the establishment of a new dietary habits that will enable normal body growth, proper swallowing and intelligible pronunciation of voices and words. All of these, along with improved aesthetic appearance, will allow normal psychological development and social integration of the child, especially in kindergarten or in school¹⁰.

The choice of the treatment modality for patients with ED depends on numerous factors: severity of hypodontia (how many teeth are existing), teeth arrangement in the dental arches, their status (sound crowns or with decay), patient's age – developmental stage of the craniofacial bones, socio-economic status of the parents / guardians, as well as presence of other disorders such as malocclusions or cheilo-gnatho-palatoschisis.

Removable complete dentures are the only solution in cases of anodontia, when bones have not reached their final developmental stage, or in cases with completed craniofacial growth but with low socio-economic status.

Overdentures may be manufactured in the cases of severe oligodontia, when the existing teeth (microdontia) allow to be covered with the denture, and serve for additional denture's retention and stabilization (teeth-retained overdenture)¹⁰. Telescopic overdenture produced over the telescopic copings made on the prepared natural teeth (taking an advantage of fixed and removable dental prosthesis), is a viable treatment alternative for ED patients with hypodontia and limited finances¹⁴. Implant-retained overdenture is the treatment of choice in the cases with anodontia or severe oligodontia¹⁵; however the patient requires a high income and completely developed bones. Mandibular implant-retained overdenture may be manufactured even during the childhood, but only if the implants are inserted in the anterior portion of the mandible¹⁶.

Partial acrylic removable dentures with retainers are a solution not only for an adult ED patient with hypodontia, but for the growing patients as well; in such patients, retaining metal clasps should not produce any pressure on the existing deciduous teeth or erupted permanent teeth with incomplete root development. Therefore, flexible dentures seem to be a better solution as they allow jaws' growth, and the flexible clasps do not create pressure on the teeth which serve for retention, and the same are tooth-colored providing better esthetic; this type of dentures are stronger and biocompatible as the material is acrylic monomer- and metal-free, and comfortable for wearing and using^{17,18}.

In the ED patients with mild or moderate hypodontia, underdeveloped maxilla or mandible and/or malposition of the existing teeth, acrylic partial denture with artificial teeth, and incorporated orthodontic elements such as expansion screw is the best solution; the treatment may continue using orthodontic/prosthetic modular appliance¹⁹. This type of mobile appliances not only replace the missing teeth, but also guide the sagittal and transversal jaws' development²⁰. Space management and definitive tooth alignment in preparation for implant-supported fixed restorations is achieved with fixed orthodontic therapy²¹.

Fixed prosthesis could be a prosthodontist's treatment choice in patients with completed craniofacial development and mild or moderate hypodontia with a sufficient number of permanent teeth only, or with severe hypodontia (at least 4 permanent teeth), but with favorable teeth arrangement in the dental arch (two canines and two molars). Dental bridge crossing the midline, interferences with a maxillary transversal development in growing patients; in such patients, frontal bridge can be made only in the mandible.

The last, along with the successfully inserted implants in the anterior mandible even in very young children²², is enabled by the growing pattern of the lower jaw: the lateral growth of the anterior mandible is usually complete by the third year of age. Despite scientific and clinical findings suggesting that the relative implants' position remained unchanged, the National Foundation for Ectodermal Dysplasia recommends implant insertion in the mandibular body around eight years of age²³ (for implant-supported overdenture). However, fixed dental prosthesis made over the implants is recommended to be produced at around 18 years of age, after additional implants have been inserted²³.

In this case report, a prosthodontic treatment of a boy suffering from Hypohidrotic ectodermal dysplasia, with severe hypodontia in the maxilla, and anodontia in the mandible is presented, from his first visit at the Department of prosthetic dentistry at 2.5-years of age, until his 8.5-years of age. The first pair of acrylic dentures, maxillary overdenture and mandibular complete denture, were made when he was 5 years old, while the second pair, maxillary denture fenestrated in the anterior region and mandibular complete denture, were made 3.5 years later.

