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KOMPARATIVNA ANALIZA EKSPANZIJE KOSTI UPOTREBOM DENASH BORERA NASUPROT CEPANJA GREBENA EKSPANDERIMA PRI POSTAVLJANJU IMPLANTATA U USKIM GREBENIMA

A COMPARATIVE ANALYSIS OF BONE EXPANSION USING DENSAH BURS VERSUS RIDGE SPLIT WITH EXPANDERS FOR IMPLANT PLACEMENT IN NARROW RIDGES

Aditi Rapriya, Varun Arya, Ajay Das T, Sanjeev Kumar, Sunil Gulia, Isha Singla

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DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY, FACULTY OF DENTAL SCIENCES, SGT UNIVERSITY, GURUGRAM, INDIA

Sažetak

Uvod: *Gubitak zuba dovodi do značajne resorpcije alveolarnog grebena, što otežava postavljanje zubnih implantata. Neposredna ugradnja implantata i tehnike kao što su vođena koštana regeneracija i tehnika cepanja grebena imaju za cilj da reše ove izazove, ali nose rizike.*
Cilj *istraživanja je bio da se proceni povećanje debljine kosti i opstanak implantata u uskim grebenima sa horizontalnom atrofijom tretiranim dvema različitim tehnikama: tehnikom cepanja alveolarnog grebena i oseodensifikacijom Densah® borerima, uz istovremenu ugradnju implantata.*
Materijal i metode*: U studiji ji uključeno ukupno 30 uskih grebena sa rasponom širine između 3–6 mm i odgovarajućom vertikalnom visinom kosti tretiranih pomoću dve različite tehnike: tehnikom cepanja grebena (RST) i oseodensifikacijom (OD) Densah® borerima.*
Rezultati: *Razlika u bukolingualnij širini (mm) između dva vremenska intervala dve grupe pokazuje značajne razlike posle procedure sa p-vrednostima < 0,001, što ukazuje na bolje rezultate u grupi sa Densah® borerima.*
Zaključak: *Nalazi sugerišu da oseodensifikacija nudi superiorne rezultate, pokazujući značajnu ekspanziju kosti i primarnu stabilnost, što je čini obećavajućom tehnikom za dentalnu implantologiju u slučajevima uskih grebena.*

Ključne reči*: Densah boreri, greben split, uski greben*

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Abstract

Introduction: *Tooth loss leads to significant alveolar ridge resorption, complicating dental implant placement. Immediate implant placement and techniques like guided bone regeneration and ridge split technique aim to address these challenges but come with risks.*
Aim *of the study was to evaluate bone thickness augmentation and implant survival in narrow ridges with horizontal atrophy treated with two different techniques: the ridge split technique and osseodensification with Densah® burs, with simultaneous implant placement.*
Material and methods: *A total of 30 narrow ridges with a width range between 3–6 mm and adequate vertical bone height were considered for the study and divided into two groups for treatment by two different techniques: the ridge split technique (RST) and osseodensification (OD) with Densah® burs.*
Results: *The difference of buccolingual width (mm) between two time intervals of two groups show significant differences post-procedure with p-values < 0.001, suggesting better outcomes in group with Densah® burs .*
Conclusion: *Findings suggest osseodensification offers superior outcomes, demonstrating significant bone expansion and primary stability, making it a promising technique for dental implantology in cases of narrow ridges.*

Key words: *Densah burs, ridge split, narrow ridge*

Introduction

Bone resorption after tooth loss is an inevitable event that often results in inadequate bone dimensions for dental implant placement in an ideal position[1]. After tooth extraction, the buccolingual alveolar ridge dimension decreases significantly, over 3–12 months, and the amount of resorption can reach approximately 50% of the original bone width[2].

Dental implantology has undergone transformative advancements in recent years, revolutionizing the restorative dentistry landscape. Dental implants can be placed into edentulous alveolar ridges where adequate buccolingual bone width is available to support a fixed-type dental prosthesis. A minimum of 1.0–1.5 mm of bone width thickness should be present on the buccal and lingual aspects of the implants. A regularly desired 4-mm diameter implant requires an average of 6 mm buccolingual ridge width. This creates a great challenge in implant dentistry for clinicians because alveolar ridge atrophy always occurs after tooth extraction, which restricts the use of dental implants to restore oral function.

Several surgical techniques have been described for augmentation of the atrophic mandibular alveolar ridge. The ridge split technique (RST) has been developed for the reconstruction of the buccolingually reduced bone width of the alveolar process. The ridge split procedure is a technique used to increase the width of a narrow ridge with simultaneous implant placement into the bone bed. The buccal cortical plate fracture is the main surgical concern associated with the RST[3].

Osseodensification is an innovative biomechanical method for bone preparation that is designed to supplant traditional bone subtractive drilling, ultimately enhancing the quality of the implant site[4]. When compared with the conventional subtractive drilling technique, this method improves the primary and secondary stability of the implant and the percentage of bone-implant contact (BIC) by up to threefold.

The most commonly used devices for evaluating primary stability are removal torque and resonance frequency analysis (RFA)[5]. OstellTM ISQ device, developed by Meredith in 1987, is a noninvasive method that can reproducibly assess bone-to-implant contact through direct attachment of a transducer to the implant body. ISQ values range from 1 to 100, with higher ISQ values denoting higher implant stability. ISQ values in the range of 40–80 indicate that the dental implant is clinically stable[6].

The rationale for undertaking this comparative evaluation stems from the imperative to establish evidence-based practices in immediate implant placement, particularly in cases involving narrow ridges.

Aim

The study aimed to evaluate bone thickness augmentation and implant survival in narrow ridges with horizontal atrophy treated with two different techniques: the ridge split technique and osseodensification with Densah® burs, with simultaneous implant placement.

1. To evaluate the increase in bone thickness obtained by RST before implant placement and after 6 months based on CBCT.
2. To evaluate the increase in bone thickness obtained by ODT before implant placement and after 6 months, based on CBCT.
3. To evaluate the implant stability obtained by RST at the time of implant placement and after 3 months based on RFA.
4. To evaluate the implant stability obtained by ODT at the time of implant placement and after 3 months based on RFA.
5. To compare crestal bone levels radiographically around implants placed at the time of implant placement, 1 week after placement, and 3 months post implant placement with RST.
6. To compare crestal bone levels radiographically around implants placed at the time of implant placement, 1 week after placement, and 3 months post implant placement with ODT.

Materials and Methods

A randomized prospective study was conducted in the Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, SGT University, Gurugram, following approval by the institutional ethical committee with clearance No. FODS/EC/OMS/2022/20

Patient Selection

A total of 30 narrow ridges with a width range between 3–6 mm and adequate vertical bone height were considered for the study. These sites were equally divided into two groups for treatment by two different techniques: the ridge split technique (RST) and osseodensification (OD) with Densah® burs.

Site selection for the two groups was done randomly by the chit system before surgery. Each patient provided informed consent before beginning the study and was free to discontinue it at any time. Patients were included in this study based on the following criteria:

Inclusion Criteria:

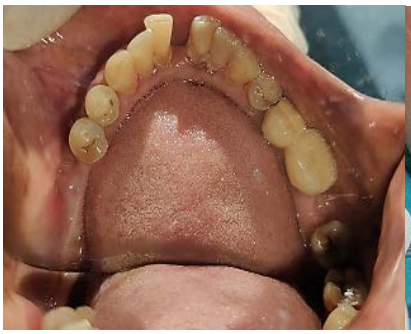
1) Patient's age ranging between 18 and 60 years.
2) Patients having narrow/atrophied ridges within a range of 3–6 mm buccolingual width irrespective of the anterior/posterior site in the maxilla/mandible.
3) Patients who were cooperative, motivated, and hygiene conscious and gave their consent to be included in the study understanding the risks involved.
4) ASA Classification Class 1 patients.

***Exclusion Criteria*:**

1) According to ASA Classification Class 3 patients—uncontrolled diabetes with complications to vascular or other organs, i.e., retinopathy, neuropathy, etc.
2) Inadequate patient compliance.
3) Poorly motivated or patients unable to keep the follow-up are excluded.
4) Patient with heavy smoking and alcohol abuse.

Surgical procedure

In a comparative study of two surgical techniques for dental implant placement, patients were treated under strict aseptic conditions and local anesthesia. The first group underwent the RST, which involved a mid-crestal incision with papillary sparing, followed by vertical releasing incisions. A mucoperiosteal flap was raised to expose the ridge, and osteotomies were created using Piezo tips to minimize bone trauma. Sequential use of rotary expanders widened the bone to accommodate the implants. Postoperative care included suturing, antibiotics, and chlorhexidine rinses. Patients were monitored for bone loss and implant stability over several follow-up visits up to six months, including CBCT scans and ISQ measurements to assess bone thickness and implant stability (Figures 1–6).



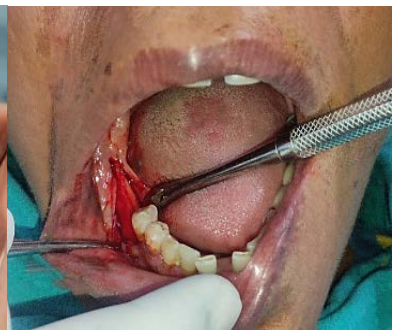
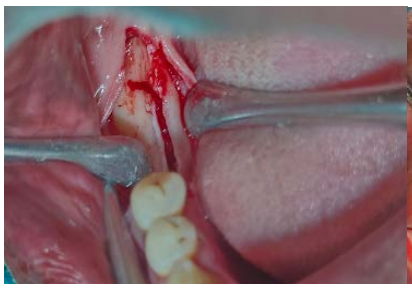


Figure 1. Pre op view of narrow ridge irt 46, 47
Figure 2. Full thickness mucoperiosteal flap elevation



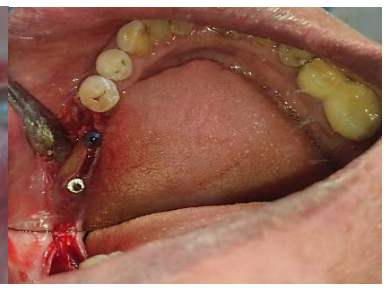


Figure 3. Intra op view of ridge split ***Figure 4***. Implants insertion

Figure 5. Closure made without tension

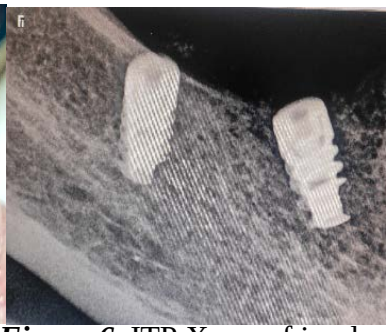


Figure 6. ITP X ray of implants placement

In contrast, the second group underwent implant placement using the ODT. This technique began with a mid-crestal incision and vertical incisions beyond the mucogingival line, followed by raising a mucoperiosteal flap. Initial osteotomies were made with a pilot drill, and osseodensification was performed using specially designed Densah® Burs in a counterclockwise motion to compact bone and expand the osteotomy gradually. Similar postoperative care and follow-up assessments were conducted as in the first group to evaluate bone changes, implant stability, and complications. (Figures 7–12)

Both groups were managed postoperatively with antibiotics, analgesics, and chlorhexidine rinses, with regular follow-ups to monitor healing and assess implant success. Data analysis, using statistical methods like the Paired t Test, aimed to compare bone thickness, Implant Stability Quotient (ISQ), and crestal bone levels between the two techniques. The study's findings were evaluated for statistical significance to determine the efficacy and outcomes of each approach in implant dentistry.

Overall, the study highlighted the procedural differences, postoperative management, and rigorous follow-up required to evaluate the effectiveness of RST and ODT in enhancing bone volume and implant stability for successful prosthetic rehabilitation.

Figure 7. Pre-op view of narrow ridge irt 24

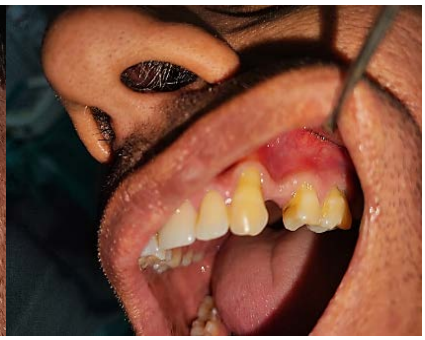


Figure 8. Densah bur expanding the osteotomy

Figure 9. Prepared osteotomy site

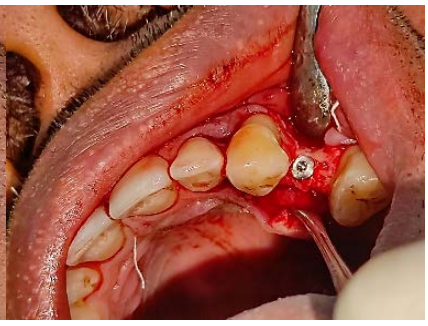


Figure 10. Implant insertion

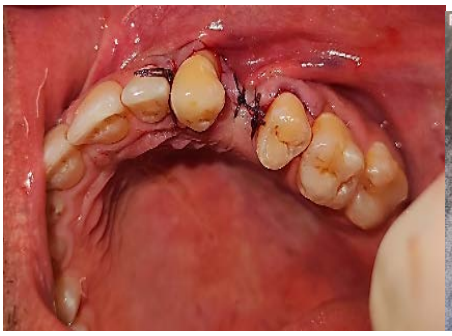
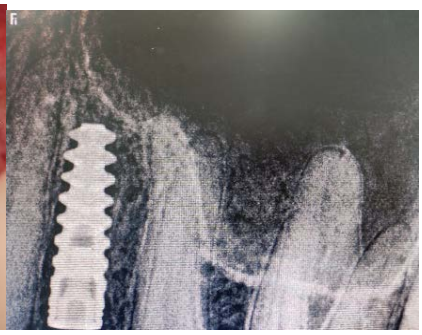



Figure 11. Closure made without tension ***Figure 12.*** Iopa showing implants placement

Results

The study compared two groups of patients undergoing dental implant procedures, focusing on various parameters such as patient demographics, site distribution, buccolingual width, ISQ, and crestal bone levels. Group 1 consisted of older patients (mean age 53.14 years), predominantly females (3 out of 5 patients), while Group 2 had younger patients (mean age 40.06 years) with an equal distribution of males and females (3 each). This demographic distribution was reflected in the frequency distribution graphs (Graph 1 and Graph 2) and the detailed tabular data (Table 1 and Table 2).

Table 1 shows the frequency N distribution of male and female patients along with their mean and SD of age among the two groups. In Group 1, 5 of 11 patients were included in the study, with a mean age of 53, of which 2 were males and 3 were females. In Group 2, 6 of 11 patients were included with a mean age of 40, of which 3 were males and 3 were females (Ref. Graph 1)

Graph 1, which pertains to Table 1, shows gender distribution along the X-axis and frequency distribution of patients along the Y-axis among the two groups.

Table 2 shows the Frequency N distribution of sites by region among two groups. It depicts in Group 1, of 15 sites, 5 in the mandibular anterior region, 8 in the maxillary anterior region, 0 in the mandibular anterior region and 2 in the maxillary posterior region. In Group 2, of 15 sites, 9 in the mandibular anterior region, 3 in the maxillary anterior region, 2 in the mandibular anterior region and 1 in the maxillary posterior region (Figure 2)

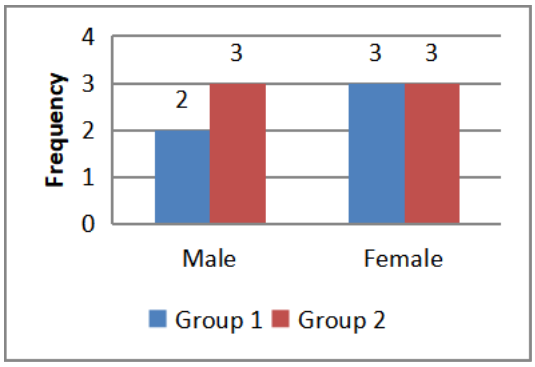
Graph 2, which pertains to Table 2, shows region distribution along the X-axis and frequency distribution of sites along the Y-axis among the two groups

Buccolingual width changes were measured before (T0) and after 6 months (T1) of implant placement using the Paired t Tests (Table 3), indicating significant reductions in both groups (Group 1: -2.44 mm, Group 2: -3.68 mm) with p-values < 0.001, highlighting effective bone expansion techniques. The Independent t Tests further compared buccolingual widths between groups at different time intervals (Table 4), showing significant differences post-procedure (T1) with p-values < 0.001, suggesting better outcomes in Group 2.

Table 3 shows the intra-group comparison of the mean difference of buccolingual width (mm) between two time intervals, T0 (buccoligual width before the procedure) and T1 (buccolingual width after 6 months of procedure), of two groups by the Paired t Test. The mean difference of buccolingual width (mm) between T0 and T1 of Group 1, -2.43667 ± 0.15045, and of Group 2, -3.67533 ± 0.11592, is $p < 0.001$

Table 1. Frequency N distribution of males and females and mean, SD of age of patients among two groups

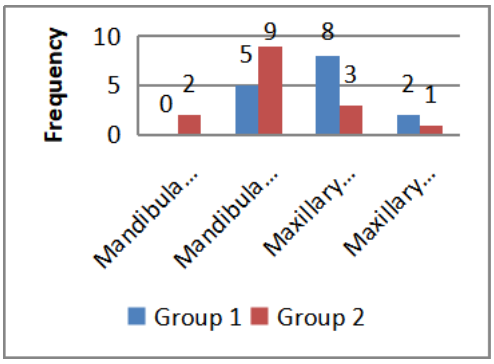
Group	Sex		Age
	Male	Female	Mean ± S.D.
Group 1	2	3	53.14 ± 5.414
Group 2	3	3	40.06 ± 13.225



Graph 1. Frequency distribution of male and female patients among two groups

Table 2. Frequency N distribution of sites by region among two groups

	Region			
	Mandibular anterior	Mandibular posterior	Maxillary anterior	Maxillary posterior
Group 1	0	5	8	2
Group 2	2	9	3	1



Graph 2. Frequency distribution of sites by their region among two groups

Table 3. Intra-group comparison of mean difference of buccolingual width (mm) between two time intervals of two groups by the Paired t Test

Group	Time Intervals	Mean difference ± S.E.M.	p-value
Group 1	TO-T1	-2.43667 ± 0.15045	< 0.001**
Group 2	TO-T1	-3.67533 ± 0.11592	< 0.001**

[NS] Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001

Table 9 shows the distribution of mean of crestal bone levels on the mesial side (mm) in two groups at different time intervals. It shows that the difference mean of crestal bone level on mesial side (mm) -0.0667 ± 0.1881 between the two groups after one week T1 is p = 0.726. The difference mean of crestal bone level on the mesial side (mm) -0.227 ± 0.170 between two groups after 3 months T2 is p = 0.194 (Graph 5)

Table 10 shows the distribution of the mean of crestal bone level on the distal side (mm) in two groups at different time intervals. The difference mean ± SD of crestal bone level on the distal side (mm) 0.2000 ± 0.1604 between the two groups after one week T1 is p = 0.233. The difference mean of crestal bone level on the distal side (mm) 0.3133 ± 0.1107 between the two groups after 3 months T2 is p < 0.05 (Graph 6)

Graphical representations (Graph 3, Graph 4, Graph 5, and Graph 6) complemented these findings, illustrating trends in buccolingual width, ISQ values, and crestal bone levels across different time intervals and between groups. Overall, the study provided comprehensive insights into the effectiveness of different implant techniques, demographic influences, and longitudinal changes in key clinical parameters, underscoring the importance of tailored approaches in dental implantology and the need for further research to validate these findings in larger cohorts and longer follow-up periods.