Despite the patient's age, all of the clinical procedures were performed regularly without major problems, even when he was five years old. Living with an older brother having the same syndrome and wearing dentures, and having enough time to get used to the dental office and acquisition of mutual trust with the therapist, as well as awareness of the benefit of the dentures regarding nutrition, phonetics, and facial appearance, enabled all of the procedures, while making the prostheses, to be performed without stress, anxiety or fear. The reflex of vomiting was reduced by taking impressions in the morning, when the child was rested, and before any meal was taken. He performed all required lips, cheek and tongue movements necessary to determine the borders of the dentures; at 5 years he was instructed to do the facial muscles' movements without trays in his mouth, imitating the prosthodontist and his older brother; when he was 8.5 he performed all of the movements on his own. Time was needed to establish proper maxillo-mandibular

relations as there were no pair of antagonist teeth that, in closing position, would provide secured individual's mandibular position and occlusion. Moreover, the child had no sense of centered positioning of the mandible in relation to the maxilla, unlike most of the edentulous adult patients who had their natural teeth before. Due to the lack of children's artificial teeth, standard teeth (except second molars) with smallest dimensions were selected, reduced, and reshaped when needed for the manufacturing of the first pair of dentures, while smallest dimensions of standard teeth (except second molars and maxillary frontal teeth) were selected for the second pair of dentures.

Since a maxillary overdenture was produced when the boy was five, the deciduous canines started to erupt. In the period that followed, occasional adjustments to the maxillary denture were inevitably necessary in order to make space for the canines, and to keep its stability. During the first several months of the COVID 19 pandemic, the deciduous canines reached their final position. However, the impossibility of providing health care resulted in discomfort while wearing, lost retention, and stability. The lengthening of the clinical crown of the existing deciduous teeth resulted in the maxillary prosthesis perforating the frontal region when adjusted, and loosening the vacuum. On the other hand, retroalveolar radiography, made before starting a procedure for manufacturing the second pair of dentures, revealed lower position of the permanent teeth in the alveolar bone causing physiologic apical root resorption of the deciduous central incisors. Extraction of the deciduous incisors was not recommended as the root development of the permanent teeth was not completed, a reason why pedodontist decided to reshape the deciduous teeth with a composite material instead.

Adjustments of the firstly made mandibular complete denture have been conducted many times in order to enable jaw growth. Three and a half years later, the complete denture became short, not covering the mandibular tubers as the mandibula has shown significant sagittal growth.

The abovementioned changes influenced the decision to produce a new pair of prostheses considering the patient's age, and an upcoming eruption of the permanent frontal teeth: complete mandibular denture and maxillary denture fenestrated in the intercanine region so the deciduous teeth can be exposed to the oral cavity. Metal clasps were not inserted in the acrylic base, because they would retain on the deciduous canines and produce a pressure on them; the aim of the prosthodontics treatment in this patient is to preserve the deciduous teeth as long as possible, especially canines, as there are no permanent canine teeth buds in the maxillary bone. However, frequent adjustment of the vestibular part of the denture will be

performed in order to allow transversal growth of the anterior part of the maxilla.

Subsequent visits are scheduled at 2-months interval; regular adjustments of the removable prosthesis and making a new pair after the periods of expressed body growth during the childhood, will enable unimpeded development of the maxillary and mandibular bone.

Proper and regular oral and denture hygiene was recommended in order to prevent inflammation of the oral mucosa and gingivitis, as well as to prevent tooth decay; preserving the teeth in the mouth as long as possible is a paramount of dental care, thus preventing teeth extraction and consequent bone resorption.

Conclusion

Early dental treatment of children with Ectodermal Dysplasia, having hypodontia or anodontia, is of great importance. The missing teeth should be replaced by the time they reach the school age, not only for masticatory efficiency and improved nutrition, but for improved speech and aesthetic facial appearance that should help children be accepted by their peers and friends. All these will have a positive impact on the psychological and emotional development of the affected persons.

The treatment choice depends on several factors such as severity of the hypodontia, patient's age i.e. skeletal maturation stage, presence of malocclusion, as well as the socio-economic status of the patient's family. Production of a removable acrylic dentures is recommended, reasonable, and a cost-effective treatment in the growing ED patients. Completing of the cranio-facial bones' development enables definite dental treatment based on a dental implants insertion and production of implant-supported overdentures or fixed prosthesis.

Reference

1. Felsher Z. Hereditary ectodermal dysplasia: Report of a case, with experimental study. *Arch Derm Syphilol*. 1944;49(6):410-4. doi:10.1001/archderm.1944.01510120024005.
2. Freire-Maia N. Ectodermal dysplasias. *Hum Hered*. 1971;21(4):309-312. doi:10.1159/000152419.
3. Wright JT, Fete M, Schneider H, Zinser M, Koster MI, Clarke AJ, Hadj-Rabia S, Tadini G, Pagnan N, Visinoni AF, Bergendal B, Abbott B, Fete T, Stanford C, Butcher C, D'Souza RN, Sybert VP, Morasso MI. Ectodermal dysplasias: Classification and organization by phenotype, genotype and molecular pathway. *Am J Med Genet A*. 2019;179(3):442-7. doi:10.1002/ajmg.a.61045.
4. Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet C Semin Med Genet*. 2004;131C(1):45-51. doi:10.1002/ajmg.c.30033.
5. Der Kaloustian VM. Hidrotic Ectodermal Dysplasia 2. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; April 25, 2005.
6. García-Martín P, Hernández-Martín A, Torrelo A. Ectodermal dysplasias: a clinical and molecular review. *Actas Dermosifiliogr*. 2013;104(6):451-70. doi:10.1016/j.ad.2012.07.012.
7. Wohlfart S, Meiller R, Hammersen J, Park J, Menzel-Severing J, Melichar VO, Huttner K, Johnson R, Porte F, Schneider H. Natural history of X-linked hypohidrotic ectodermal dysplasia: a 5-year follow-up study. *Orphanet J Rare Dis*. 2020;15(1):7. doi:10.1186/s13023-019-1288-x.
8. Hammersen JE, Neukam V, Nüsken KD, Schneider H. Systematic evaluation of exertional hyperthermia in children and adolescents with hypohidrotic ectodermal dysplasia: an observational study. *Pediatr Res*. 2011;70(3):297-301. doi:10.1203/PDR.0b013e318227503b.
9. Blüschke G, Nüsken KD, Schneider H. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Early Hum Dev*. 2010;86(7):397-9. doi:10.1016/j.earlhumdev.2010.04.008.
10. Bajraktarova Valjakova E, Miševska C, Korunoska Stevkovska V, Gigovski N, Sotirovska Ivkowska A, Bajraktarova B, Guguvceviski Lj. Prosthodontic management of Hypohidrotic Ectodermal Dysplasia: A case report. *South Eur J Orthod Dentofac Res*. 2015;2(2):20-6.
11. Mancini AJ, Lawley LP, Uzel G. X-linked Ectodermal dysplasia with immunodeficiency caused by NEMO mutation: Early recognition and diagnosis. *Arch Dermatol*. 2008;144(3):342-6. doi:10.1001/archderm.144.3.342.
12. Kawai T, Nishikomori R, Heike T. Diagnosis and treatment in anhidrotic ectodermal dysplasia with immunodeficiency. *Allergol Int*. 2012;61(2):207-17. doi:10.2332/allergolint.12-RAI-0446.
13. Clauss F, Mathis R, Obry F, Kamm Q, Perrin-Schmitt F, Manière M. Multidisciplinary treatment plan for multiple dental agenesis associated with hypohidrotic ectodermal dysplasias. *J Dentofacial Anom Orthod*. 2014;17(1):106. doi:10.1051/odf/2013406.
14. Gupta C, Verma M, Gupta R, Gill S. Telescopic overdenture for oral rehabilitation of ectodermal dysplasia patient. *Contemp Clin Dent*. 2015;6(Suppl 1):S258-S261. doi:10.4103/0976-237X.166821.
15. Chrcanovic BR. Dental implants in patients with ectodermal dysplasia: A systematic review. *J Craniomaxillofac Surg*. 2018;46(8):1211-7. doi:10.1016/j.jcms.2018.05.038.
16. Wang Y, He J, Decker AM, Hu JC, Zou D. Clinical outcomes of implant therapy in ectodermal dysplasia patients: a systematic review. *Int J Oral Maxillofac Surg*. 2016;45(8):1035-43. doi:10.1016/j.ijom.2016.03.011.
17. Jain N, Naitam D, Wadkar A, Nemane A, Katoch S, Dewangan A. Prosthodontic rehabilitation of hereditary ectodermal dysplasia in 11-year-old patient with flexible denture: a case report. *Case Rep Dent*. 2012;2012:489769. doi:10.1155/2012/489769doi:10.1155/2012/489769.
18. Kalaskar R, Kalaskar A. Functional esthetic rehabilitation of a 7 year old female patient with hereditary ectodermal dysplasia using flexible denture. *Indian J Dermatol Venereol Leprol*. 2013;79:826-7.
19. Celli D, Manente A, Grippaudo C, Cordaro M. Interceptive treatment in ectodermal dysplasia using an innovative orthodontic/prosthetic modular appliance. A case report with 10-year follow-up. *Eur J Paediatr Dent*. 2018;19(4):307-12. doi:10.23804/ejpd.2018.19.04.11.
20. Ioannidou-Marathiotou I, Kotsiomiti E, Gioka C. The contribution of orthodontics to the prosthodontic treatment of ectodermal dysplasia: a long-term clinical report. *J Am Dent Assoc*. 2010;141(11):1340-5. doi:10.14219/jada.archive.2010.0078.
21. Suri S, Carmichael RP, Tompson BD. Simultaneous functional and fixed appliance therapy for growth modification and dental alignment prior to prosthetic habilitation in hypohidrotic ectodermal dysplasia: a clinical report. *J Prosthet Dent*. 2004;92(5):428-33. doi:10.1016/j.prosdent.2004.07.014.