Graph 3, which pertains to Table 4, shows time interval distribution T0 and T1 along the X-axis and mean values of buccolingual width (mm) readings along the Y-axis among the two groups

Graph 4, which pertains to Table 6, shows the time interval distribution T0 and T1 along the X-axis and the mean values of ISQ readings along the Y-axis among two groups Graph 5, which pertains to Table 9, shows the time interval distribution T0 and T1 along the X-axis and the mean values of crestal bone levels on the mesial side (mm) readings along the Y-axis among two groups

Graph 6, which pertains to Table 10, shows the time interval distribution T0, T1 and T2 along the X-axis and the mean values of crestal bone levels on the distal side (mm) readings along the Y-axis among two groups

Table 4. Inter-group comparison of the mean of buccolingual width (mm) between the two groups at different time intervals by the Independent t Test

Time Intervals	Group	N	Mean	Std. Dev.	Mean difference ± S.E.M.	p-value
T0 *(Buccolingual width before procedure)*	Group 1	15	3.9913	0.64167	0.03267 ± 0.20971	0.877^{NS}
	Group 2	15	3.9587	0.49795		
T1 *(Buccolingual width after 6 months of procedure)*	Group 1	15	6.4280	0.32591	-1.20600 ± 0.12683	< 0.001**
	Group 2	15	7.6340	0.36750		

^{NS} Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001

Table 5. Intra-group comparison of mean difference of ISQ values between two time intervals of the two groups by the Paired t Test

Group	Time Intervals	Mean difference ± S.E.M.	p-value
Group 1	TO-T1	-2.846 ± 0.465	< 0.001**
Group 2	TO-T1	-8.067 ± 0.636	< 0.001**

^{NS} Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001

Table 6. Inter-group comparison of the mean of ISQ values between two groups at different time intervals by the Independent t Test

Time Intervals	Group	N	Mean	Std. Dev.	p-value
T0 *(At the time of implant placement)*	Group 1	15	63.53	1.642	0.066[NS]
	Group 2	15	64.53	1.187	
T1 *(After 3 months of implant placement)*	Group 1	15	66.38	1.387	< 0.001**
	Group 2	15	72.60	2.849	

[NS] Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001

Table 7. Intra-group comparison of mean difference of crestal bone level on the mesial side (mm) between two time intervals of two groups by the Paired t Test

Group	Time Intervals	Mean difference ±S.E.M.	p-value
Group 1	TO-T1	-0.3333 ± 0.1351	0.027*
	T1-T2	-0.7333 ± 0.1453	< 0.001**
	T0-T2	-1.067 ± 0.137	< 0.001**
Group 2	TO-T1	-0.4000 ± 0.1309	0.009*
	T1-T2	-0.8933 ± 0.1127	< 0.001**
	T0-T2	-1.293 ± 0.101	< 0.001**

[NS] Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001

Table 8. Intra-group comparison of mean difference of crestal bone level on the distal side (mm) between two-time intervals of two groups by the Paired t Test

Group	Time Intervals	Mean difference ± S.E.M.	p-value
Group 1	TO-T1	-0.5000 ± 0.1380	0.003*
	T1-T2	-0.5933 ± 0.0902	< 0.001**
	T0-T2	-1.0933 ± 0.0848	< 0.001**
Group 2	TO-T1	-0.3000 ± 0.0816	0.003*
	T1-T2	-0.4800 ± 0.0782	< 0.001**
	T0-T2	-0.7800 ± 0.0712	< 0.001**

[NS] Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001

Table 9. Inter-group comparison of the mean of crestal bone level on the mesial side (mm) between two groups at different time intervals by the Independent t Test

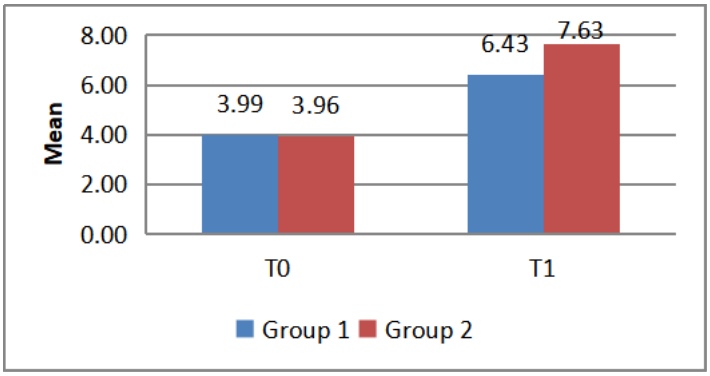
Time Intervals	Group	N	Mean	Std. Dev.	Mean difference ± S.E.M.	p-value
T0 *(Immediate post-op)*	Group 1	15	0.00	0.000	0.000	Not calculated
	Group 2	15	0.00	0.000		
T1 *(after one week)*	Group 1	15	0.333	0.5233	-0.0667 ± 0.1881	0.726^{NS}
	Group 2	15	0.400	0.5071		
T2 *(after 3 months)*	Group 1	15	1.07	0.530	-0.227 ± 0.170	0.194^{NS}
	Group 2	15	1.29	0.392		

^{NS} Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001

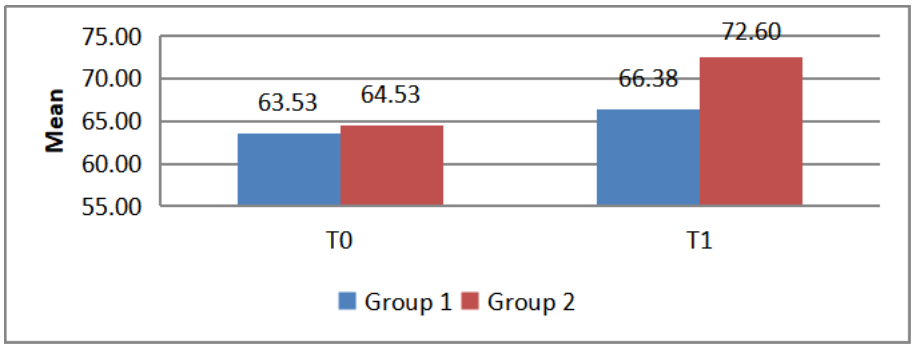
Table 10. Inter-group comparison of the mean of crestal bone level on the distal side (mm) between two groups at different time intervals by the Independent t Test

Time Intervals	Group	N	Mean	Std. Dev.	Mean difference ± S.E.M.	p-value
T0 *(Immediate post-op)*	Group 1	15	0.00	0.000	0.000	Not calculated
	Group 2	15	0.00	0.000		
T1 *(after one week)*	Group 1	15	0.500	0.5345	0.2000 ± 0.1604	0.223^{NS}
	Group 2	15	0.300	0.3162		
T2 *(after 3 months)*	Group 1	15	1.093	0.3283	0.3133 ± 0.1107	0.009**
	Group 2	15	0.780	0.2757		

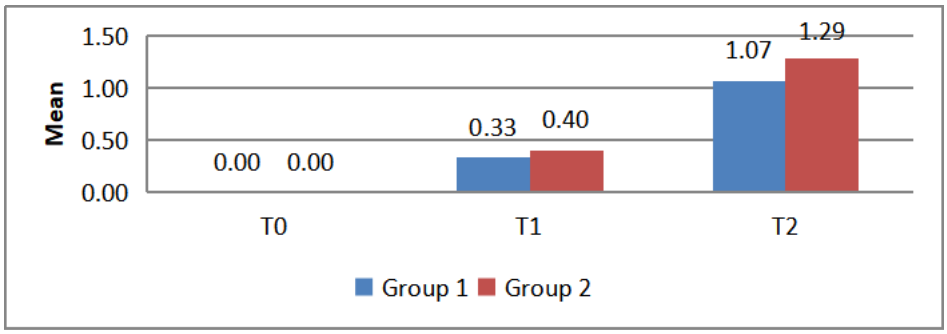
^{NS} Not significant p > 0.05, * Significant p < 0.05, ** Highly significant p < 0.001



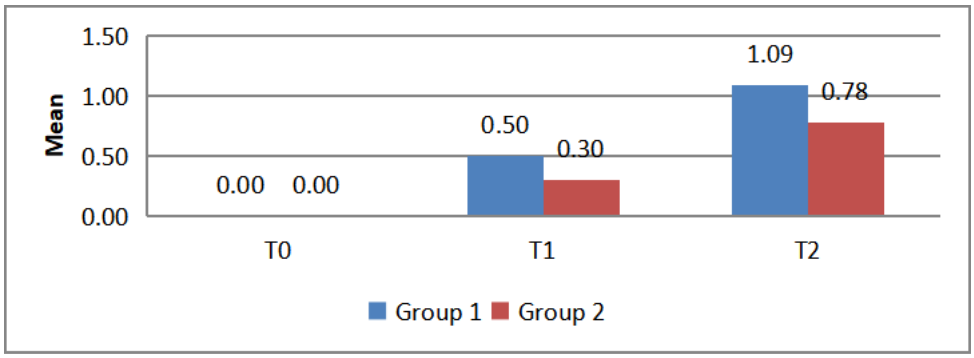
Graph 3. Comparison of mean of buccolingual width (mm) between the two groups at different time intervals



Graph 4. Comparison of mean of ISQ values between the two groups at different time intervals



Graph 5. Comparison of mean of crestal bone level on the mesial side (mm) between two groups at different time intervals



Graph 6. Comparison of mean difference of crestal bone level on the distal side (mm) between two groups at different time intervals

Discussion

In recent decades, dental implants have revolutionized treatment for patients with missing teeth by offering reliable long-term outcomes through osseointegration. However, a significant challenge remains in cases where the alveolar ridge lacks sufficient width for successful implant placement. Adequate bone width of 1 to 1.5 mm on both the labial and lingual/palatal aspects of the implant site is crucial for predictable results[7]. To address this, various surgical techniques have been proposed, including alveolar ridge split osteotomy and osseodensification, as alternatives to traditional bone grafting methods.

The study discussed herein aimed to compare bone expansion techniques using Densah® burs versus ridge split with expanders for implant placement in narrow ridges. Thirty implants were placed across 11 patients, with sites randomized into two groups. Group 1 utilized the RST for bone expansion, while

Group 2 employed the ODT. Age was a critical factor influencing technique selection, with younger patients typically better suited for RST due to superior bone quality and healing capabilities, whereas OD was preferred for older patients with compromised bone density[8].

Results showed promising outcomes for both techniques, with successful implant integration observed in the majority of cases over a six-month follow-up period. Two implants in Group 1 failed, potentially due to low bone density, a known risk factor for implant failure, especially in the maxillary anterior region. The OD group demonstrated significantly greater bone expansion compared to the RST group, attributed to the unique properties of Densah® burs, which compact bone laterally without causing fractures, thereby facilitating effective ridge expansion.

In 2019, Tretto et al.[9] conducted a comprehensive literature review on implant preparation methods and found that OD has produced encouraging and promising biomechanical outcomes.

Chan in 2013 assessed the amount of ridge expansion achieved with screw expanders. His findings indicated that the use of screw spreaders or expanders increased the ridge width by an average of 0.79 mm[10].

The primary stability of implants was evaluated using Resonance Frequency Analysis (RFA) with the Osstell™ ISQ device, showing a statistically significant increase in stability over the three-month postoperative period for both groups. This method proved effective in monitoring osseointegration progress and implant stability, crucial for long-term success. Radiographic evaluation using intraoral periapical radiographs revealed minimal crestal bone loss, essential for maintaining implant stability and overall success.

As for complications, a systematic review by Lin et al.[11] concluded that according to seven studies, ARS can have problems during or after surgery, such as exposure, infection, poor split, dehiscence, fracture, paraesthesia, and soft tissue retraction[12,13–18]. Furthermore, if OD drills are not used in conjunction with abundant irrigation, they have been discovered to raise the temperature and may cause the nearby osteoblasts to necrotize[19].

Complications were minimal, with only two cases of thin buccal cortical plate fractures observed in the mandibular posterior region in the patients of Group 1. This underscores the importance of careful patient selection and technique application to minimize adverse events during implant procedures. Overall, the study supports OD as a potentially superior technique for achieving adequate bone expansion and implant stability in narrow ridges compared to traditional ridge splitting methods.

In conclusion, while both RST and ODT offer viable solutions for implant placement in narrow ridges, OD appears to provide greater bone expansion and stability advantages. Further research and larger-scale studies are warranted to confirm these findings and optimize treatment protocols for enhancing dental implant outcomes in patients with ridge deficiencies.

Conclusion

This study compared the Ridge Split Technique (RST) and the Osseodensification Technique (ODT) for dental implant placement in narrow ridges. Both techniques demonstrated practicality and predictability with significant increases in ridge thickness and minimal complications. However, the data strongly favored OD for enhancing implant primary stability and achieving a greater buccolingual width. Osseodensification, utilizing Densah® burs, showed superior performance in terms of implant stability over time and mitigated risks associated with buccal cortical plate fractures, which are common with ridge splitting.

Key findings included successful ridge expansion with both techniques, evidenced by increased primary stability as measured by Resonance Frequency Analysis (RFA). The study highlighted crestal bone loss of 1.0 to 2.0 mm at three months post-implantation, underscoring the importance of subcrestal implant placement to maintain stability. Ultimately, the study rejected the Null Hypothesis and supported the Alternate Hypothesis I, affirming OD as a more patient-friendly and effective method for implant placement in narrow ridges.

However, the study acknowledged limitations such as a small sample size and short follow-up duration, necessitating larger prospective cohorts and randomized control trials to further validate the clinical efficacy and long-term success of OD in diverse patient populations. This research underscores the evolving landscape of implant dentistry, emphasizing the need for refined techniques that enhance predictability and patient outcomes.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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ANESTEZIJA SA PALATINALNE STRANE ZA PREDNJE I SREDNJE GRANE GORNJEG ZUBNOG PLEKSUSA KAO PRIMARNA TEHNIKA U ORALNO-HIRURŠKIM INTERVENCIJAMA

THE PALATINAL SIDE ANESTHESIA FOR THE ANTERIOR AND MIDDLE BRANCHES OF THE SUPERIOR ALVEOLAR PLEXUS AS A PRIMARY TECHNIQUE IN ORAL SURGICAL INTERVENTIONS

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Sažetak

Uvod: *Anestezija za prednje i srednje grane gornjeg alveolarnog pleksusa (AMSA) se smatra sprovodnom tehnikom, za prvih pet maksilarnih zuba (od centralnih sekutića do drugog premolara). Naime, ova tehnika do sada je opisana kao dopunska tehnika anestezije koja cilja na subneuralni dentalni pleksus koji se nalazi u blizini vrhova korena premolara.*
Cilj *istraživanja je bio da se utvrdi da li AMSA tehnika anestezije može poslužiti kao primarna i samostalna metoda za vađenje prvih pet zuba gornje vilice (sekutića, očnjaka i pretkutnjaka).*
Materijali i metode: *Studijom su obuhvaćena 24 zdrava pacijenta raspoređena u I grupu (primili 4% artikain sa adrenalinom) i II grupu (primili lidokain sa adrenalinom), koji su imali avitalne maksilarne zube (od sekutića do premolara). AMSA tehnika je korišćena kao primarna anestezija za ekstrakciju zuba. Praćeni parametri anestezije obuhvatali su: percepciju bola tokom primene anestezije i tokom hirurške procedure, ukupan uspeh anestezije, vreme početka, trajanje anestezije i postekstrakcione komplikacije.* ***Rezultati:*** *Trajanje anestezije u prvoj je bilo 52±17,10 min, dok je u drugoj 40,25±7,629 min (p=0,044). Nivo bola tokom ekstrakcije bio je 3,42±1,73 dok je u drugoj grupi 5,25±2,41 sa statistički značajnom razlikom između grupa (p=0,046). Potreba za dodatnom anestezijom bila je 2 (16,66%), u prvoj i 5 (41,66%). u drugoj grupi.* ***Zaključak:*** *AMSA tehnika anestezije sa upotrebom artikaina može poslužiti kao primarna tehnika lokalne anestezije za ekstrakciju prvih avitalnih maksilarnih zuba, dok manju anestetičku efikasnost kao primarna tehnika uspoljava u slučaju upotrebe lidokaina.*

Ključne reči: *AMSA, ekstrakcija zuba, artikain, lidokain*

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Abstract

Introduction: *Anterior Middle Superior Anesthesia (AMSA) is considered a conductive technique for the first five maxillary teeth (from central incisors to the second premolar). This alternative anesthesia is considered a supplementary technique targeting the subneural dental plexus located near the root apices of the premolars.*
The study aimed *to determine whether AMSA anesthesia technique can serve as a primary and independent method for extracting of the first five upper jaw teeth (incisors, canines, and premolars).*
Materials and methods: *The study included 24 healthy patients allocated in the group I (received 4% articaine with adrenaline) and the group II (received lidocaine with adrenaline) . The patients had avital maxillary teeth (from incisors to premolars). AMSA technique was used as primary anesthesia for extraction. The monitored anesthesia parameters included: pain perception during the application of anesthesia and the surgical procedure, overall success of anesthesia, onset time, and duration of anesthesia and post extraction complications.*
Results: *The duration of anesthesia was 52±17,10 min in the first group, while it was 40,25±7,629 min (p=0,044).in the second The level of pain during the extraction was 3,42± 1,73in the first group, while it was 5,25±2,41 in the second, with statistically significant difference between groups (p=0,046). The need for additional anesthesia was 2 (16,66%), in the first and 5 (41,66%). in the second group.*
Conclusion: *The AMSA technique has demonstrated high efficacy for simple extractions when articaine is used; it shows less anesthetic efficacy when lidocaine is used. The AMSA anesthesia technique with articaine may be considered a primary local anesthesia technique for the extraction of the first five maxillary teeth when they are not vital.*

Key words: *AMSA, tooth extraction, articaine, lidocaine*

Introduction

The extraction of upper jaw teeth is enabled by local anesthesia, which is performed by injecting an anesthetic solution subperiosteally into the region of the buccal and palatal branches of the superior dental plexus at the root apex of the tooth. This anesthesia technique requires a minimum of two punctures—one on the buccal and one on the palatal side. The buccal injection is always accompanied by varying degrees of numbness in the soft tissues of the cheek and upper lip, with potential complications such as hematoma, transient paralysis of the oculomotor nerve[1].

The superior dental plexus consists of the anterior, middle, and posterior alveolar nerves, which innervate the incisors and canines (anterior), premolars (middle), and molars (posterior alveolar nerves). The middle and anterior superior alveolar nerves originate from the infraorbital nerve. The anterior superior alveolar nerve arises from the lateral side of the infraorbital nerve, approximately at the mid-point of the infraorbital canal. It travels through the infraorbital canal, medially toward the nose, before turning downward and branching out to supply the incisors and canines, contributing to the formation of the superior dental plexus. The anterior superior alveolar (ASA) nerve originates approximately 5–8 mm posterior to the infraorbital foramen and provides pulpal innervation to the central incisor, lateral incisor, and canines.

The middle superior alveolar nerve runs downward and forward within the infraorbital canal, along the lateral wall of the maxillary sinus. The middle superior alveolar (MSA) nerve arises about 10 mm posterior to the infraorbital foramen, and is responsible for the pulpal innervation of the premolars and the mesio- buccal root of the first molar. The branches of the middle superior alveolar nerve merge with the posterior and anterior superior alveolar branches, forming the superior dental plexus[2]. The middle superior alveolar nerve is a variable branch—it can be duplicated or even absent. Human dissection studies have shown that the MSA nerve is not always present, with its occurrence varying between 30% and 72% of cases[3].

Neurovascular (nutrient) canals on the palate are most commonly located in the premolar region. The palatal cortex is generally more porous, with a greater average width and number of canals. These neurovascular canals contain the terminal branches of the greater palatine artery and nerve. The presence of these canals and the porosity of the palatal cortex create favorable conditions for the diffusion of anesthetic solution during conduction anesthesia for the anterior and middle alveolar nerve branches via a palatal approach[4].

In 1997, Friedman and Hochman introduced this maxillary anesthesia technique under the name Anterior Middle Superior Anesthesia (AMSA)[5], which targets the subneural dental plexus located near the root apices of the premolars. In this technique, the anesthetic is injected once from the palatal side, at a site with nutrient canals that allow diffusion through the maxillary bone, blocking these nerves without inducing anesthesia in the buccal soft tissues.

Since the needle penetrates the hard palate between the first and second premolars, approximately midway between the mid-palatine raphe and the free gingival margin, the local anesthetic (LA) solution spreads beneath the mucoperiosteum. This diffusion allows the anesthetic to reach the branches of the greater palatine and nasopalatine nerves, effectively numbing most palatal tissues.

Given the clinical significance of AMSA anesthesia for specific indications in dentistry, this study focuses on evaluating the success of this local anesthesia technique with different anesthetic agents for maxillary tooth extraction.

The aim of this study was to evaluate the overall success rate of anesthesia when applying the AMSA local anesthesia technique using the two most commonly used local anesthetics in dentistry for the first five maxillary teeth. Additionally, the study aimed to determine whether this anesthesia technique could serve as a primary and independent method for the extraction of the first five upper jaw teeth (incisors, canines, and premolars).

Materials and Methods

This prospective, double-blind, crossover randomized study included healthy volunteers classified as ASA I and II according to the American Society of Anesthesiologists. Participants were patients who had one or more avital maxillary teeth, in the region of incisors, canine or premolars. The routine dental extractions were performedat the Department of Oral Surgery, Clinic for Dental Medicine Niš, Serbia. After obtaining the Ethics Committee's approval of the Clinic for Dental Medicine Niš (No:2069/2-E-P;2024.), the study was performed respecting ethical principles outlined in the Declaration of Helsinki[6].

After obtaining medical data, patients were fully informed about the study and provided written consent for participation. Before the procedure, relevant data on the anesthetic effect were collected for each subject and recorded in a research chart (Figure 1).

The patients did not consume any medication that could alter their pain perception.

Patients partly completed the questionnaire at the clinic, partly at home, and returned it after completing, at the first check-up.

Twenty-four participants of both genders and varying ages (18-65) who had one or more avital maxillary teeth were included in the study and divided into two groups.

Group 1 (12 participants) received 4% articaine with epinephrine 1:100,000 (Pierrel S.p.A, Italy) as the local anesthetic.

Group 2 (12 participants) received 2% lidocaine with epinephrine 1:100,000 (Galenika a.d., Belgrade).

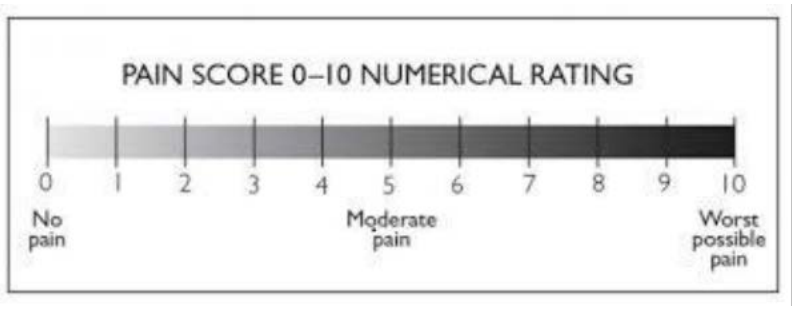
All patients received a topical anesthetic spray on the palatal side before the injection.

The total amount of anesthetic administered using the AMSA technique was 1,5 mL of articaine in the first group and 1,5 mL of lidocaine in the second group.

Technique of AMSA anesthesia: The procedure was performed with the position of the patient's head and neck slightly extended. A topical anesthetic was applied with a cotton ball soaked in anesthetic to the injection area for 30 seconds. The target point was located at the intersection of imaginary lines drawn between the premolars towards the middle of the palate, exactly halfway between the tip of the palatal suture and the edge of the free gingiva of the premolars; The needle was positioned so that the bevel was in contact with the palatal tissue, and was rotated 45º clockwise followed by 45º counterclockwise during insertion. The anesthetic solution was then delivered slowly at a consistent amount of 1.5 ml. Once the proper amount of anesthetic was in place, the needle was left undisturbed for 5 seconds before being withdrawn

The monitored anesthesia parameters included:

Subjective Pain Assessment (evaluated by patient): The Numeric Rating Scale (NRS) was used to assess subjective pain during surgery, represented horizontal line ranging from 0 (no pain) to 10 (worst possible pain)[7].



1. Pain perception during anesthesia was evaluated while needle insertion and anesthetic application at the target point on the palate.

2. Pain perception was also evaluated perioperatively, during the surgical procedure, while the tooth was extracted.

Anesthesia was considered successful if the tooth was simply extracted and the patient reported no pain (NRS score 0-2), or mild pain (NRS score 3-4).

3. Onset Time (min): The time elapsed from the administration of anesthesia to the first signs of its effect, manifested loss of sensitivity of palatal mucosa during puncture with a blunt instrument

4. Duration of Anesthesia Effect: The time from the onset of anesthesia to the cessation of its effects, including the appearance of sensitivity of palatal mucosa during puncture with a blunt instrument.

5. Appearance of post-extraction pain, was evaluated using NRS scale

6. Appearance of post-extraction complications, was noticed at the first tomorrow check- up.

The patient who experienced certain pain that required the addition of local anesthetic, received the dose of 1,8 ml of the same anesthetic of the belonging group, using the buccal infiltration technique.

Immediately after anesthesia administration and tooth extraction, patients recorded their pain intensity during these procedures.

Statistical analysis

For each parameter, the mean, standard deviation and standard error were calculated.

The statistical difference between the means of different groups was calculated using the independent samples T test. The significance level was established at $p<0,05$. Statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, IL, USA).

Results

Twenty-four adult patients participated in this study, 12 men and 12 women equally allocated in two groups of 6 patients of both sexes (total 12 patients per group), with an average age of 47,8 and 50,2 years. All the patients received an AMSA nerve block using a conventional syringe, in total amount of 1,5 ml of atricaine with ardenaline (group I) or lidocaine with adrenaline (group II). The anesthetic success of the AMSA nerve block technique using a conventional syringe with two different aneshtetics is presented in Table 1.

The onset of anesthesia ranged from 2 to 8 minutes (on average 3,92± 1,73 min.) in the first group, and from 3 to 9 (on average 5,08± 1,73 min) in the second. Pain assessed during anesthesia application ranged 2-6 in both groups (on average 3,33±1,43 and 4,42±1,56) with no statistical difference. Pain during the extraction ranged from 2-7 in the first group (on average 3,42±1,730), while 3-9 in the second group (on average 5,25±2,417) with statistically significant difference between groups (p=0,046) Figure 1. Duration of anesthesia was 52±17,10 min in the first group, and 40,25±7,629 min in the second, with statistically significant difference between groups (p=0,044) Figure 2. Additional anesthesia was needed in two cases in the first group 16,66% (both for incisors), and in five casesin the second 41,66% (3 for premolars, 2 for incisors). The pain after the procedure was noticed in four cases in the first group, with NRS ranging from 3-4 (mild pain). The post-extraction pain occurred in one case on the third day, and was treated successfully. Detailed average and statistical data are presented in Table 1. and Table 2.

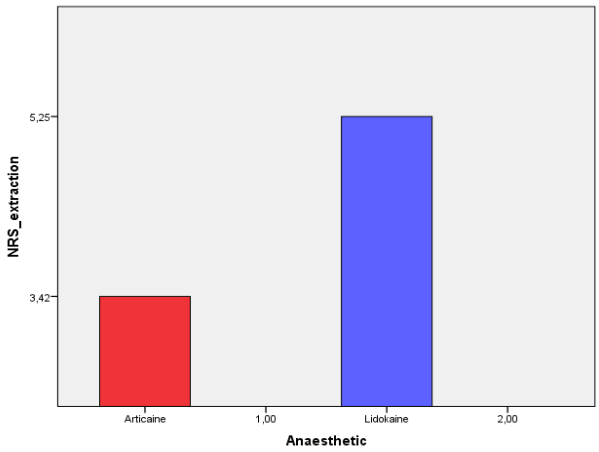


Figure 1. NRS of pain during the extraction

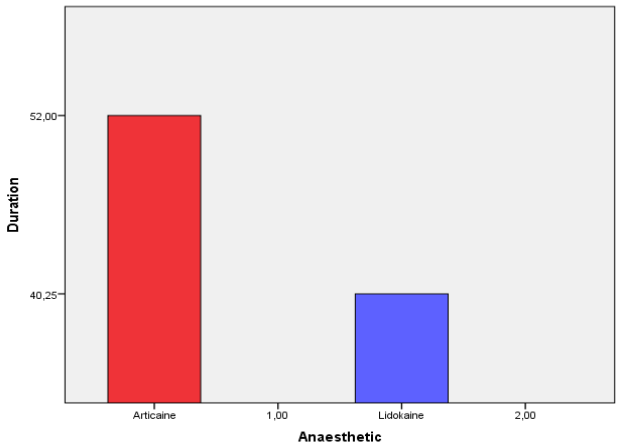


Figure 2. Duration of anesthesia

Table 1. Comparison of anesthetic parameters

	Anaesthetic	N	Mean	Std. Deviation	Std. Error Mean
NRS_anaesthesia_pain	Articaine	12	3,33	1,435	,414
	Lidocaine	12	4,42	1,564	,452
NRS_extraction_pain	Articaine	12	3,42	1,730	,499
	Lidocaine	12	5,25	2,417	,698
Onset_time	Articaine	12	3,92	1,730	,499
	Lidocaine	12	5,08	1,730	,499
Duration	Articaine	12	52,00	17,104	4,937
	Lidocaine	12	40,25	7,629	2,202
NRS_post-extraction_pain	Articaine	12	1,17	1,749	,505
	Lidocaine	12	,25	,622	,179

Table 2. Statistical analysis of anesthetic paremeters

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
NRS_anaesthesia	Equal variances assumed	,063	,804	-1,768	22	**,091**	-1,083	,613	-2,354	,188
	Equal variances not assumed			-1,768	21,840	,091	-1,083	,613	-2,355	,188
NRS_extraction	Equal variances assumed	3,607	,071	-2,137	22	**,044***	-1,833	,858	-3,613	-,054
	Equal variances not assumed			-2,137	19,928	,045	-1,833	,858	-3,623	-,043

Onset_time	Equal variances assumed	,004	,952	-1,652	22	**,113**	-1,167	,706	-2,631	,298
	Equal variances not assumed			-1,652	22,000	,113	-1,167	,706	-2,631	,298
Duration	Equal variances assumed	7,678	,011	2,173	22	,041	11,750	5,406	,538	22,962
	Equal variances not assumed			2,173	15,210	**,046***	11,750	5,406	,240	23,260
NRS_postextraction_pain	Equal variances assumed	25,192	,000	1,710	22	,101	,917	,536	-,195	2,028
	Equal variances not assumed			1,710	13,734	**,110**	,917	,536	-,235	2,068

Discussion

The AMSA (Anterior Middle Superior Alveolar) nerve block technique is used for anesthesia of the central and lateral incisors, canines, and premolars in the maxilla. The injection site corresponds to the region where the anterior and middle superior alveolar nerve branches merge into the dental neural plexus, allowing a single AMSA block to effectively anesthetize the entire area including pulp and surrounded palatal soft tissue in the same region[8]. This technique could be advantageous, as the bilateral AMSA nerve block is believed to anesthetize 10 maxillary teeth, ranging from the second premolar on one side to the opposite side, without affecting the facial muscles. This makes it particularly beneficial for restorative dentistry. Research indicates that this technique allows for pulpal anesthesia while preserving sensation in the soft tissues, including the upper lip, cheek, and surrounding structures. This anesthetic technique was previously defined as infiltration rather than conduction anesthesia[9]. Certainly, AMSA anesthesia could also be defined as an intraosseous technique, since the anesthetic solution is deposited directly into the bone tissue. This method of applying anesthetic into highly vascularized bone tissue facilitates rapid absorption of the local anesthetic. Nevertheless, most of the authors advocated it as a conduction technique[10].

The results of this study show that this technique of anesthesia provides success in non- complicated extraction of non -vital teeth. Better results in the group treated with articaine could be explained by the pharmacology of articaine and its local anesthetic potential[11]. Articaine is an amide local anesthetic notable for its molecular structure that differs from the other amide local anesthetic thanks to the presence of a thiophene ring. The structure of the ring improves its lipid solubility, allowing articaine to more easily diffuse through soft tissue and bone compared to other local anesthetics and higher potency for anesthetic solution to penetrate through the alveolar and palatal bone. Articaine has partition coefficient of 17 (due to its lipophilicity), whlile lidocaine has 4, so articaine enables a greater concentration of active molecules to effectively penetrate the lipid nerve membrane, which accounts for its high anesthetic potency. The longer duration of anesthesia achieved with articaine could be explained by its higher binding affinity to proteins at the receptor site (95%), compared to lidocaine—the gold standard (65%)—which results in a prolonged anesthetic effect of articaine[2].

Success rates were observed in both groups during the extraction. Tomić at al. recorded high success in painless extraction of the upper premolars using AMSA technique, regardless of the local anesthetic or injection system that was used[11]. Chuorasia at al.[4] reported a success rate of AMSA anesthesia in 71.5% of cases, while Lee et al[12] reported a success rate of 35 to 58%. In our study, additional anesthesia was used in two cases in the first group (16,66%), while it was used in five cases in the second (41,66%). The greatest addition of anesthesia was demanded for extraction of the first premolar (66,6% of all additional anesthesia) in the lidocaine group. This could be related to anatomical variations in the innervation of the first premolar region. The first premolar usually has two separate roots, while the second premolar typically has a single connected root. The buccal root of the first premolar is positioned on the buccal side, meaning that an anesthetic solution

administered on the palatal side must diffuse over a longer distance to reach it. The width of the maxilla in this region is wider than in the mesial region, so lidocaine with its low lipophilicity could not achieve the buccal branches of the medial superior alveolar nerve. Additionally, the buccal root of the first premolar may receive innervation from accessory branches of the posterior superior alveolar nerve, which is not influenced by anatomical structures on the palate. Other studies have also reported the unpredictable effect of the AMSA technique on the buccal periodontium[13].

Additional anesthesia was also needed during the extraction of the incisors, in both groups. In the lidocaine group the need for additional anesthesia for incisors was 44,4% (of all additional anesthesia), while in the articaine group it was 100% (of all additional anesthesia). The greater distance between the central incisor's root and the injection site may hinder the diffusion of the anesthetic solution, resulting in a relatively lower success rate of bone anesthesia. Velasko at al. noticed the similar success rate in pulp anesthesia[14]. The vestibular root of the first premolar, as well as the position of the central incisor's root, are located further away compared to the roots of the other teeth in the upper jaw, considering the injection site on the palatal side. This distance may reduce the success of AMSA palatal anesthesia technique. Research has shown that the AMSA technique is particularly effective for orthodontic premolar extractions, In cases of periodontally compromised premolars, success rates are similarly high. The complete success of second premolar extractions in the articaine group further supports our findings. Some studies also highlight the advantages of this technique in pediatric dentistry, where increased bone porosity allows for faster and more effective anesthetic diffusion.

Previous studies have reported that when the AMSA nerve block is administered using 2% lidocaine with epinephrine, the onset time with conventional injection techniques typically falls between 6 and 12 minutes[15]. The onset of anesthesia in this study was 5,07 minutes in the lidocaine group, and in 3,83 minutes in the articaine group, likely due to the presence of nutrient foramina and canals in the maxilla. Articaine exhibited a faster onset compared to lidocaine, attributable to its high liposolubility. Conversely, the anesthetic effect lasted longer in the lidocaine group, which is expected given its slower metabolism and longer half-life compared to articaine. This was expected, because the spreading of anesthetic through palatal mucosa and periosteum is fast, while we did not test the pulpal anesthesia (all teeth were non vital).

Ćetković at al.[16] noticed anatomical morphology bases of AMSA anesthesia success. Female skulls exhibited significantly wider nutrient canal foramina compared to male skulls. Despite the increased thickness, the palatal cortex at the AMSA injection site displayed slightly greater porosity than the buccal cortex. They also noticed a significantly higher number of micro canals fully penetrated the cortical thickness in the palatal bone compared to the buccal cortical bone, so the structural features of the palatal cortex offer a strong anatomical foundation for achieving a high success rate with the AMSA injection technique[16]. In this study male/female portion was equal, so gender had no effect on the overall success of anesthesia.

One of the main drawbacks of the AMSA technique is the pain experienced during anesthetic administration on the palate, often perceived as the most painful part of the procedure. Even with the use of topical anesthesia, the pain was rated as moderate to intense, consistent with the findings of Wahl et al., who reported that palatal injections cause significantly more pain than other intraoral applications due to the pressure of anesthetic infiltration[17].

As an alternative, infraorbital anesthesia can provide adequate anesthetic effect but carries risks such as hematoma, transient muscle paralysis of the eye, and prolonged facial numbness. The success rate of pulpal anesthesia using the infraorbital technique ranges 57.9%[18] to or 75-92%, though articaine administration via this method has been associated with transient ocular muscle paralysis in 15% of cases.

A key advantage of the AMSA technique is the preservation of facial muscle mobility, which is particularly significant in aesthetic dentistry as it prevents lip and facial numbness, maintaining the natural smile line. Additionally, this technique has proven beneficial in periodontal surgery due to its excellent hemostatic effect on the palate.

However, our study results indicate that the success of AMSA anesthesia varies depending on the tooth group. Success rates were lower for incisors and canines, likely due to anatomical variability in the maxilla, specifically the presence of the middle superior dental nerve branch in certain patients. Dissection studies have shown that this

anatomical variant occurs in 30% to 72% of cases, which may explain the differences in anesthesia effectiveness among patients[19].

Conclusion

The AMSA local anesthesia technique has broad applications in conservative dentistry and periodontology, and it is particularly advantageous due to its preservation of facial muscle function. It can also be especially suitable for minor oral surgery depending on interventions. While it has demonstrated high efficacy for simple extractions when articaine is used, it shows less anesthetic efficacy when lidocaine is used. AMSA anesthesia technique with articaine may be considered a primary local anesthesia technique for the extraction of the first five maxillary teeth when they are not vital, or a supplementary technique for the overall anesthetic effect of lidocaine for the same purpose.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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EVALUACIJA STILOIDNOG PROCESUSA KOD POREMEĆAJA TEMPOROMANDIBULARNIH ZGLOBOVA

EVALUATION OF THE STYLOID PRECUSSUS IN TEMPOROMANDIBULAR JOINT DISORDERS

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Sažetak

Cilj *studije bila je procena stiloidnog procesusa kod različitih oboljenja zgloba.*
Materijali i metode: *Istraživanje je obuhvatilo 150 ispitanika, 50 ispitanika sa dijagnozom I grupe istraživačkih dijagnostičkih kriterijuma (RDC/TMD), 50 ispitanika sa dijagnozom II grupe i 50 ispitanika bez TMD kao kontrolne grupe. Izvršen je klinički pregled praćen radiografskim pregledom digitalnim panoramskim rendgenskim snimkom. Radiografije su procenjene i analizirane u pogledu dužine i vrste stiloidnog nastavka.*
Rezultati: *Srednja dužina stiloidnog nastavka bila je 32,33 ± 4,14 mm u RDC/TMD I grupi, 29,08 ± 5,26 mm u RDC/TMD II grupi i 29,94 ± 7,02 u kontrolnoj grupi. Dužina stiloidnog nastavka kod RDC/TMD I bila je veća, a zatim kod kontrolne i RDC/TMD grupe II. Razlika između grupa je bila značajna (p < 0,05). U grupi RDC/TMD I najviše je dominirao stiloidni proces tipa II, zatim tip I i tip III. U grupi RDC/TMD II najviše je dominirao stiloidni nastavak tip I, zatim tip II, tip III. Dalje, u kontrolnoj grupi, stiloidni nastavak tip I bio je najistaknutiji, zatim tip II i tip III. Utvrđena je značajna povezanost između grupa i tipa stiloidnog nastavka (p = 0,000).*
Zaključak: *Izduženje stiloidnog nastavka se češće javlja kod poremećaja temporomandibularnog zgloba kod RDC/TMD I dijagnoze nego kod RDC/TMD II dijagnoze. Studija predlaže procenu stiloidnih procesa kod pacijenata sa TMD.*

Ključne reči: *Orlov sindrom, izduženi stiloidni procesus, panoramska radiografija, poremećaji temporomandibularnog zgloba*

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Abstract

Aim *The present study was undertaken with the aim of evaluating the styloid process in various TMD.*
Materials and Methods: *The study included 150 subjects, 50 subjects with Research Diagnostic Criteria (RDC/TMD) group I diagnosis, 50 subjects with group II diagnosis and 50 subjects without TMD as a control group. Clinical examination followed by radiographic examination using digital panoramic radiograph was carried out. The radiographs were evaluated and analysed for the length and type of the styloid process.*
Results: *The mean length of the styloid procesus was 32.33 ± 4.14 mm in the RDC/TMD I group, 29.08 ± 5.26 mm in RDC/TMD II group and 29.94 ± 7.02 in the control group. The length of the styloid procesus in RDC/TMD I was higher followed by the control and RDC/TMD group II. The difference between the groups was significant (p < 0.05). Styloid procesus type II was the most predominant in the RDC/TMD I group, followed by type I, and type III. In RDC/TMD II group, styloid procesus type I was the most predominant, followed by type II, type III. Further, in the control group, styloid process type I was the most prominent, followed by type II and type III. A significant association between the groups and the type of styloid process was found (p = 0.000).*
Conclusion: *Elongation of the styloid procesus is more predominantly found in temporomandibular joint disorders RDC/TMD I diagnoses than RDC/TMD II diagnoses. The study suggests evaluating the styloid procesuses in TMD patients.*

Key words: *Eagle syndrome, elongated styloid procesus, panoramic radiography, temporomandibular joint disorders*

Introduction

Temporomandibular joint (TMJ) is one of the most complex bilateral synovial joints present in the human body. It plays a crucial role in managing the mandibular movements and regulating the major functions of the stomatognathic system such as speech and mastication[1]. World Health Organization (WHO) report refers to temporomandibular joint disorders (TMD) as the third most predominant stomatological problem after dental caries and periodontal diseases, under the category of population diseases[2]. The global prevalence of TMDs in adults is estimated to be about 31%[3]. The etiology of TMD is multifactorial and the pathogenesis remains to be diverse and poorly understood. Pain in the TMJ region and restriction of mandibular movements were reported to be the most common clinical presentation of TMDs[4]. The presentation of pain in the TMJ and jaws region may be a common presentation of various other disorders as well, such as referred odontogenic pain, otologic pain, and pain due to the elongated styloid procesus. It is clinically difficult to delineate the pain related to TMD from that due to an elongated styloid, without the aid of radiographic investigations[5]. The anatomical proximity of the styloid procesus to the TMJ is also a major reason that could lead to misperception of the symptoms. The average length of styloid procesus is about 20–30 mm, when their length exceeds 30 mm it is said to be elongated leading to Eagle syndrome[6,7]. The evidence exploring the association between the styloid procesus and temporomandibular joint disorders are scanty in the literature. Hence, present study was undertaken to evaluate the styloid process in various temporomandibular joint disorders.

Material and methods

The study was conducted after the institutional research and ethical committee approval. A total of 150 subjects attending the outpatient Clinic of Oral Medicine and Radiology were involved in the study. All subjects were within the age group of 18–40 years. Study subjects were divided into three groups based on the clinical findings. Study groups 1 and 2 consisted of 50 subjects each with pain in the TMJ region and were diagnosed with TMD falling under the Research Diagnostic Criteria (RDC/TMD) group I and II respectively. Study group 3 included 50 control subjects without TMD and required panoramic radiographs for diagnosis and treatment planning. Subjects who had TMJ pain for a period less than 3 months or pure arthrogenic pain (RDC/TMD group III), history of systemic disorders and syndromes, history of craniofacial trauma or any history of head and neck surgery were excluded from the study.