22. AD Guckes, GR McCarthy, J Brahim. Use of endosseous implants in a 3 year old child with ectodermal dysplasia: case report and 5-

year follow-up. *Pediatr Dent*. 1997;19(4):282-5.
23. https://www.nfed.org/blog/advice_treatment_dental_implants_hed/

Figures 1-10: took out during the production of the first pair of dentures at an age of 5:



Figure 1. Extraoral photo shows characteristic features of Ectodermal Dysplasia in a 5-years-old boy:

- a.)** profile view - deep mentolabial and nasolabial folds and lower facial height (vertical dimension), protruding lips and pointed chin.
- b.)** hands with dry skin and thick and striated nails.

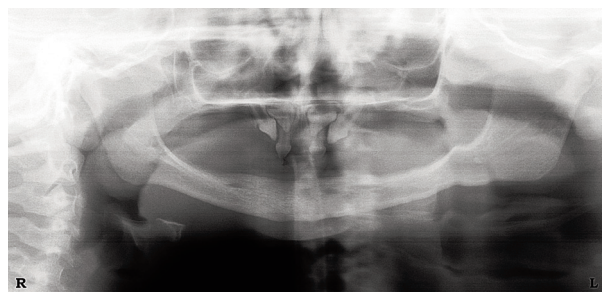


Figure 2. Orthopantomogram reveals severe hypodontia and undeveloped alveolar ridges: four deciduous teeth and two developing permanent teeth in the frontal region of the maxilla, and anodontia in mandible.

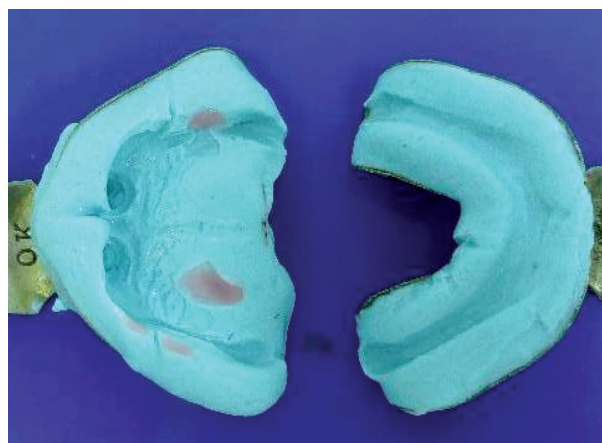


Figure 3. Preliminary impressions made with irreversible hydrocolloid material.



Figure 4. Stone models.



Figure 5.

- a.)** Custom-made trays.
- b.)** Final impressions made using thermoplastic material and light body polyvinyl siloxane impression material.



Figure 6. Temporary bases with wax rims.



Figure 7. Artificial teeth embedded in wax and arranged according to a balanced occlusion:

- a.)** frontal view;
- b.)** profile view.