The study subjects who fulfilled the inclusion criteria were given explanations about the study procedures in detail and written informed consents were signed by the subjects who were willing to take part in the study. A well-trained oral medicine specialist carried out the complete clinical TMJ assessment by abiding to the clinical diagnostic criteria for diagnosing TMD[8]. The study subjects were divided into three groups, group 1 comprised 50 subjects with myogenic pain (RDC/TMD I), group 2 comprised 50 subjects who had disc displacements (RDC/TMD II) and group 3 was the control group. The radiographic investigation with digital orthopantomogram (OPG) was done for the preliminary evaluation of the dentition, TMJ and styloid complex. The digital radiographs were procured using Planmeca ProMax S2-2D (Helsinki, Finland, 2008) under standard exposure parameters (average exposure of 64–70 kV; 8–13 mA). Radiographic imaging was undertaken by a well-trained radiographer and the radiographic images were assessed in full-screen monitor using Planmeca Romexis software (version 4.6.2) by two independent maxillofacial radiologists who were blinded about the clinical group of the subjects. Maxillofacial radiologists were trained and calibrated for the measurements. The radiographic evaluation assessed the morphology of the condylar head, the extent of movement of the condylar head, and the length and type of the styloid procesus. The measurement of the styloid procesus was recorded using the measurement tool from the point where the styloid exits the tympanic plate to the tip of the styloid procesus[9]. The classification system of the styloid complex that was put forth by Langlais was followed to categorize the type of styloid (Figure 1)[10].

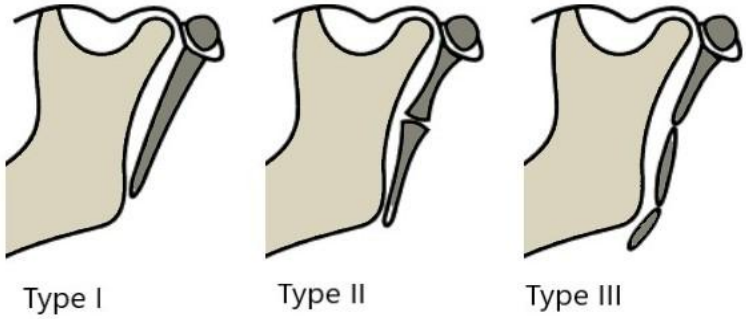

Figure 1. Classification of styloid procesus[10]

Statistical analysis

The data obtained from the study were tabulated and subjected to statistical analysis using Statistical Package for the Social Sciences software version 26 (SPSS Inc., Chicago, IL, USA). The comparison between the lengths of the styloid procesus between the three groups was done using ANOVA followed by Tukey post hoc analysis, while Chi-square test was used to compare the distribution of various types of styloid processes among the study subjects. P-value < 0.05 was considered to be statistically significant.

Results

Our study included a total of 150 subjects (98 females and 52 males), the clinical details of the subjects included in the study are given in Table 1. The mean age of the study subjects in the myogenic and disc displacement groups was 30.32 ± 4.78 and 25.84 ± 6.27 years, respectively and the mean age of subjects in the control group was 25.92 ± 6.07. The mean length of the styloid procesus in the RDC/TMD I/myogenic group was 32.34 ± 4.14 mm and in the RDC/TMD II/disc displacement group, it was 29.08 ± 5.26 mm. The mean length of the styloid procesus in the control group was 29.94 ± 7.02. The length of the styloid procesus in RDC/TMD I was higher than in the RDC/TMD II group and it was statistically significant with a p-value of 0.012 (Table 2). On assessment of the type of styloid procesus in the study groups, type II was the most predominant in the RDC/TMD I group, followed by type I and type III. In the RDC/TMD II group, type I was the most predominant type, followed by type II, and type III. A significant association (p = 0.000) between the groups and the type of styloid procesus was found (Table 3, Figure 2). Panoramic radiographs of our study samples representing different type of styloid procesuses are shown in the figures, styloid procesus type I (Figure 3), styloid procesus type II (Figure 4) and styloid procesus type III (Figure 5).

Table 1. Characteristics of the study subjects

	RDC/TMD I	RDC/TMD II	CONTROL
Number (n)	50	50	50
Gender n (%)	Males = 17 (34%)	Males = 14 (28%)	Males = 21 (42%)
	Females = 33 (66%)	Females = 36 (72%)	Females = 29 (58%)
Mean age (in years)	30.32 ± 4.78	25.84 ± 6.27	25.92 ± 6.07
Mean duration of Pain (in months)	4 ± 0.23	4 ± 1.82	No Pain
Visual Analogue Scale for pain (Out of 10)	7 ± 0.96	6 ± 1.07	Not applicable

Table 2. Comparison of length of styloid procesus between the 3 groups

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Sum of Squares	F	Sig.
					Lower Bound	Upper Bound			
RDC/TMD I	50	32.33	4.145	0.58627	31.15	33.50	283.570	4.518	0.012*
RDC/TMD II	50	29.08	5.260	0.74389	27.58	30.57			
Control	50	29.94	7.021	0.99298	27.94	31.93			

Table 3. Comparison of type of styloid procesus between the three groups

		Styloid process		
		I	II	III
Groups	RDC/TMD I	19	24	7
	RDC/TMD II	31	17	2
	Control	43	6	1

$X^2 = 26.001$, $p = 0.000$*

Chi-square test was used. A significant association between the groups and the type of styloid procesus was found (p = 0.000)

Table 4. Multiple Group Comparisons

(I) Groups	(J) Groups	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
RDC/TMD I	RDC/TMD II	3.25000*	1.12044	0.012*	0.5971	5.9029
	Control	2.39000	1.12044	0.087	-0.2629	5.0429
RDC/TMD II	RDC/TMD I	-3.25000*	1.12044	0.012*	-5.9029	-0.5971
	Control	-0.86000	1.12044	0.723	-3.5129	1.7929
* The mean difference is significant at the 0.05 level						

The comparison between the lengths of the styloid procesus between the three groups was done using ANOVA followed by Tukey post hoc analysis. The length of the styloid procesus was highest in the RDC/TMD I group followed by the control and RDC/TMD II group. The difference between the groups was significant ($p < 0.05$). Post hoc analysis confirmed that the difference between RDC/TMD I and RDC/TMD II groups was significant (p = 0.012)

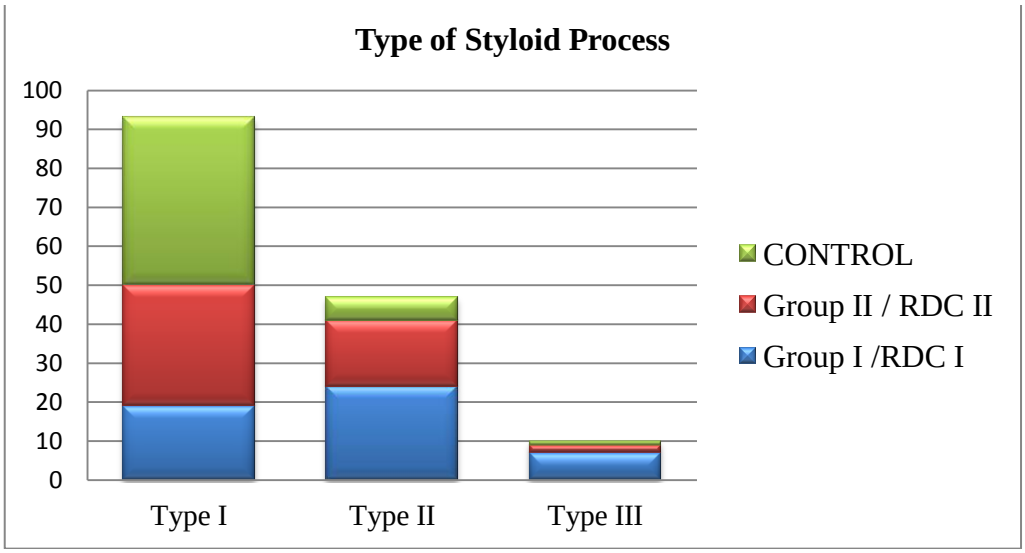

Figure 2. Distribution of various types of styloid procesus in the study subjects

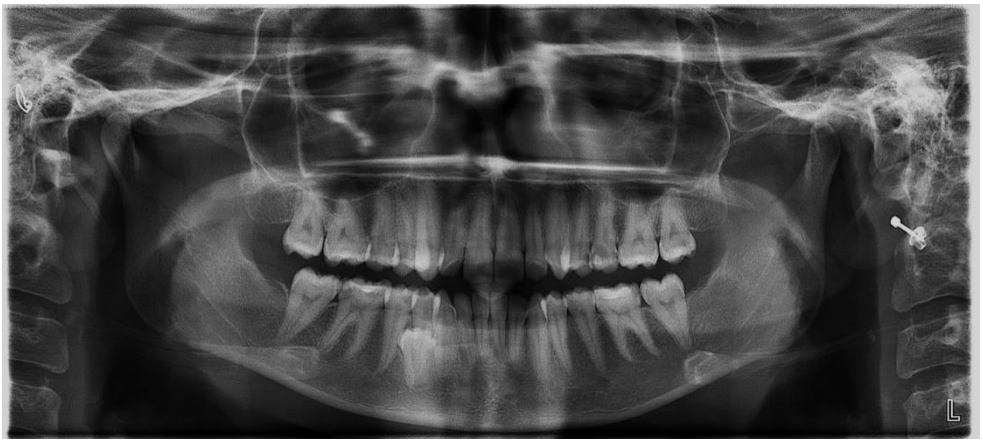

Figure 3. Panoramic radiograph showing styloid procesus type I

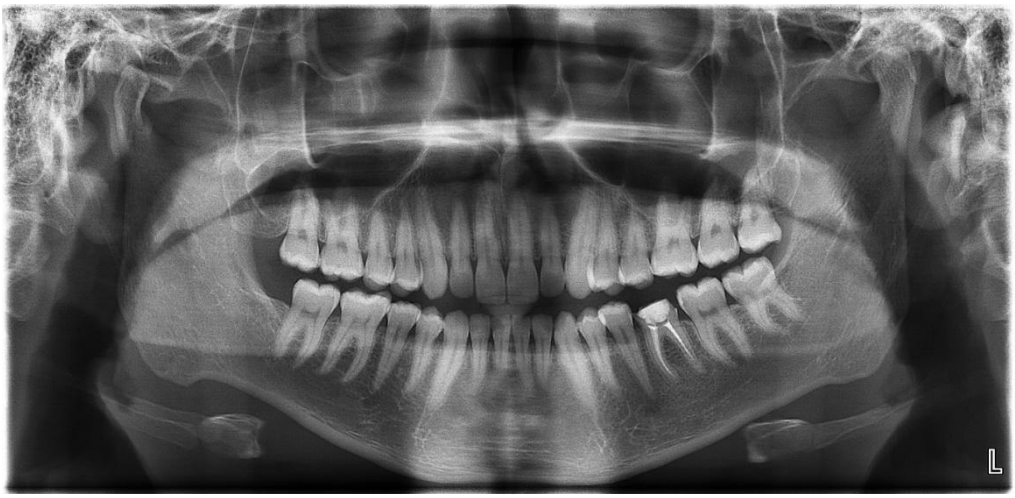

Figure 4. Panoramic radiograph showing styloid procesus type II

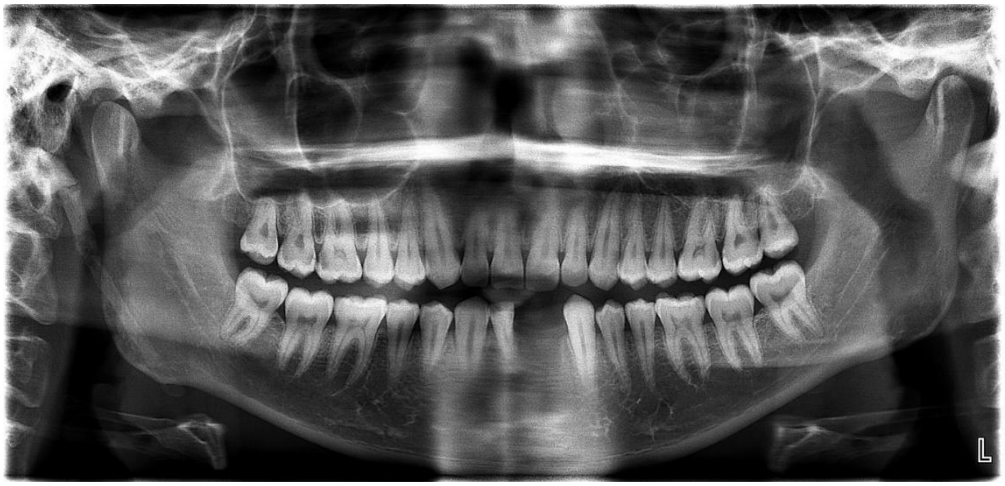

Figure 5. Panoramic radiograph showing styloid procesus type III

Discussion

Temporomandibular joint diseases are commonly encountered in women, especially among young adults[11]. Pain and functional limitation are the most common features of TMD. Pain associated with TMDs may radiate to the dental arches, ears, forehead, occipital and cervical spine region, or even to the shoulder girdle. Despite the high prevalence of TMD globally, relatively only a few patients seek treatment[12].

Myofascial TMD pain is associated with the masticatory muscles and gets aggravated by jaw movements, by provocation testing of the masticatory muscles or in the region within the border of the muscle. Myofascial pain is reported to be the most common cause of orofacial pain[13]. The medical literature reports that the pain associated with TMD is the most pronounced in the neck region, where the lack of lateral support balance can cause the neck to bend to the affected side[12]. Among disc displacements of the TMJ, disc displacement with reduction is the most frequently reported type with a prevalence up to 41%[14,15]. The initial stages of disc displacement with reduction may not exhibit any pain or functional limitation because of the ability of the joint to adapt to various disc positions however, in time the clinical symptoms develop due to the progression of the condition[16].

The clinical assessment of TMJ and establishment of relevant diagnosis is complex and requires expertise because of the anatomy of the joint and its close proximity to other anatomically significant structures[1]. The RDC/TMD diagnostic algorithm is a reliable and widely accepted criteria for the diagnosis of TMD[8]. In this study, the subjects were categorized based on the RDC/TMD criteria as RDC/TMD I/myogenic group and RDC/TMD II/disc displacement group. Literature evidence reports TMDs to be more prevalent in the age group of 20–40 years with a strong female predilection[17,18]. In the present study, 69% of the respondents were females, and the female predilection for TMDs can be attributed to various factors including psychological and hormonal influences[17,19]. In most instances, radiographic evaluation of the joint is vital for establishing a diagnosis of TMD. Various conventional and advanced modalities aid in the imaging of the TMJ. Panoramic radiography is useful only in gross morphological evaluation of the joint. However, panoramic radiography provides visualization of the lateral view of the condyles in comparatively low radiation exposures. Panoramic radiographs can serve as a preliminary radiographic tool to rule out significant changes in the osseous morphology of the joint[20,21].

The styloid procesus is located in the temporal bone adjacent to the stylomastoid foramen. The morphology of the styloid process appears as a cylindrical structure tapering at the end, with stylohyoid ligament attaching at its tip. Various vital structures such as the carotid arteries are in the close proximity of the styloid procesus, making it clinically important[22]. Anatomical alterations in the styloid procesus or stylohyoid ligament may manifest clinically as features similar to TMD. Eagle syndrome is a well-known phenomenon

characterized by the extension of styloid apophysis[23]. Elongation of the styloid process demands radiographic examination to determine the extent of the abnormality and for treatment planning. Bruno et al. conducted a systematic review to evaluate the validity of panoramic radiographs in the elongated styloid procesus. They reported panoramic radiography a valuable modality in the diagnosis of elongated styloid process (ESP). Panoramic radiography can serve as a primary radiographic modality for the evaluation of styloid in symptomatic individuals and to differentiate ESP from other painful orofacial conditions[24].

According to the literature reports, a styloid procesus that exceeds 30 mm in length is said to be elongated[7]. Generally, the mean length of the styloid procesus is reported to be within the range of 20–25 mm[25,26]. However, the average length of the styloid procesus differs widely in the observations of various authors. The mean length of the styloid process in the control group of our study was 29.94 ± 7.02. This variation is due to the population studied. In the present study, the styloid procesus length in RDC/TMD I (32.33 ± 4.145 mm) was higher than in the RDC/TMD II group (29.08 ± 5.26mm). Yavuz et al. in their study, reported individuals with TMD to have longer styloid processes with a mean length of 32.65 mm, which is similar to our findings[27]. However, the report of Yavuz et al. assessed the length of the styloid procesus in TMD as a single entity, without categorizing the type of TMD. Krohn et al. reported elongated styloid processes in individuals with TMD, but they did not find any significant difference in the association between the styloid procesus and specific RDC/TMD diagnoses[7].

Though evidence is supporting the association between the elongated styloid procesus and TMD, Sancio-Goncalves et al. reported a lack of association among the two conditions[28]. We observed an association between the elongated styloid procesus and the TMD—the RDC/TMD I group rather than the RDC/TMD II group. Our observation of the association between the elongated styloid and myogenic TMD could be related to various factors. Siéssere et al. in their clinical trial demonstrated hyperactive masticatory muscles in subjects with Eagle syndrome[29]. The hyperactive state of the masticatory musculature may result in myogenic pain. The mechanical irritation to mechanoreceptors due to an elongated styloid may alter their discharge in the area of cranial nerve endings of the 5^{th}, 7^{th}, 9^{th} and 10^{th} nerves[30]. The abnormal discharge in the mechanoreceptors can affect the neurological impulses to the TMJ region and the adjacent masticatory muscles leading to co-occurrence of TMD. Hormonal influence is also known to exert a direct effect on styloid chain calcification and elongation, similarly, hormones such as oestrogen were reported to be a major etiological factor in the development of TMD, especially in females[31–33].

We observed altered ESP (Styloid > 30 mm) in 62% of the study subjects in the RDC/TMD I group, 38% of the RDC/TMD II group and 36% of the control group. Yavuz et al.[27] and Mathew et al.[34] have also reported a similarly high prevalence of ESP in TMD, whereas Zaki et al.[35] and Guimarães et al.[36] have reported a comparatively lesser prevalence of ESP in TMD. The variations in the prevalence can be attributed to various factors such as the characteristics of the studied population, design of the study, presence of other systemic factors in the population studied etc. On analysis of the morphological type of the styloid procesus, we found type II to be the most predominant in the RDC/TMD I group, while type I was the most predominant type in the RDC/TMD II group and type I was more prominent type in control group. A significant association between the groups and the type of styloid procesus was found. Our study findings are in line with those of Andrade et al., where styloid type I was found to be the most common type in subjects with temporomandibular joint disorders[23]. Reddy et al. have reported styloid type I to be more prevalent in the South Indian population in general[37]. Hence, we did not find any specific attribute to the finding of styloid procesus type I in our study subjects with TMD.

Our study was an attempt to evaluate the styloid procesus in various types of TMD using panoramic radiography. This process involves a two-dimensional radiographic technique, which has its limitations. Therefore, further prospective large-scale studies are needed to evaluate the styloid process using 3-dimensional modality such as cone beam computed tomography (CBCT), particularly in specific types of TMD. Such studies will help provide an in-depth understanding of the association between these two conditions.

Conclusion

Elongation of the styloid procesus is associated with temporomandibular joint disorders, predominantly with RDC/TMD I diagnosis rather than RDC/TMD II diagnosis. Hence, clinicians must carefully evaluate the styloid procesuses in all cases of

temporomandibular joint disorders before establishing the diagnosis and developing the treatment plan.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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PROCENA PARODONTALNOG STATUSA KOD PACIJENATA SA FIKSNIM PROTETSKIM NADOKNADAMA

ASSESSMENT OF PERIODONTAL STATUS AMONG PATIENTS WITH FIXED PROSTHETIC RECONSTRUCTIONS

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Sažetak

Cil: *Imajući u vidu značaj parodontalnog zdravlja zuba koji nose fiksne protetske konstrukcije, postavili smo osnovni cilj - proceniti zdravlje parodonta kod ispitanika koji su imali fiksne protetske nadoknade u jednom regionu iz Republike Severne Makedonije.*
Materijal i metod: *Istraživanje je sprovedeno u pet stomatoloških ordinacija. Za svakog pacijenta tokom kliničkog pregleda utvrđeni su sledeći parametri koji se odnose na potporne zube fiksno-protetskih nadoknada: navike oralne higijene, dubina parodontalnih džepova i klinički gubitak epitelnog pripoja, prisustvo recesije gingive, stepen upale gingive i prisustvo lokalnih iritirajućih faktora koji mogu uticati na potporna tkiva zuba koji nose protetske nadoknade.*
Rezultati: *Nakon obrade podataka, konstatovano je da je procenat ispitanika koji ne peru zube 20%. Većina ispitanika je imala umerene inflamatorne promene gingive. Prosečna vrednost za dubinu parodontalnih džepova bila je 5,5±0,7 mm, a za klinički gubitak epitelnog pripoja 4,2 ± 0,2 mm. Prisustvo recesije gingive je vizuelno utvrđeno kod 31,66 % ispitanika. Najčešći predisponirajući faktor bilo je neadekvatno modeliranje fiksno-protetskih nadoknada. 48,33% ispitanika ima vertikalni gubitak koštane mase potvrđen radiografskim promenama.*
Zaključak: *Parodontalni problemi kod pacijenata koji nose fiksne protetske nadoknade su značajno izraženi, zbog nedovoljnog održavanja oralne higijene od strane pacijenata, kao i neredovnih odlazaka na stomatološke preglede. Veoma je važno da se fiksno-protetske nadoknade pravilno urade i adaptiraju.*

Ključne reči: *parodontalno zdravlje, gingivitis, fiksno-protetski uređaji, parodoncijum*

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Abstract

Aim: *Recognizing the importance of periodontal health for teeth with fixed prosthetic constructions, the main goal of the present study was to assess the periodontal health of respondents who underwent fixed prosthetic reconstructions in one region of the Republic of North Macedonia.*
Materials and Methods: *Research was conducted in five dental offices. For each patient, the following parameters related to the supporting teeth of the fixed prosthetic reconstructions were determined: oral hygiene habits, periodontal pockets depth and clinical loss of attachment, presence of gingival recession, degree of gingival inflammation and presence of local irritating factors that can affect the supporting tissues of the teeth wearing the prosthetic devices.*
Results: *After processing the data, it was noted that the percentage of subjects who did not brush their teeth was 20%. Most of the subjects had moderate gingival inflammatory changes. The average value for periodontal pocket depth was 5.5 ± 0.7 mm, and for clinical loss of attachment, it was 4.2 ± 0.2 mm. The presence of gingival recession was visually determined in 31.66% of subjects. The most commonly predisposing factor was inadequate modelling of the fixed prosthodontic appliances. Forty-eight point thirty-three percent of the subjects had vertical bone loss confirmed by radiographic changes.*
Conclusion: *Periodontal problems among patients that wear fixed prosthetic reconstructions are significantly pronounced, due to insufficient maintenance of oral hygiene by the patients, as well as irregular dental examinations. It is of great importance that the fixed prosthetic reconstructions are properly made and properly adapted.*

Key words: *periodontal health, gingivitis, fixed prosthodontic devices, periodontium*

Introduction

In contemporary dentistry, periodontal health is a crucial precondition for effective comprehensive treatment. Because periodontal health and dental restorations are intimately intertwined, both the fixed prosthetic restorations and all other restorations depend on periodontal health for properly functioning. Understanding the contribution of the restoration to the formation of dental plaque and the onset of periodontal disease is crucial.

Dental practitioners can effectively check and evaluate patients' oral and periodontal health if they have a fundamental understanding and knowledge of the periodontium[1]. In the assessment of the initial diseases that occur at the level of the periodontium, the first changes occur primarily in the gingiva. Furthermore, the gingiva is the only part of the periodontium that can be examined clinically[2]. Knowing that a healthy gingiva has a coral-pink color, any alteration in this color will signify the existence of an illness. It should be mentioned that the wearing of the fixed prosthetic reconstructions also causes alterations in the gingiva.

The loss of the periodontal tissues, including the resorption of the alveolar bone, is a hallmark of periodontal disease, an inflammatory condition of the periodontal tissues that eventually results in tooth loss[3]. It is commonly known that perio-pathogenic bacteria, the host's compromised immune system, and different local irritants that are present can cause periodontal inflammatory diseases[4,5,6]. For these reasons, patients frequently opt for prosthetic restorations due to the disruption of the tooth's anatomical-morphological properties or the loss of the tooth.

Patients receiving therapy with fixed prosthetic reconstructions are treated to achieve the following fundamental objectives:

1) To replace lost teeth
2) To restore the function of the dental system
3) To enhance aesthetics and
4) To maintain the periodontal tissues' health.

Proper diagnosis and treatment plan are crucial for patients to regain function and appearance. It is also crucial that fixed prosthetic restorations are well-made and polished, meaning they have the potential to self-clean, and they are aesthetically pleasing to maintain the health of the periodontal tissues and, consequently, the periodontal support. This will keep food remains from getting dipper in the gingival sulcus and minimize the amount of dental plaque, protecting the teeth's supporting structure. Many periodontal alterations will frequently emerge as a result of poorly and inadequate constructed restorations[7].

The final fixed prosthetic restorations that will be cemented need to be thoughtfully designed and have a harmonious relationship with the periodontium.

The potential for invasion of the gingiva's biological width is one of the most crucial things to think about and evaluate since it can lead to gingival inflammation, a loss of connective tissue and bone loss. It should also be kept in mind to prevent any harmful effects on the periodontium as well as to prevent and maintain the health of the gingiva.

Crowns and bridges should not be overextended in any direction and should be as smooth as possible with supragingival margins placed whenever possible. According to Jernberg et al.[8], in this way, the impaction of the food remains, and thus the accumulation of dental plaque, will be prevented. Fixed prosthetic devices must have a protective and preventive role in maintaining the health of all parts of the dental system[9].

Clinicians in their daily routine must and should pay special attention to the assessment of oral hygiene[10]. Especially in patients with fixed prosthetic devices, the physiological process of self-cleaning can be limited or completely impossible. Locations susceptible to the accumulation of dental plaque are mostly the marginal gingiva around the crowns, contact surfaces and bridge connectors. These areas require increased care in removing all food debris and accumulated plaque. Due to inadequate marginal adaptation[11], rough surfaces of the restoration and overextended contoured restorations[12], localized inflammation of the periodontium related to the fixed prosthetic reconstruction, can occur. Thus, the fixed prosthetic construction must allow adequate cleaning procedures. Educating patients about the importance of oral hygiene leads to an improvement in the level of hygiene[13]. Therefore, patients should be instructed in the appropriate way to clean teeth and prosthetic restorations, as well as to use additional tools for cleaning that allow more efficient removal of dental deposits.

Frequent careful professional cleaning of the teeth of patients with fixed prostheses helps to maintain satisfactory oral hygiene[14], thereby preventing further progression of the inflammatory component in depth. As already mentioned, failure can occur as a consequence of errors made during the treatment planning or construction process, but it can also be reflected due to inadequate care of the prosthetic construction by the patient. There are many studies on this topic, which indicate

that fixed prosthetic restorations lead to an increased accumulation of dental plaque, which in turn has a negative impact on the condition of the gingiva, due to insufficient and inadequate care, although there are authors who do not report a statistically significant difference in the values related to the presence of dental plaque between the teeth that have fixed prosthetic restorations in relation to the compared teeth, i.e., teeth that do not carry fixed prosthetic constructions[15,16].

Factors associated with prosthetic restorations such as crown margin, poor marginal adaptation, inadequate restoration contours, and rough margins are often associated with periodontal tissue inflammation[17]. Other studies have shown that insufficient oral hygiene is an important factor in the development of inflammatory changes of the oral mucosa under the bridge constructions[18]. This can lead to a reduced ability to load the tooth carriers of the fixed prosthetic structure, and thus to the reconstruction. The success of fixed prosthetic reconstructions, however, is only seen if the restoration remains in place for as long as possible and does not cause disease[19].

Therefore, periodontal assessment around prosthetic work is of the utmost importance in clinical dentistry, especially when identifying risk indicators for adverse events. A healthy periodontium is a basic prerequisite for the functional value of fixed devices. All restorations are good only if they do not have a harmful effect and functionally fit into the tissue of the body[20].

In a certain number of cases that have undergone periodontal treatment, the remaining healthy periodontium may be unable to resist the action of masticatory forces. Therefore, in such cases, it is necessary to make a correct assessment of whether the tooth will be used as a carrier of a prosthetic appliance, if it should be left out of the plan, or if it needs to be removed due to advanced periodontal disease[21].

Considering the previously stated facts that refer to the periodontal health of the teeth that are carriers of fixed prosthetic reconstructions, the main goal of this paper was to assess the periodontal health of respondents who underwent fixed prosthetic reconstructions in one region of the Republic of North Macedonia. Recognizing the importance of the periodontal tissues and their health on fixed prosthetic reconstructions, as well as their longevity, it is crucial to determine the prevalence, representation and the type of periodontal changes that are present in people with fixed prosthetic reconstructions.

Materials and Methods

In order to realize the set main goal, a research involving five dental offices (two with specialist for dental prosthetics and three offices for general dentistry) was conducted in the period from June to August 2024. A cross-sectional study referring only to a current assessment of conditions was performed.

The examination included a total of 60 subjects wearing fixed prosthetic devices who visited these dental offices. The age of the study population was between 40 and 80 years old.

When conducting the examination, all respondents who did not cooperate due to various behavioral disorders, aggression or did not allow a clinical examination to be performed were excluded from the examined population. The subjects must have used the fixed prosthetic devices for at least 6 months, and periodontal treatment should not have been performed for at least six months.

Regarding the exclusion criteria for the examined subjects from the medical anamnesis, it was necessary to confirm that the patients were free from acute or chronic diseases (diabetes mellitus, uremia, blood diseases, autoimmune diseases, etc.). Also, all persons undergoing therapy with drugs that could have an impact on the gingiva and oral mucosa were excluded from the examined group.

When performing the clinical examination, the basic postulates for preserving the patient's privacy and dignity were always respected.

The subjects underwent an extraoral examination of the neck and maxillofacial region in order to observe changes in this region of the body. This was followed by an intraoral examination in order to objectively observe the changes, as well as the state of the patients' oral health as a whole. A dental probe and a dental mirror and disposable gloves were used during the examination. Disposable materials were stored in appropriate medical waste storage areas. The instruments used after the examination, were subjected to the appropriate protocol for disinfection and sterilization of the instruments in the dental office.

For each patient during the clinical examination, the following parameters related to the supporting teeth of the fixed prosthetic reconstructions were determined:

- Oral hygiene habits

- Depth of the periodontal pockets(PD) and the clinical loss of attachment (CAL)
- Presence of gingival recession
- Degree of gingival inflammation and
- Presence of local irritating factors that can additionally affect the supporting tissues of the teeth.

In the majority of epidemiological studies, sequential probing of periodontal pockets is performed to determine the conditions of periodontal tissues. The measurement may refer to the depth of the periodontal pockets or the clinical loss of attachment.

The depth of the periodontal pockets was determined for each of the present pockets of the teeth supporting fixed orthotic constructions. The largest measured dimension related to the depth of the periodontal pocket was taken as a value of comparison in the examination to determine the greatest degree of destruction of the periodontal tissues of these teeth.

However, despite the approximate determination of the depth of the periodontal pockets, to prevent subjective and interpersonal differences in the measurement of the depth of the periodontal pockets and the clinical loss of attachment, only one person participated.

The presence of gingival recession among subjects was determined clinically as visual extension of the tooth and exposure of the root. Recession values were determined by measuring the distance from the enamel-cement junction (ECJ) to the marginal edge of the marginal gingiva.

The assessment of gingival inflammation was done with the Gingival Index of Loe and Silness (1963). The assessment of the progress of gingivitis in this index is based on changes in the color, configuration and consistency of the gingiva, as well as on the presence of bleeding on probing. For the purposes of this research, a modification was made so that instead of the representative group of teeth, the research was performed on all teeth supporting fixed prosthetic reconstructions. Grading of gingival changes was done according to the following quantitative criteria:

0 - There were no gingival changes but a normal gingival configuration (the gingiva was pale pink in color, with a firm and fine-grained configuration, without the presence of edema or ulceration);

1 - Mild inflammation characterized by a slight change in color, i.e. the gingiva was slightly reddened, there was light edema, and no bleeding occurs during probing;

2 - Moderate inflammation characterized by moderate redness, moderate edema, the gingiva became smooth, and bleeding occurred on probing;

3 - Strong inflammatory changes of the gingiva characterized by strong redness, presence of strong edema and tendency to spontaneous gingival bleeding, enlargement of the gingiva as well as the presence of ulcerations.

The examination was performed by gentle probing in the gingival sulcus or periodontal pocket. When estimating the final values for a subject, if the index value was between 0.1 and 1.0, it was a mild inflammation of the gingiva, values from 1.1 to 2.0 indicated moderate gingival inflammation, while values above 2.1 indicated severe gingivitis.

During the intraoral examination, the characteristics of the prosthetic reconstructions necessary for the preservation of periodontal health were determined. Such features included optimal marginal closure, contours and occlusal surface. Due to the negative effect of the supporting tissues of the teeth, the following participating factors were determined for each of the examinees: inadequate edge closure of the fixed prosthetic device, insufficient dimensioning and modeling of the fixed prosthetic reconstructions or their roughness.

In all subjects, a radiological status was made to assess the level of the alveolar bone. The retro-alveolar intraoral images, as well as the panoramic extraoral images, were used from the X-ray examinations. The recordings were read and discussed on a negatoscope.

The data obtained from the anamnesis and clinical examination after they were collected were appropriately statistically processed using special software for statistical data processing Statistica 7.1.

Results

The research included an equal number of subjects who visited specialist and general dentistry offices, that is, the examination of 30 subjects was done in specialist offices, while the examination of the remaining 30 subjects was conducted in general dentistry offices.

Also the number of male and female subject were equal.

In the forthcoming text, the data related to the subjective attitudes toward oral health and oral hygiene of the respondents were processed.

The number of people who did not maintain regular oral hygiene—the percentage of people who did not brush their teeth at all was quite small, 20% of the examined people (Figure 1). Only three subjects (5%) used additional chemical-pharmacological agents for disinfection of the oral cavity or prosthetic devices. Further, none of the subjects used dental floss or an interdental brush and only seven subjects (11.66%) brushed their teeth two to three times during the day.

Figure 2 shows the obtained values that refer to the values obtained for the Gingival Index of Loe and Silness (1963). According to the present research, most of the subjects had moderate inflammatory changes and women had greater inflammatory changes, i.e., 65% of women compared to 42% of men (Figure 3).

The assessment of periodontal status was done by determining the depth of periodontal pockets and by determining the clinical loss of attachment. A high prevalence of periodontal disease was observed. The average value related to the depth of periodontal pockets was 5.5 ± 0.7 (range from 2.5 to 6.7, with a confidence interval from 5.3 to 6.8). The average value referring to the clinical loss of attachment was 4.2 ± 0.2 (range from 2.3 to 6.2, with a confidence interval from 3.1 to 4.2). Hence, it was observed that most of the examined population had a moderate form of periodontal disease.

Out of the total number of subjects, the presence of gingival recession was visually determined in 19 (31.66 %) subjects (Figure 4).

Due to the negative effect of the supporting tissues of the teeth, the following contributing factors were determined for each of the subjects: inadequate marginal closure of the fixed prosthetic device, inadequate dimensioning and modeling of the fixed prosthetic reconstructions or their roughness. Figure 5 shows the presence of such predisposing factors.

At the end, an analysis of X-rays of the tissues around the teeth supporting the fixed-prosthetic constructions was made. The data related to the analysis of X-rays were made only for 34 subjects who had retroalveolar or orthopantomographic images. The results were read in retroalveolar or orthopantomography images. For the existence of horizontal bone loss, the value of two millimeters between the limbus alveolaris and the enamel-cement border was taken as the limit. Any distance greater than two millimeters was considered bone resorption. Such a value of tissues around the teeth supporting fixed-prosthetic devices was determined in 29 of the subjects, that is, in 48.33% of the examined population (Figure 6).