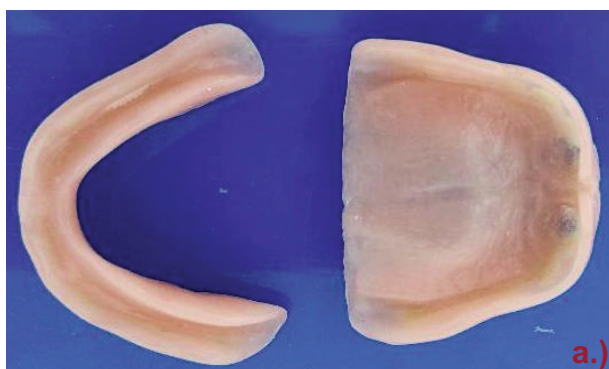


Figure 8 a-d. Prosthesis made of heat cure acrylic resin: Teeth-supported overdenture in the maxilla and complete denture in the mandible.



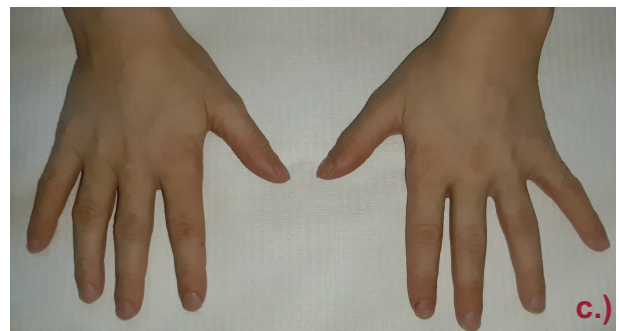
Figure 9. Improved facial appearance after insertion of the dentures:

- a.)** frontal view;
- b.)** profile view.



Figure 10. Satisfied patient after insertion of the dentures.

Figures 11-18: took out during the production of the second pair of dentures at an age of 8.5:



Figures 11. Extraoral photo of the patient:

- a.)** frontal view;
- b.)** profile view;
- c.)** hands;
- d.)** arm: dry skin with scratches.



Figures 12.

- a.)** Intraoral photo of the maxilla: 4 deciduous teeth: 2 incisors and 2 canines;
- b.)** Intraoral photo of the mandible: atrophic alveolar ridge and prominent tubers;



Figure 13. Retroalveolar radiography (8.5 years of age) reveals lowered position of the permanent incisors teeth with a cusp instead of incisal edge and partially developed radices; deciduous canines are completely erupted without radices resorption while deciduous incisors are with complete radices resorption.

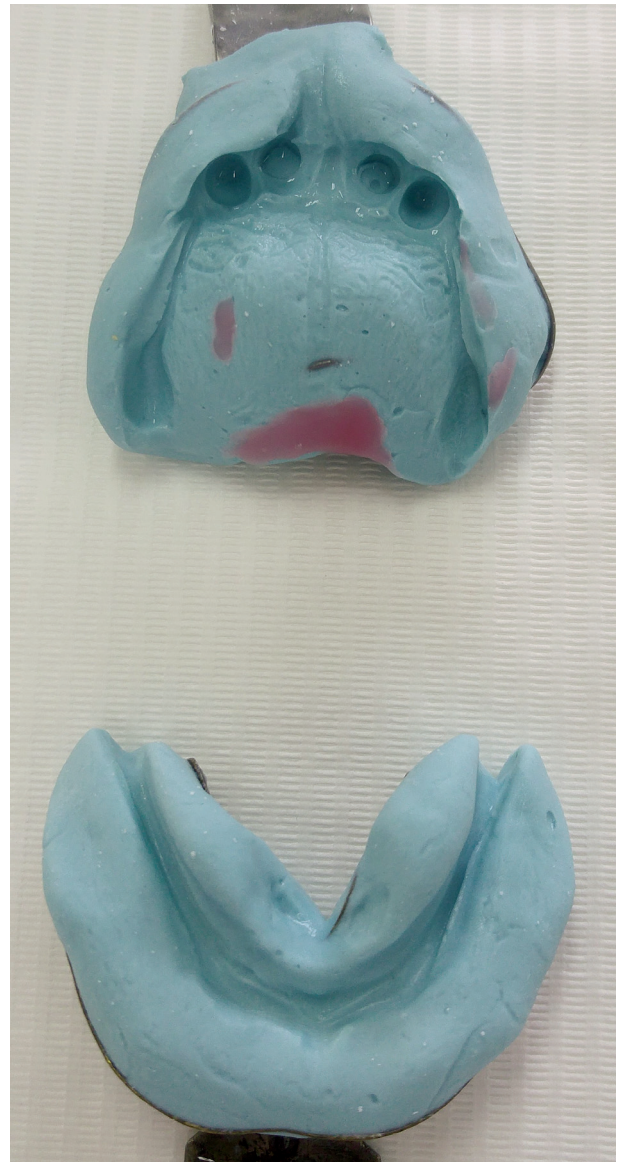


Figure 14. Preliminary impressions made with irreversible hydrocolloid material.