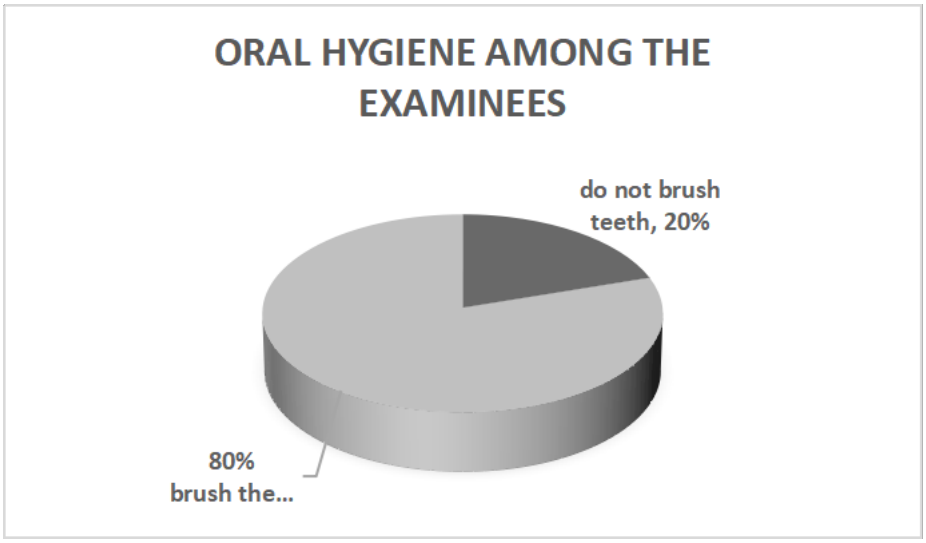

Figure 1. Oral hygiene among the examinees

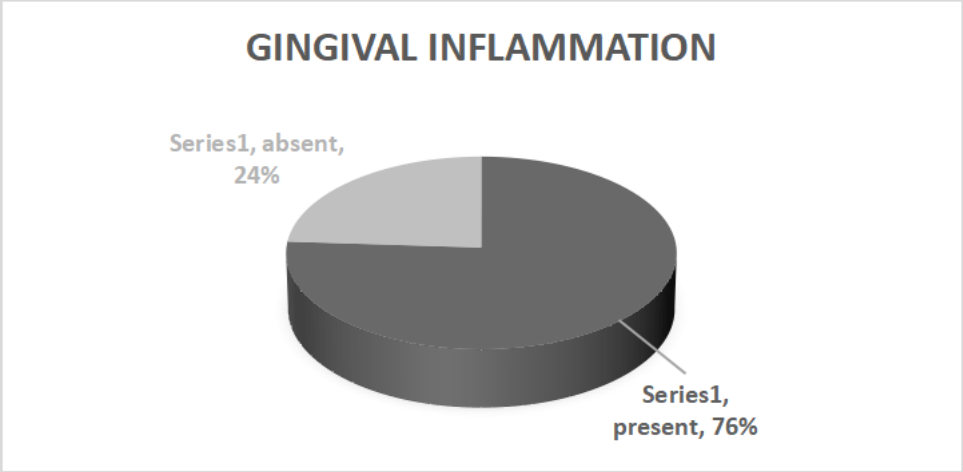

Figure 2. Presence of gingival inflammation

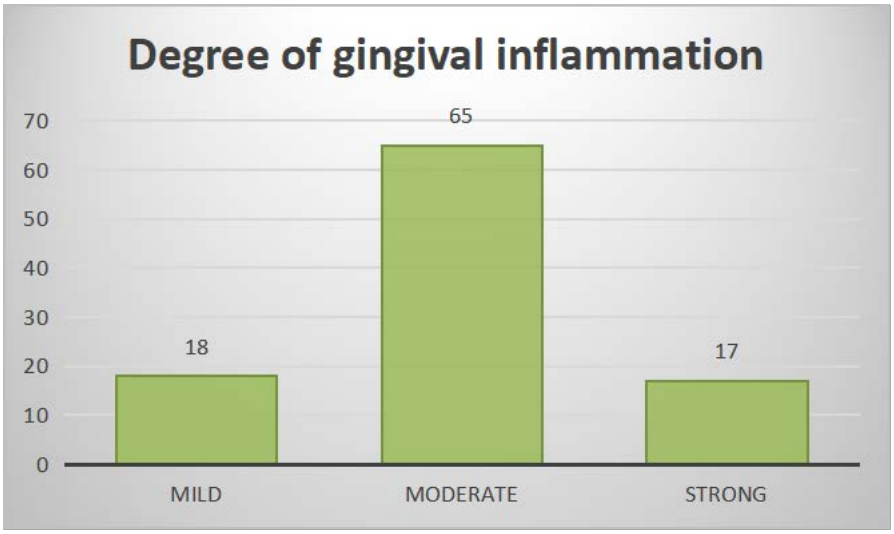

Figure 3. Degree of gingival inflammation

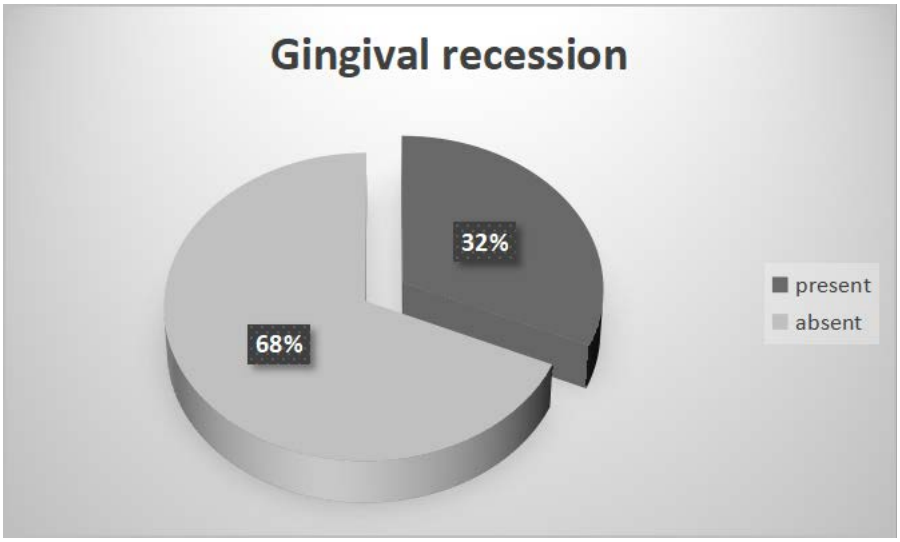

Figure 4. Presence of gingival recession

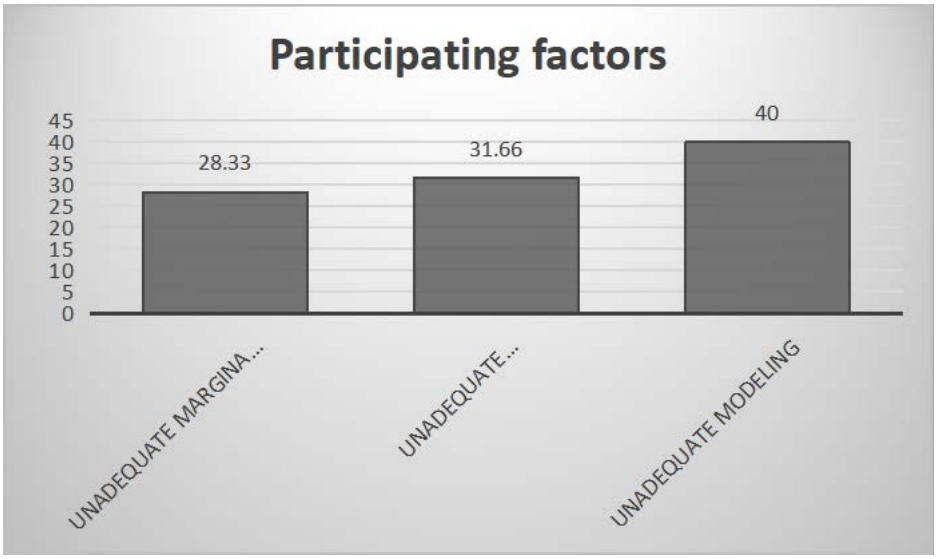

Figure 5. Presence of participating factors

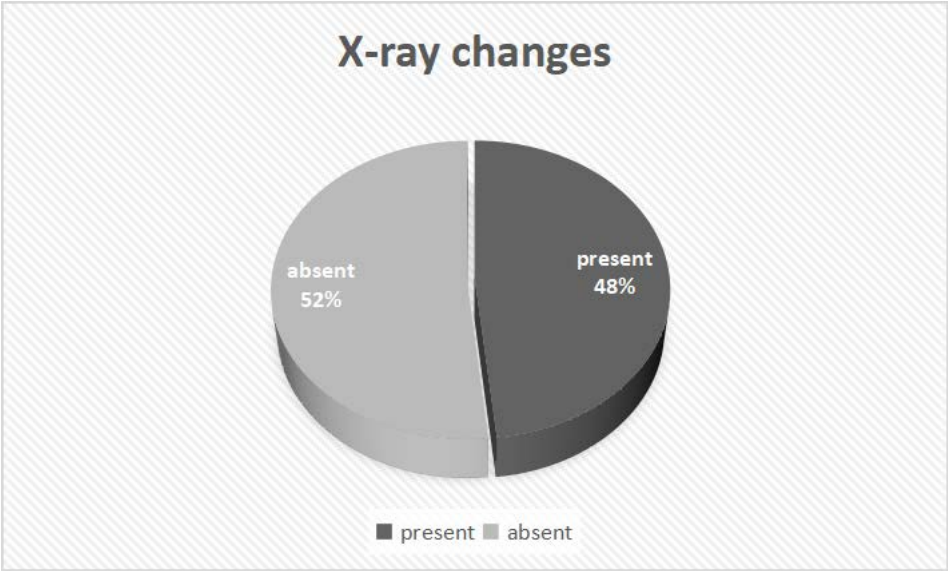

Figure 6. X-ray changes

Discussion

This study refers to the assessment of periodontal support in people with fixed prosthetic reconstructions. It is a cross-sectional study and all results presented in it are original.

Comparison of the data from this study with other epidemiological studies is complex due to the existence of numerous variations regarding the diagnostic methodology and criteria between different studies. A special problem is the lack of multiple published data on this problem in our country, which takes away any possibility of comparison with our data. But, this is precisely what increases the significance of our study which covers dental practices from only one region of the Republic of North Macedonia.

Adequate understanding of the relationship between periodontal tissues and restorative dentistry is essential for achieving proper form, function, aesthetics and comfort of the dentition. While most clinicians are

aware of this important relationship, uncertainty remains regarding specific concepts such as biological gingival width and indications and applications for crown lengthening.

The impact of fixed-prosthetic reconstructions on periodontal health has been investigated by numerous authors. Thus, Srimaneepong et al.[22] determined the relationship between the marginal adaptation of the tooth by fixed prosthetic reconstructions and the health of the periodontal tissues. Their results determined that there was a significant quantitative relationship between marginal crown discrepancy and gingival and periodontal inflammation.

Regardless of the type of treatment, consistent and permanent home care and, of course, professional prophylaxis are necessary for patients with fixed-prosthetic reconstructions.

Subgingival restorative margins of fixed-prosthetic reconstructions are associated with the development of plaque-related inflammatory periodontal disease, primarily due to a change in the subgingival microflora from a health-related to a disease-related profile[23].

The degree of marginal inflammation is influenced by four factors: (1) failure to maintain an adequate microorganism profile, (2) inability to adequately close the margins of fixed-prosthetic reconstructions, (3) placement of the gingival margins of fixed-prosthetic reconstructions in the area of attachment gingiva and (4) violation of biological width[24]. Placement of the margins of fixed-prosthetic reconstructions in the supragingival region is the location of choice for all restorative margins regardless of the reconstruction to avoid iatrogenic injury to the periodontal tissues[25]. However, consideration of these four factors will help in reducing the negative impact of the edges of fixed prosthetic constructions that in certain cases must be placed subgingivally.

What is important to note is the fact that both clinically deficient restorations, as well as clinically acceptable restorations, can contribute to gingivitis. However, recent research and evidence do not show increased clinical attachment loss near crowns or fixed partial dentures. During fixed prosthetic reconstruction, it is necessary to document the periodontal health before the prosthetic therapy and periodically after the placement of the restoration, so that each tooth will serve as its own control. Also, the patient's own history of periodontal disease, the impact of the restoration on the formation of dental plaque and the composition of the periodontal microflora must be recorded. In that way, all the reactions of the periodontal tissue after the placement of artificial crowns and bridges, as well as fixed partial dentures, would be revealed.

In their research, Chadwell et al.[26] determined a linear regression model concerning the years of use of the prosthetic devices and the number of lost prosthetic devices. Also, according to the authors, there is no possibility of predictability regarding the possibility of losing prosthetic aids.

According to Axelsson et al.[27], gingivitis and localized periodontal disease were mainly associated with unacceptable hygiene but were also observed in association with satisfactory restorations. However, the authors in their research do not indicate the possible reasons for this phenomenon.

Strategic decisions in the choice of a certain design of partial dentures supported by fixed prosthetic reconstructions and the choice of teeth or implants as carriers seem to influence the risks of complications that can be expected concerning the fixed reconstruction. If possible, extension of carrier teeth should be avoided or used only after careful clinical evaluation of all options.

In a trial conducted by Müller, patients were treated for existing periodontal disease and called for prophylaxis sessions once every 2 or 3 months. The clinical data after the examination indicated a slight inflammation of the gingival tissues of teeth with crowns located subgingivally. In contrast, in teeth with crowns that have edges placed supragingivally, marginal tissues showed little or even no clinical signs of inflammation[28].

The high prevalence of periodontal pockets and the average occlusion of 5 mm observed in the majority of subjects in the present study coincide approximately with the study of Napankangas and Raustia[29]. The data collected in our study population concerning gingival inflammation, showed a value of 43.3%. This value differs from the data obtained by Napankangas and Raustia29 which reported that gingival bleeding occurred in only 12% of the subjects.

The present research showed that the most common reason for applying fixed prosthetic constructions was the loss of one or more teeth or the unsatisfactory appearance of the tooth or previously existing prosthetic reconstruction, which was expected. This finding aligns with numerous studies conducted worldwide.

Despite the fact that the largest number of subjects do not have all their teeth and have empty spaces in their dental arches (the average number of teeth in our research among the respondents is 14.7 ± 6.8), still, the number of fixed prosthetic restorations, and in general prosthetic aids among these respondents do not satisfy.

The results related to the X-ray evaluation of the periodontal conditions indicate that vertical loss of the alveolar bone is present in 65% of the subjects. Similar data were obtained by Lungren et al.[30], although in their randomized controlled clinical trial that included subjects partially susceptible to periodontitis, it was found that the loss of bone mass during the first year of operation, as well as every year after, was significantly small. The results of this study show that the functional capacity of extension bridges is good in patients despite the severe loss of periodontal tissues. Additionally, the masticatory effectiveness achieved with these bridges is comparable with the forces in people with natural teeth.

Recession is not only a loss of gingival tissue, it involves a clinical loss of attachment and loss of alveolar bone, as well as all those tissues under the gingiva, all of which occur simultaneously. Numerous factors affect the appearance of gingival recession, but it must be noted that a significant factor in the appearance of gingival recession is fixed-prosthetic reconstructions. Inadequate marginal closure, improper techniques for their cleaning, as well as inadequate premature contacts can further complicate the condition of the periodontium. According to our research, the presence of gingival recession was visually determined in 36.66% of the total number of respondents. The presence of gingival recession refers to the action of the previously mentioned iatrogenic factors, but also to the inadequacy of brushing techniques, which is why dentists themselves have the task of individually adjusting brushing techniques to meet the needs of individual patients.

The high prevalence of mobility of the supporting teeth is expected and likely occurs because some teeth are tied in bridge structures or in block crowns. Additionally, one tooth may possess significantly greater strength, which can contribute to the reduced mobility of the other tooth. We believe that the mobility observed in our subjects, particularly in teeth bearing prosthetic constructions, can be a consequence of: inflammation of the gingiva and periodontium, the present profunctional habits, premature contact of the teeth, loss of alveolar bone, etc. The luxation of the supporting teeth of the fixed-prosthetic reconstructions is usually reversible, unless it results from substantial loss of the supporting tissue, which may prevent the full restoration of tooth stability. It has been published in the literature that the probability of restoring the stability of the tooth is inversely proportional to the degree of loss of the tooth-supporting tissues[31].

Conclusion

Periodontal problems among patients who wear fixed prosthetic reconstructions are significantly pronounced. This is mostly due to insufficient maintenance of oral hygiene by the patients, as well as irregular visits to dental examinations. It is of great importance that the fixed-prosthetic reconstructions are properly made and properly adapted, with or without the presence of premature contacts, and that patients maintain adequate oral hygiene. Fixed prosthetic reconstructions need to be checked regularly and continuously, because the inspection contributes to a healthy periodontium and a longer lifespan of the prosthetic reconstructions.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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UPOREDNA ANALIZA TAČNOSTI I PRECIZNOSTI TOTALNIH PROTEZA IZRAĐENIM KOMPJUTERSKI VOĐENOM TEHNOLOGIJOM U POREĐENJU SA KONVENCIONALNOM TEHNIKOM

COMPARATIVE ANALYSIS OF ACCURACY AND PRECISION IN COMPLETE DENTURES FABRICATED USING COMPUTER-AIDED TECHNOLOGY COMPARED TO CONVENTIONAL TECHNIQUES

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Sažetak

Cilj: *Ova in vitro studija imala je za cilj da proceni tačnost i preciznost baze totalnih proteza izrađenih computer-aided design/computer-aided manufacturing (CAD/CAM) tehnologijom i uporedi ih sa totalnim protezama izrađenim tehnikama kompresionog i injekcionog presovanja.*
Materijali i metode: *Adaptacija baza proteza procenjivana je na 30 totalnih proteza izrađenih koristeći tri različite tehnike: kompresiono presovanje, injekciono presovanje i computer-aided design/computer-aided manufacturing (CAD/CAM) tehnologija. Master model sa bazom od legure kobalt-hroma skeniran je kako bi se dizajnirala i izradila master CAD/CAM totalna proteza. 30 gipsanih modela napravljeno je iz ovog master modela i potom skenirano. Na osnovu CAD/CAM master proteze, izrađeno je 30 totalnih proteza, za svaku ispitivanu tehniku po 10 proteza. Sve proteze su bile potopljene u destilovanu vodu na 30 dana, a njihove bazalne površine skenirane su nakon 2 dana i ponovo nakon 30 dana. Merenja su vršena u šest ključnih regija koristeći 3D softver za analizu kako bi se uporedile površine gipsanih modela i proteza. Primenjene su statističke metode analize za ispitivanje razlika u parametrima unutar svake grupe (intra-grupa) i između grupa (inter-grupa).*
Rezultati: *U rangiranju na osnovu medijane i interkvartilnog raspona za svih 12 ispitivanih parametara, CAD/CAM tehnika je pokazala najbolju kombinaciju tačnosti baza proteza i reproduktivnosti tehnike.*
Zaključak: *Baze totalnih proteza izrađenih CAD/CAM tehnologijom pokazale su veću tačnost i preciznost u poređenju sa onima proizvedenim tehnikama kompresionog i injekcionog presovanja. Visoka tačnost i preciznost baze CAD/CAM proteza dovela bi do bolje retencije, poboljšane žvačne sposobnosti i, samim tim, boljeg kvaliteta života za korisnike totalnih proteza.*

Ključne reči: *impakcija očnjaka CAD/CAM, totalna proteza, preciznost proteza, reproduktivnost*

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Abstract

Aim: *This in vitro study aimed to evaluate the accuracy and precision of the denture base of complete dentures fabricated using computer-aided design/computer-aided manufacturing (CAD/CAM) technology and to compare these results with those for complete dentures fabricated using compression and injection molding techniques.*
Materials and Methods: *The adaptation of denture bases was evaluated for 30 complete dentures fabricated with three different techniques: compression molding, injection molding, and CAD/CAM. A master model with a cobalt–chrome alloy base was scanned to design and fabricate a master CAD/CAM complete denture. A total of 30 plaster casts were developed from this master model and subsequently scanned, with 10 complete dentures fabricated using each fabrication method. All dentures were immersed in distilled water for 30 days, and their intaglio surfaces were scanned at 2 days and again at 30 days. Measurements were taken in six key regions using 3D analysis software to compare the cast and CD surfaces. The applied statistical analysis methods were used to examine differences in the parameters within each group (intra-group) and between groups (inter-group).*
Results: *Regarding the ranking based on medians and interquartile ranges across all 12 evaluated parameters, the CAD/CAM technique demonstrated the best overall combination of denture base accuracy and reproducibility. A Kruskal–Wallis analysis showed significantly greater CAD/CAM CD base precision in the vestibular surface area.*
Conclusion: *The high accuracy and precision of the CAD/CAM CD base are expected to result in better retention, improved masticatory ability, and, thus, a better quality of life for CD wearers.*

Key words: *computer-aided design/computer-aided manufacturing, complete denture, polymethyl methacrylate, denture accuracy, reproducibility*

Introduction

Edentulism is considered a disability and a significant oral health issue worldwide[1]. This condition compromises oral health, affects chewing and speech functions, alters esthetic appearance, and ultimately impacts the quality of life of affected individuals. Despite the advancements and options available through implant-supported therapy, the conventional use of complete dentures (CDs) remains the preferred choice for most edentulous patients due to various anatomical, physiological, or financial limitations[2].

Since the introduction of polymethyl methacrylate (PMMA) by Dr. Walter Wright in 1936, the processes for fabricating CDs have remained mainly unchanged[3]. PMMA rapidly became the preferred material for denture bases because of its generally acceptable clinical characteristics, although it does have some downsides[4]. One of the main drawbacks of PMMA is its volumetric contraction of 6% to 7% during the polymerization reaction, which results in dimensional changes in the denture base, that is, a linear distortion ranging from 0.45% to 0.9%. Additional distortion in the denture base is attributed to the thermal expansion coefficient of the PMMA material[5]. Several methods have been developed to overcome these issues and improve the qualities of PMMA. However, the most popular process for processing dentures is still compression molding, also known as the "pack and press" method[4]. Conversely, injection molding has been shown to be a superior technique for reducing volumetric shrinkage[6]. In addition to material issues, patients and dentists find the traditional denture fabrication procedure time-consuming, as it involves at least five clinical steps and a substantial amount of laboratory work.

The development and advancement of computer-aided technology in CD fabrication aim to address the challenges associated with traditional CDs and streamline the fabrication process. At present, two computer-aided design/computer-aided manufacturing (CAD/CAM) methods are used to create complete dentures: subtractive milling from a pre-polymerized PMMA block and additive manufacturing (3D printing), in which the denture base is formed through VAT polymerization using a light-cured liquid[7]. Using computer-aided technology to manufacture CDs entails gathering clinical data and using computer software to design prostheses digitally. The subtractive method is currently the more widely used approach[8,9]. Beyond the improved fabrication process, the quality of CAD/CAM CDs is further enhanced by the superior physical and mechanical properties of the materials used for the denture bases in digital manufacturing. The PMMA blocks used for subtractive milling are industrially polymerized under controlled conditions, utilizing high temperatures and pressure during the injection process[10].

These highly condensed and cross-linked pre-polymerized acrylic blocks successfully address the problems of polymerization shrinkage and dimensional distortion observed in conventional PMMA dentures. One of the most important factors influencing the quality of CDs is achieving maximal congruence between the denture base and the underlying tissues[11]. Retention, stability, and, consequently, masticatory performance and speech directly depend on the intimate fit of the denture to the underlying tissues.

The dimensional accuracy of CAD/CAM-fabricated CDs, compared to conventionally fabricated ones, has been the subject of several studies. The first published study by Goodacre et al., which compared the adaptation of the prosthetic base between CAD/CAM CDs and CDs fabricated using three different traditional techniques, confirmed the superiority of CAD/CAM CDs in terms of the accuracy of the denture base and reproducibility[12]. In contrast to the first study by Srinivasan et al., no significant differences in the trueness of the overall prosthetic base were found when comparing CAD/CAM CDs and CDs fabricated using conventional techniques[13]. CAD/CAM CDs showed significantly better adaptation only in the vestibular area, which, in a clinical context, could mean improved adhesion of the CD and a more intimate internal seal effect[13].

Steinmassl et al. examined the congruence of the prosthetic base with the underlying tissues for four different commercially available CAD/CAM prosthetic systems (AvaDent, Merz Dental, Whole You, Wieland/Ivoclar)[14]. They compared these bases with conventionally fabricated prosthetic bases (with long-term hot polymerization). All CAD/CAM prosthetic bases showed higher congruence with the master model than conventionally fabricated ones[14]. The findings of several in vitro studies on the better adaptation of CDs fabricated with CAD/CAM technology explain the better retention of CAD/CAM CDs observed in clinical studies[15-18].

As per the ISO standard definition, accuracy pertains to the variation in the intaglio surface of CDs created from the plaster model, while precision indicates the reproducibility of this same surface across different production methods. Accuracy denotes the degree to which a measurement corresponds to the true value, whereas precision describes the consistency of

repeated measurements under constant conditions[7,19]. In this context, accuracy relates to the variation in the intaglio surface of CDs created from the plaster model, while precision indicates the reproducibility of this same surface across different production methods[7].

For this in vitro study, the accuracy and precision of complete dentures produced using three fabrication methods—CAD/CAM technology, compression molding, and injection molding—were assessed and compared. The null hypothesis was that there would be no statistically significant differences in accuracy and precision between CDs produced using CAD/CAM fabrication, compression molding, or injection molding techniques.

Material and methods

This in vitro study was conducted at the University Dental Clinical Center "St. Panteleimon" in Skopje. The conventional complete denture samples were prepared in the Removable Prosthetics dental laboratory, while the CAD/CAM CDs were fabricated at AvaDent™ (Global Dental Science Europe, Tilburg, Netherlands). The methodology was adapted from the study of Goodacre et al.[12].

Reference master model and master CAD/CAM Denture

To create the reference master model with a cobalt–chromium alloy base, an edentulous maxillary study model (Study Model KaVo™) was used due to its lack of undercuts. The model was duplicated, and three wax pyramids were positioned at key points on the alveolar ridge: over both tuberosities and along the anterior midline. The model was then invested and cast in a cobalt–chromium alloy (Figure 1). These pyramids allowed for precise superimposition of STL files from scanned plaster models and CDs during software analysis, ensuring consistent measurement of discrepancies between the same points. The master model was scanned using a 3D optical laboratory scanner (NeWay, Open Technologies, Rezzato, Italy) connected to the Exocad (Full Denture Module) software. According to the manufacturer, the scanner has an accuracy of up to 2 μm and a resolution of 5 μm. The resulting STL file was sent to AvaDent via AvaDent Connect for fabrication of the master complete denture. The denture was designed using the AvaDent Design Software and, once approved, the master CAD/CAM denture was milled from a PMMA disc (AvaDent Denture Base High Impact Puck) (Figure 2). Teeth from AvaDent's library (Ivoclar Vivadent, SR Vivodent DCL) were manually bonded into the pre-designed recesses.

The reference master model was duplicated using silicone impression material (Xantopren M Mucosa; Heraeus Kulzer, Germany) and 30 plaster models were cast: 10 for each test group. After a 24-hour drying period, the plaster models were scanned using the same 3D optical laboratory scanner (NeWay, Open Technologies, Rezzato, Italy).

Tested Groups

From the master CAD/CAM CD, a silicone mold (Optosil, Heraeus Kulzer) with a vestibular silicone key was created to fabricate CDs using two traditional techniques. An identical set of acrylic teeth, matching those in the master denture, was placed in the silicone mold and molten wax was applied to form wax dentures with the same tooth arrangement as the master denture (Figure 3). A total of 20 wax dentures were produced on previously marked and scanned plaster models. The compression-molded CDs were processed using heat-polymerized PMMA (SR Triplex Hot Acrylic Resin, Ivoclar), following the manufacturer's instructions. For dentures fabricated via the injection molding technique (Ivocap™ technique, Ivoclar Vivadent AG, Schaan, Liechtenstein), a modified PMMA acrylic material in capsules (Ivobase High Impact, Ivoclar) was used. Material preparation and fabrication were performed according to the manufacturer's guidelines.

Each of the 10 CAD/CAM group dentures was designed and fabricated based on a separate 3D scan of a plaster model. The STL scans were sent to AvaDentTM, where the dentures were milled from AvaDent PMMA discs. The same set of teeth was manually bonded onto these dentures (Figure 4).

Preparation and Scanning Protocol of the Test Specimens

After fabrication, the compression- and injection-molded dentures were hydrated in containers with distilled water for 2 days at room temperature. The CAD/CAM dentures from AvaDent arrived 2 days post-fabrication in special packaging that maintained a moist environment. These dentures were hydrated in distilled water for 1 day. Following this hydration period, all specimens were prepared

for scanning by applying an anti-reflective spray (MASTERmill CAD/CAM Scanning Spray, Talladium, INC, USA). All 30 dentures were scanned using a 3D optical laboratory scanner, and the scans were saved in STL format. After scanning, the dentures were returned to containers with distilled water for 30 days at room temperature. Scanning of the denture's intaglio surface was repeated after this period. The scanning process produced 90 STL files, including 3 for each denture: q from the plaster model, 1 from the first scan after 2 days in water, and 1 from the second scan after 30 days in water.

Method for Testing denture base accuracy

The software analysis was performed at the Faculty of Mechanical Engineering, University Ss. Cyril and Methodius. To measure and compare the accuracy, a 3D surface matching software (Geomagic Qualify 12.0, 3D Systems, Informer Technologies, Inc.) was used, enabling graphical comparisons between 3D models. This software allows for the semi-automatic alignment of scanned data for precise comparison, with discrepancies represented graphically in different colors. For each denture, STL files were superimposed: the STL file from the plaster model was compared with the STL file from the first denture scan (after 2 days in water), and then the plaster model STL file was compared with the STL file from the second denture scan (after 30 days in water). The triangular surfaces of the pyramids served as reference points for superimposition of the two STL files. Deviation measurements were taken at the same points in 6 regions for all 30 dentures: 13 points along the vestibular border, 11 points 6 mm from the vestibular border, 8 points along the highest surface of the alveolar ridge, 6 points along the midline of the palatal plate, 8 points at the pharyngeal border, and 12 randomly selected points on the palatal plate. After importing the STL files into the 3D software, the comparison points were marked on the intaglio surface of the denture. Using MATLAB (MathWorks), which supports 3D graphics, the corresponding points on the plaster model were automatically identified. The software then displayed the distance (deviation or compression) between each compared point (Figure 5).

The statistical analysis was performed using Statistica 7.1 for Windows software.

For the numerical data series (vestibular border, 6 mm from the vestibular border, highest point on the alveolar ridge, midline of the palatal plate, pharyngeal border, and palatal plate), descriptive statistics were calculated (mean; standard deviation; 95% CI; minimum; maximum).

The distribution of the data was tested using the Kolmogorov–Smirnov test, Lilliefors test, and Shapiro–Wilks test (p-value). Differences between groups for the numerical data series were analyzed based on the data distribution using either Analysis of Variance (ANOVA [F/p]/LSD post hoc) or Kruskal–Wallis ANOVA by Ranks (H, p/Multiple Comparisons p-values [2-tailed]). The differences in analyzed parameters within each group, comparing the denture base measurements after 2–3 days in water versus after 30 days in water, were tested using either a T-test for dependent samples (t/p) or the Wilcoxon Matched Pairs Test (Z/p), depending on the data distribution. The accuracy and reproducibility (precision) of the tested fabrication techniques were evaluated by ranking the median values and interquartile ranges.

Statistical significance was set at $p < 0.05$.

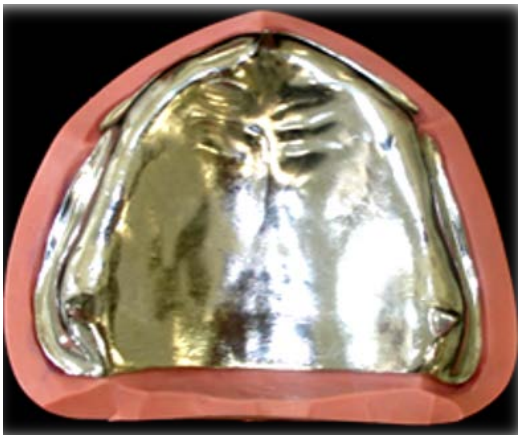

Figure 1. Reference master model

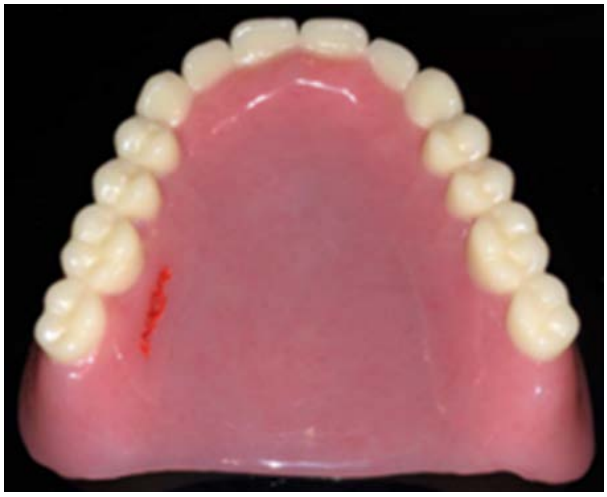

Figure 2. Reference master CAD/CAM denture

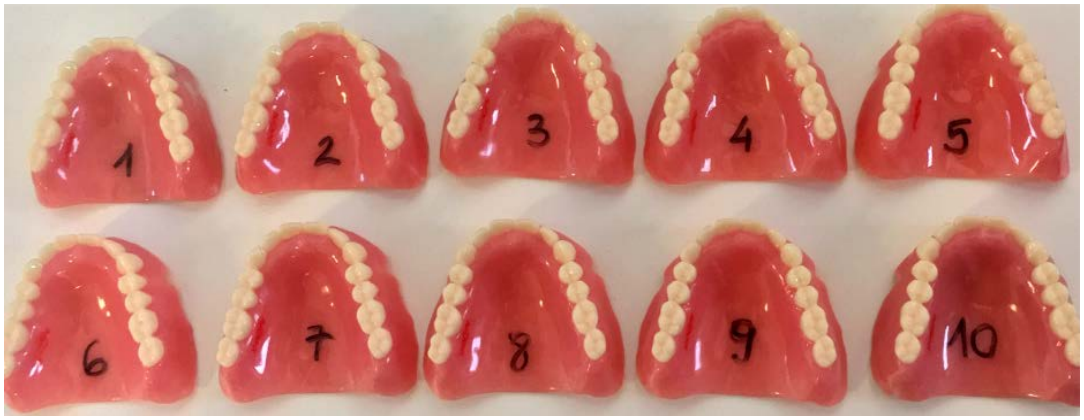

Figure 3. Tested group—CAD/CAM complete dentures

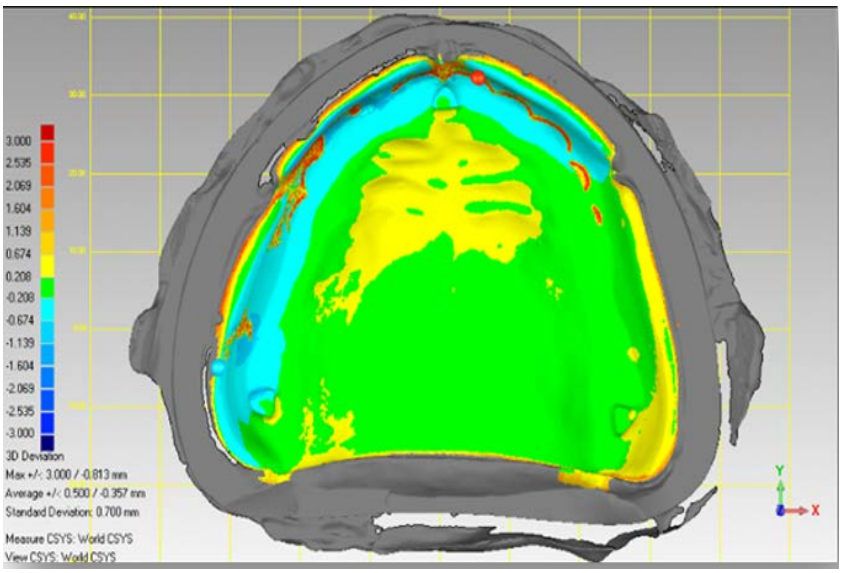

Figure 4. Superimposed STL file of the plaster model and complete denture

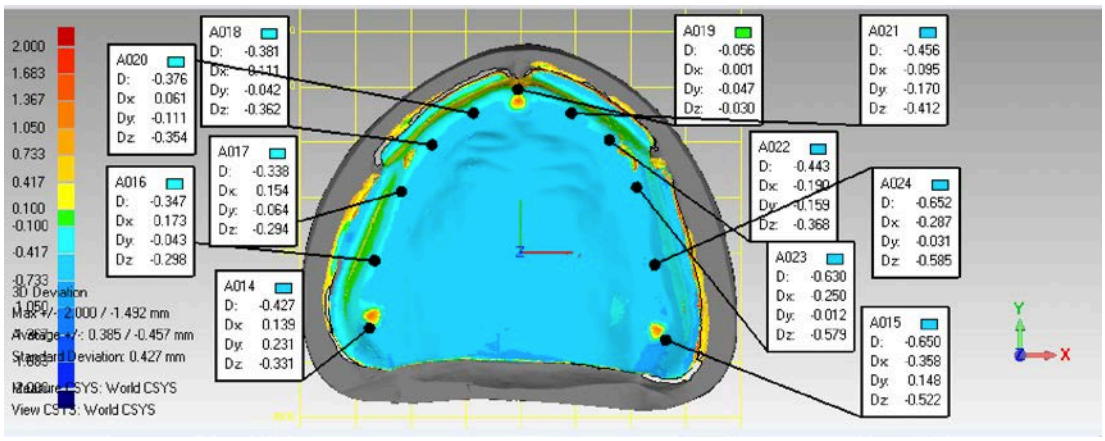

Figure 5. Color map of values of deviations between superimposed files of the plaster model and the denture base at specific points

Results

The applied statistical analysis methods were used to examine differences in the parameters within each group (intra-group) and between groups (inter-group).

The descriptive statistics obtained for the six regions in each tested group, comparing the precision of denture bases (adaptation to the plaster model) across the three techniques, did not confirm any impact of water in terms of improved adaptation of the denture bases.

Table 1 presents the descriptive statistics for all six locations across the three tested techniques after two days of denture hydration in distilled water, and Figure 6 shows the associated box plots.

Table 2 presents results based on the median and interquartile range rankings, which were used to determine the accuracy and precision (reproducibility) of the tested fabrication techniques. Ranking of the results based on median and interquartile range revealed that, in 11 of the 12 analyzed locations, the CAD/CAM technique showed the best combination of accuracy and precision among the tested fabrication techniques. The conventional technique demonstrated the highest precision only at the alveolar crest in the denture base after two days in water.

Table 1. Mean and standard deviation (Std Dev) of discrepancies of denture bases for all six locations across the three tested techniques after two days of denture hydration in distilled water

	COMPRESSION -MOLDED	INJECTION -MOLDED	CAD/CAM
Location			
Vestibular border			
Mean	-0.05	0.03	0.01
Std Dev	0.22	0.23	0.02
6 mm from the denture border			
Mean	-0.19	-0.07	0.002
Std Dev	0.26	0.16	0.01
Alveolar crest			
Mean	-0.13	0.14	-0.007
Std Dev	0.41	0.29	0.001
Midline of the palate			
Mean	0.03[a]	0.16	-0.008
Std Dev	0.50	0.30	0.001
Palate			

Mean	0.01	0.14	-0.007
Std Dev	0.52	0.26	0.001
Posterior palatal seal			
Mean	-0.02	0.13	-0.008
Std Dev	0.56	0.15	0.001

The statistically significant difference found between:

[a]$p < 0.05$ ($p = 0.04$) for compression-molded and CAD/CAM

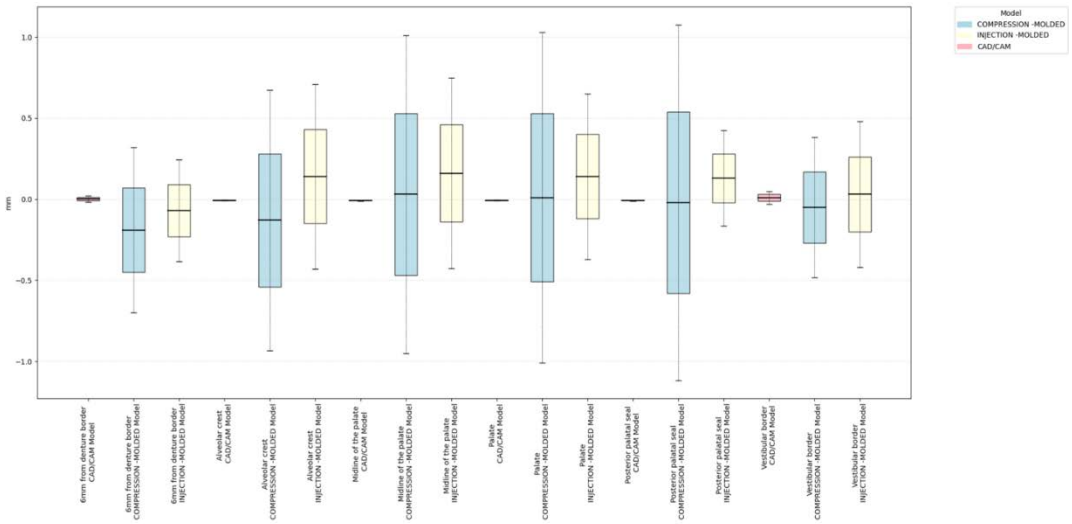

Figure 6. Comparison of mean and standard deviation values for each fabrication technique across the various locations

Table 2. Ranking by accuracy and precision (reproducibility) of the fabrication technique based on location and hydration period duration

Rank of Accuracy: Proximity to Zero (Median)	**COMPRESSION-MOLDED**	**INJECTION-MOLDED**	**CAD/CAM**
Rank of Reproducibility (Interquartile Range)	**Acc./Repr.**	**Acc./Repr.**	**Acc./Repr.**
	Median/Quartile	**Median/Quartile**	**Median/Quartile**
Vestibular border (after 2 days)	-0.028(2)/0.282(3)	-0.035(3)/0.170(2)	0.003(1)/0.009(1)
Vestibular border (after 30 days)	0.011(2)/0.340(3)	-0.126(3)/0.291(2)	0.004(1)/0.020(1)
6mm from CD border (after 2 days)	-0.121(3)/0.331(3)	-0.081(2)/0.174(2)	0.004(1)/0.004(1)
6 mm from CD border (after 30 days)	-0.199(3)/0.276(3)	-0.040(2)/0.244(2)	0.004(1)/0.009(1)
Alveolar crest (after 2 days)	-0.002(1)/0.284(3)	0.041(3)/0.191(2)	-0.007(2)/0.002(1)
Alveolar crest (after 30 days)	-0.075(3)/0.361(3)	0.054(2)/0.191(2)	-0.007(1)/0.001(1)
Midline of the palate (after 2 days)	0.199(3)/0.282(2)	0.067(2)/0.213(2)	-0.008(1)/0.001(1)
Midline of the palate (after 30 days)	0.169(3)/0.371(3)	0.033(2)/0.308(2)	-0.008(1)/0.001(1)

Palate (after 2 days)	0.178(3)/0.418(3)	0.096(2)/0.199(2)	-0.007(1)/0.002(1)
Palate (after 30 days)	0.161(3)/0.477(3)	0.059(2)/0.244(2)	-0.008(1)/0.001(1)
Posterior palatal seal (after 2 days)	0.116(2)/0.838(3)	0.132(3)/0.103(2)	-0.007(1)/0.003(1)
Posterior palatal seal (after 30 days)	0.099(3)/0.710(3)	0.084(2)/0.224(2)	-0.007(1)/0.003(1)

*Range O

Discussion

In this *in vitro* study, the accuracy and precision of denture bases fabricated with CAD/CAM technology were compared to those fabricated using compression and injection molding techniques. Compression molding is widely used for denture fabrication due to its simplicity and relatively high accuracy, making it the gold standard for comparison[20]. Among conventional denture fabrication methods, injection molding was also selected for this study as it is recognized for its ability to effectively compensate for the contraction of PMMA[21–24]. For both conventional and injection techniques, PMMA acrylic material from the same manufacturer (Ivoclar Vivadent, Schaan, Liechtenstein) was used to ensure that the observed characteristics depended solely on the fabrication technique, thus eliminating material composition as a variable.

The sample size for each group (n = 10) aligns with similar in vitro studies in the published literature[12,24,25]. To maintain consistency, the compression- and injection-molded samples were produced by an experienced technician with strict adherence to the manufacturer's protocol. Each sample was fabricated as a complete denture with teeth, which allowed for a direct correlation between dimensional changes in the denture bases and the fabrication technique. This approach is crucial, as Barco et al. demonstrated 45% greater space under a denture with teeth than under a denture base alone[26]. Keenan et al.[27] further indicated that testing dimensional changes in acrylic samples of different shapes, such as plates or denture bases without teeth, can yield different contraction patterns in PMMA material.

Dimensional accuracy and precision were assessed at 2 days post-fabrication and again after 30 days. Immersing the dentures in distilled water was chosen over artificial saliva products, as these products—while containing the inorganic components of human saliva—lack saliva's natural viscosity and do not fully simulate the conditions of the oral cavity. According to some authors, water storage induces expansion in denture bases through water sorption (both adsorption and absorption), which separates macromolecules and expands the material[28]. This expansion offsets the polymerization shrinkage of acrylic materials, improving the fit of the denture base to the underlying tissues[29].

Descriptive statistics for the six regions in each group, comparing the denture base fit with the plaster model over 2 days and after 30 days, did not demonstrate a significant impact of water on denture base adaptation after extended immersion. Clinically, this suggests no substantial improvement in the fit of CDs with prolonged wear in the moist environment of the oral cavity.

In the group of CDs fabricated using conventional techniques, comparing the parameters for each region between 2 days in water and 30 days in water showed dimensional changes across all regions, although none were statistically significant. Goodacre et al.[12] posited that a 24-hour water immersion period suffices for hydrating conventional CDs, with no expected improvement from more prolonged water exposure—a conclusion supported by our findings here.

For the CAD/CAM group, no significant differences were found in measurements after 2 and 30 days in water, potentially affirming the manufacturers' claims that CAD/CAM acrylic blocks, due to factory polymerization, are denser, highly cross-linked and, thus, highly hydrophobic[30–32]. However, in a study by Srinivasan[13], improved accuracy in the denture bases of CDs fabricated with CAD/CAM, injection, and conventional techniques was observed after 21 days in artificial saliva, when compared to measurements taken immediately after fabrication, although this improvement was not statistically significant. After 21 days, conventional CDs exhibited the highest base

accuracy[13]. The study indicated variations in the accuracy of the intaglio surface in CAD/CAM CDs. These findings may be influenced by the size of the cutting tool, which can create a slightly rougher denture surface. The micro-rough intaglio surface of CAD/CAM CDs is not a disadvantage in a clinical context; on the contrary, these micro-spaces for saliva can provide additional adhesive strength for CDs[13].

The median and interquartile range figures helped in the assessment and ranking of the fabrication methods. The median value demonstrates the accuracy and consistency of CD base adaption. At the same time, the interquartile range reflects the precision or reproducibility of the technique—essentially, the ability to reliably produce a high-precision denture base each time the technique is applied. When evaluating the efficacy of a fabrication technique, a median value close to zero and a narrow interquartile range are ideal[12].