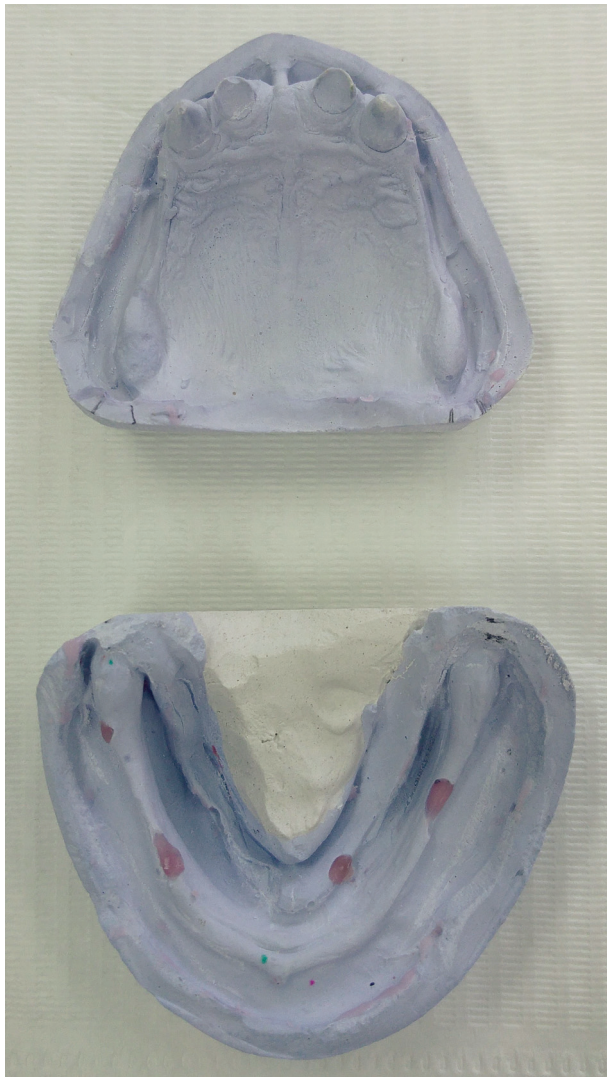


Figure 15. Stone models.



Figure 17. Artificial teeth embedded in wax:

a.) frontal view;

b.) profile view.

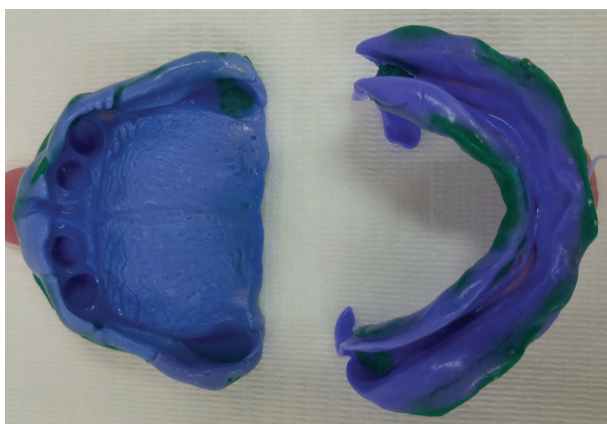


Figure 16. Final impressions made using thermoplastic material and condensation silicone impression material.



Figure 18. Prosthesis made of heat cure acrylic resin: maxillary prosthesis fenestrated in the frontal region; mandibular complete denture:

- a.) frontal view;
- b.) right profile view;
- c.) left profile view;
- d.) comparison of the dimensions with a dentures made for an adult patient;
- e.) dentures inserted in the mouth; deciduous teeth reshaped with composite material.



Figure 19. Extraoral photo of the patient with inserted dentures in the mouth (frontal view).