Regarding the ranking based on the medians and interquartile ranges across all 12 evaluated parameters, the CAD/CAM technique demonstrated the best overall combination of denture base accuracy and reproducibility in 11 of the 12 parameters analyzed (Table 2), while the compression molding technique showed the highest accuracy on the alveolar ridge crest after 2 days in water. Notably, the ranking according to the median value for accuracy on the alveolar ridge surface (after 2 days in water) differed from the conventional technique's mean value for this same parameter in inter-group comparisons. In particular, the standard deviation for measuring this parameter in CDs produced with the conventional technique was 0.41 mm, that for the injection-molded CDs was 0.29 mm, and that for the CAD/CAM-manufactured CDs was 0.001 mm. When comparing mean values across groups, measurements at identical points can be analyzed and compared, while the median value provides a generalized overview of results[12].

The interquartile range for the CAD/CAM technique was the narrowest of the three techniques, encompassing all 12 evaluated parameters and ranging from 0.001 to 0.009. This narrow range positions CAD/CAM as the most reproducible technique for denture base fabrication. The injection technique followed, with the second-narrowest interquartile range across all parameters, making it the second most reliable in terms of reproducibility. In contrast, the compression molding technique had the widest interquartile range (from 0.276 to 0.838). These findings are consistent with the results of Goodacre et al., who compared four fabrication techniques and noted similar performance variations[12].

The narrow range of median values observed in this study (from -0.199 to 0.199) has no clinical significance and indicates that all three techniques achieve clinically acceptable levels of accuracy. Notably, the master model used in this study features idealized alveolar ridges, that is, without undercuts and with a shallow palatal vault. In cases where the palatal vault is steeper and deeper or undercuts are present, polymerization shrinkage would likely be more pronounced when using compression and injection techniques. For these more complex ridge forms, CAD/CAM technology could be expected to achieve even greater precision in the fit of denture bases; however, this assumption warrants validation through further research.

Conclusion

Based on the results obtained, the null hypothesis outlined in this study was rejected. According to the ranking of the three techniques based on mean values and interquartile ranges, the denture bases of complete dentures produced using CAD/CAM technology demonstrated superior accuracy and precision to those produced using compression and injection molding techniques. The CAD/CAM method obtained the highest reproducibility, indicating consistent precision in CD fabrication. In contrast, the conventional technique exhibited the most significant variability in terms of the precision of the denture bases.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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VARIJACIJA U BOJI LABIJALNE POVRŠINE GORNJIH CENTRALNIH SEKUTIĆA

VARIATION IN THE COLOR OF THE LABIAL SURFACE OF THE UPPER CENTRAL INCISORS

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Sažetak

Uvod*: Tokom procesa starenja, organi i tkiva čoveka podležu strukturnim i funkcionalnim promenama, koje se takođe mogu registrovati i na zubima, usled promene njihove boje i strukture.*
Cilj *ove studije bio je da se utvrdi varijacija u boji labijalne površine gornjih centralnih sekutića u gingivalnoj, srednjoj i incizalnoj trećini.*
Materijali i metode*: Istraživanje je sprovedeno kod 52 pacijenta. Istraživanje je obuhvatilo 103 zdrava, vitalna gornja centralna sekutića. Analizirane su gingivalna, srednja i incizalna površina gornjih centralnih sekutića, vizuelnom metodom uz pomoć ključa za boju (Philips zoom shade guide). Nijanse za boju su podeljene u tri grupe: svetle, srednje boje i tamne. Statistička analiza je urađena korišćenjem Hi kvadrat i Mann-Whitney U testa u IBM SPSS verzija 26.0, sa nivoom statističke značajnosti postavljenim na p < 0,001.*
Rezultati: *Kod najvećeg broja muškaraca (46,8%) na gingivalnim trećinama zuba su registrovane srednje nijanse boja, dok su na srednjim i incizalnim trećinama zuba u najvećem broju slučajeva uočene svetle nijanse (66% i 80,9%). Kod većine ženskih ispitanika gingivalne, srednje i incizalne trećine labijalnih površina gornjih centralnih sekutića imale su svetle nijanse (69,6%, 92,9%, 94,6%). Uočeno je da boje nisu podjednako rasp oređene prema trećinama zuba kod ispitanika oba pola (p=0,000).*
Zaključak: *Boja zuba varira među ispitivanim trećinama zuba. Ispitanici ženskog pola su imali svetlije nijanse zuba u odnosu na muškarce.*

Ključne reči*: boja zuba, centralni sekutići, ključ za boju*

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Abstract

Introduction: *During the ageing process, human organs and tissues undergo structural and functional changes which can also be registered in the teeth, due to changes in their color and structure.*
The aim *of this study was to determine the color variation of the labial surface of the upper central incisors in the gingival, middle and incisal thirds.*
Materials and Methods: *The research was conducted on 52 dental students and included 103 healthy, vital upper central incisors. The gingival, middle, and incisal surfaces of the upper central incisors were analyzed using a visual method, with the help of a color key. Color shades were divided into three groups: light, medium and dark. Statistical analysis was performed using the Chi-square and Mann–Whitney U test in IBM SPSS version 26.0, with the level of statistical significance set at p < 0.001.*
Results: *In the largest number of male students (46.8%), medium shades of color were registered in the gingival thirds of the teeth, while light shades were observed in the middle and incisal thirds of the teeth in the largest number of cases (66% and 80.9%, respectively). In the majority of female students, the gingival, middle, and incisal thirds of the labial surfaces of the upper central incisors had light shades (69.6%, 92.9%, 94.6%, respectively). It was observed that the colors were not equally distributed according to the thirds of the teeth in subjects of both sexes (p < 0.001).*
Conclusion: *Tooth color varies among the thirds of teeth examined. Female subjects had lighter shades of teeth compared to males.*

Key words: *tooth color, central incisors, color key*

Introduction

The phenomenon of tooth color has a significant social impact, as confirmed by numerous studies. The results of those studies indicate that people with whitened teeth are considered younger and more attractive[1]. Besides contributing to the aesthetic experience, the importance of tooth color is also reflected in the motivation to maintain oral health. A study by Vlasov et al.[2] concluded that after teeth whitening, patients showed a significantly greater interest in taking care of oral hygiene and regular dental examinations. These findings highlight a deeper social and psychological aspect of tooth color in the context of the perception of beauty and preservation of oral health.

Natural tooth color is the result of a complex set of factors such as illumination, light scattering and translucency. The color of the teeth is determined by numerous factors such as the structure and thickness of the hard dental tissues, which can vary from individual to individual. In addition, bad habits such as smoking and drinking colored drinks can affect the color of the teeth. Dental diseases as well as endodontic dental treatments, during which various medications are used, can affect the color of the teeth[3].

During the ageing process, human organs and tissues undergo structural and functional changes. These changes can also be registered in the teeth, due to changes in their color and structure. Therefore, the color of the teeth and their structure can serve as an additional factor in estimating the age of a person[4]. While numerous studies have indicated significant changes in the color of the teeth that occur with ageing significantly more in men[5], other studies have pointed out that women have significantly lighter teeth[6]. Researches that examined tooth color variations in different groups of teeth observed significant differences in the color of different groups of teeth of the same individuals[5,6].

Studying tooth color variations in relation to the region of the tooth is important in order to obtain information that can be useful in achieving the desired aesthetic results during tooth restoration, which can be achieved by using restorative materials of different colors and shades.

Due to the greater and more serious demands of patients in the field of dental aesthetics, various methods for determining the color of teeth are being developed. We can measure tooth color by visual methods or instrumental methods using a colorimeter[3]. The visual method is the most frequent method in modern dental practice for determining tooth color shades[5].

The aim of this study was to determine the differences in the color of maxillary first incisors in dental students, specifically focusing on the gingival, middle, and incisal thirds of the teeth.

Materials and Methods

The research was conducted at the Clinic of Dental Medicine, Faculty of Medicine, University of Niš in the period from January to March 2024. This research was conducted on 52 fourth-year dental students (24 male and 28 female students) aged 22 to 23 years. In the research, 103 maxillary upper incisors were examined.

The teeth included in this study were healthy, vital upper central incisors, without carious lesions as well as teeth that were not exposed to the bleaching process. Restored teeth as well as teeth with any prosthetic restoration or fracture were excluded from the study. Before the actual color determination procedure, each tooth was carefully cleaned of hard and soft dental deposits and polished with an eraser and abrasive paste.

Determining the color of the teeth was done visually using a color guide (Philips Zoom shade guide). By observing the labial surfaces of the upper central incisors, the shade of color was determined individually for the incisal, middle and gingival thirds. Dental observation was done by one researcher in daylight, without direct sunlight after a short observation without intense colors and contrast in the visual field. Color shades were divided into three groups: light, medium and dark.

Statistical analysis was performed using the Chi-square and Mann–Whitney U test in IBM SPSS version 26.0, with the level of statistical significance set at $p < 0.001$.

Results

A statistically significant difference was observed in the distribution of colors according to the thirds of teeth in male students ($p = 0.004$). In the largest number of males (46.8%), medium shades of color were registered in the gingival thirds of the teeth, while light shades were observed in the middle and incisal thirds of the teeth in the largest number of cases (66% and 80.9%) (Table 1).

The chi-square test revealed a significant difference in the distribution of colors according to the thirds of teeth in female students ($p = 0.001$).

Although in the majority of female students the gingival thirds of the labial surfaces of the maxillary incisors were of a light shade, a significantly smaller number of female subjects had light gingival (69.9%) thirds of the teeth, compared to the number of female subjects in whom a light shade of color was observed in the middle (92 .9%) and incisal (94.6%) thirds of teeth (Table 2).

Table 1. Color distribution according to the thirds of teeth in male subjects

		Color			Number of examined teeth	Chi-square test
		Light	Medium	Dark		
Gingival third	Number	20	22	5	47	
	Percent	42.6%	46.8%	10.6%	100%	
Medium third	Number	31	14	2	47	$\chi^2 = 15.53$
	Percent	66%	29.8%	4.2%	100%	$p = 0.004$*
Incisal third	Number	38	8	1	47	
	Percent	80.9%	17.0%	2.1%	100%	

*—significant at $p < 0.05$

Table 2. Color distribution according to the thirds of teeth in female students

		Color			Number of examined teeth	Chi-square test
		Light	Medium	Dark		
Gingival third	Number	39	15	2	56	
	Percent	69.6%	26.8%	3.6%	100%	
Medium third	Number	52	4	0	56	$\chi^2 = 18.63$
	Percent	92.9%	7.1%	0%	100%	$p = 0.001$*
Incisal third	Number	53	3	0	56	
	Percent	94.6%	5.4%	0%	100%	

*—significant at $p < 0.05$

Table 3. Color distribution according to the thirds of teeth in students of both sexes

		Color			Number of examined teeth	Chi-square test
		Light	Medium	Dark		
Gingival third	Number	59	37	7	103	
	Percent	57.3%	35.9%	6.8%	100%	
Medium third	Number	83	18	2	103	$\chi^2 = 29.80$
	Percent	80.6%	17.5%	1.9%	100%	$p = 0.000$*
Incisal third	Number	91	11	1	103	
	Percent	88.3%	10.7%	1%	100%	

*—significant at $p < 0.001$

It was observed that the colors were not equally distributed according to the thirds of the teeth in subjects of both sexes (p = 0.000). Although light shades predominated in all examined thirds of teeth, medium and dark color shades were significantly more represented in the gingival thirds of the teeth (35.9% and 6.8%) than in the middle thirds (17.5% and 1.9%) and incisal thirds (10.7% and 1.0%) of teeth (Table 3).

A statistically significant difference was observed in the distribution of colors in the gingival thirds between the sexes (p = 0.005). While medium shades were more prevalent in the gingival thirds of teeth in male students, light shades were dominant in the gingival thirds of female students (Figure 1).

Although in both male and female students the middle thirds of the teeth were dominated by light shades of color, in a significantly higher percentage (p = 0.001) of female students, light shades were observed in the middle thirds of the teeth, compared to male students, while medium and dark shades were observed in a higher percentage of male students compared to female students (Figure 2).

In subjects of both sexes, the highest percentage had incisal thirds of a light color, however, the results of the Mann–Whitney U test showed that the incisal thirds of female students were significantly more often (p = 0.029) light, compared to the incisal thirds of male students (Figure 3).

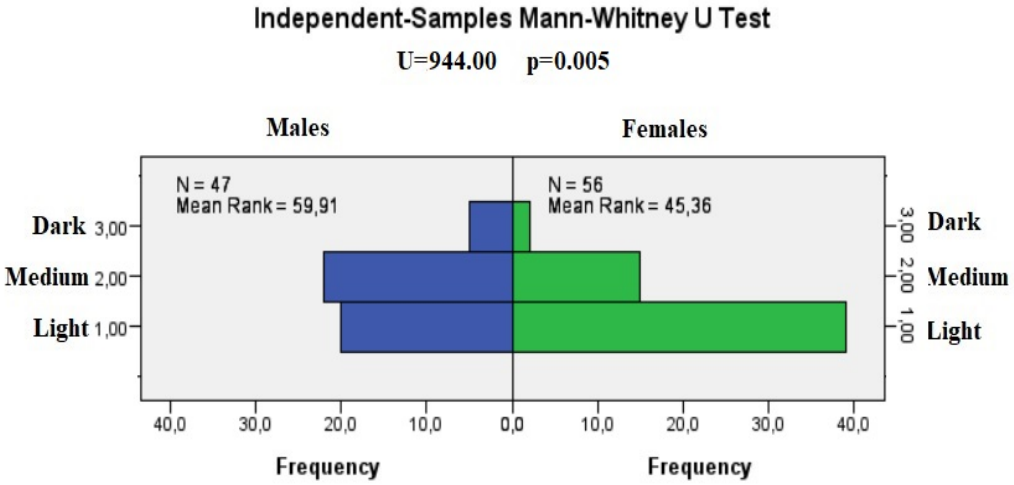

Figure 1. Distribution of the color shade of the gingival third of the teeth according to gender

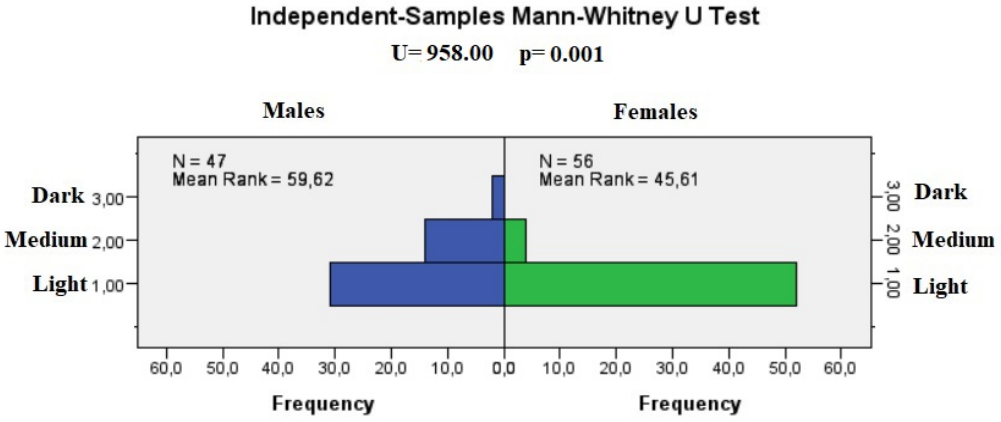

Figure 2. Distribution of the color shade of the middle third of the teeth according to gender

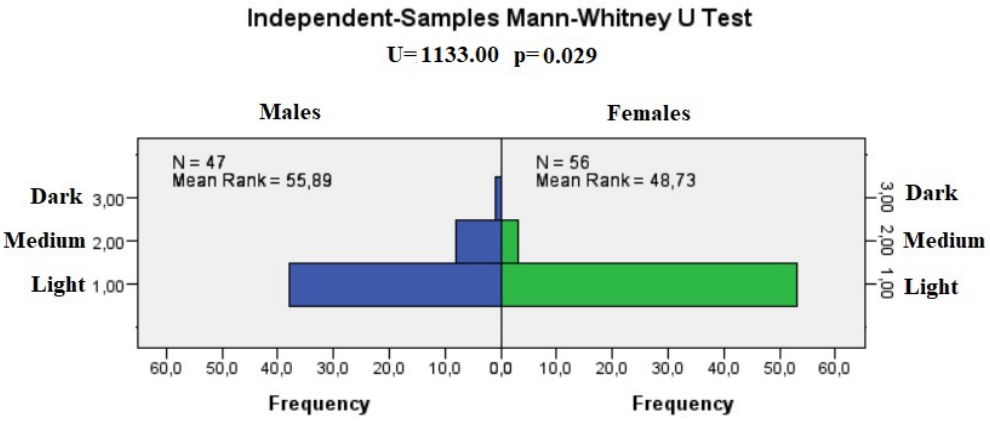

Figure 3. Distribution of the color shade of the incisal third of the teeth according to gender

Discussion

Color represents the most important optical property that determines the aesthetics of patients' teeth. The optical properties of hard dental tissue are very complex and include color, translucency, opalescence and fluorescence[7]. Precisely, one of the basic tasks of aesthetic dentistry is to imitate the properties of dental tissues with modern restorative materials so that such a tooth has as natural an appearance as possible. Large variations in the color of the hard tooth tissue make the restoration of the upper central incisors particularly demanding, both in the incisal and in the middle and gingival thirds[8].

Today, there are numerous methods used to determine the color of teeth, starting with visual, subjective methods based on the use of a color key, paper or colored porcelain, but also methods in the form of a spectrophotometer, colorimeter and image analysis technique[3]. In addition to numerous shortcomings that can be reflected in the limited presence of colors that will be compared with the teeth but also in the presence of artificial light, the visual method is one of the most popular methods for determining tooth color shades[9,10]. While the middle third of the teeth is the optimal place for color determination, when determining colors on the incisal third, the transparency of the enamel should also be taken into account. However, the determination of tooth color by visual method is a very common and useful method used in an everyday dental practice when choosing the appropriate color of restorative materials for restorative dental tissues or prosthetic restoratives. This technique is often used because it allows easy and quick determination of tooth color. Research has shown that this method is not subject to the influence of examiner characteristics such as gender or experience, which further confirms its objective character[11].

The importance of the distribution of different shades of color on the labial surfaces of the front teeth is reflected in the observations of the study by Karabaş et al.[12], which suggest that based on the color of one third of the teeth, the color of the second third of the same tooth can be predicted. This may have clinical significance in cases of fractures and cavity IV, where it is necessary to compensate aesthetically for the tooth's incisal third whose color is unknown to us due to the lack of this part of the tooth.

In the majority of examined gingival thirds of maxillary central incisors in this study, in male subjects, medium shades of color were observed in the gingival third, which characterized this part of the teeth as darker compared to the significantly lighter middle and incisal thirds of the teeth. In one study that examined the color of upper central incisors, it was observed that the gingival thirds were darker compared to the middle and incisal thirds of the mentioned teeth[13,14]. This can be explained by the fact that the gingival third contains much more dentin and a significantly thinner layer of enamel, while the surrounding soft tissue that covers the neck of the tooth affects the color itself[15].

In the study by Bosch et al.[16], the important role of dentin in determining the color of teeth was confirmed, while the role of enamel was reduced to adding bluish shades to the color of teeth. When removing the labial

surface of the enamel for veneer preparation, it was observed that the prepared teeth were yellower after preparation. All this indicates that surfaces covered with enamel have lighter shades[17].

Examination of tooth color in this study in females showed that the gingival thirds were mostly of lighter shades. The presence of lighter natural teeth in women has been confirmed in numerous studies[6]. In the study by Stošić et al.[6], who examined the degree of change in the color of upper central incisor teeth with the age of the patient and in relation to gender, it was shown that females had a significantly lighter color of the upper central incisors compared to men. The mentioned study also showed that younger patients had a significantly lighter shade of teeth.

In a recent study conducted by Wee et al.[18] it was observed that women have a significantly lighter shade of color compared to men, and that in addition to gender, the color of the teeth is also influenced by ethical differences.

Conclusion

The results of this study showed that female students had lighter shades of teeth compared to male students. Also, this study showed that in the majority of males, medium shades of color were registered in the gingival thirds of the teeth, while in the middle and incisal thirds of the teeth, light shades were observed in the majority of cases, i.e., that in the largest number of females, a lighter shade was observed in all examined thirds of the labial surface.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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PROCENA RADIOGRAFSKIH RAZLIKA U TIPOVIMA IMPAKTRANIH I IZNIKLIH MANDIBULARNIH TREĆIH MOLARA

EVALUATION OF RADIOGRAPHIC DIFFERENCES IN TYPES OF IMPACTED AND ERUPTED MANDIBULAR THIRD MOLARS

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Sažetak

Uvod: *Smatra se da faktori poput neusklađenosti između veličine zuba i vilice, širine ramusa i donje okluzalne ravni igraju značajnu ulogu u impakciji donjeg trećeg molara (M3M).*
Cilj *studije bio je procenjivanje radiografske razlike u angularnim i linearnim merama kod različitih tipova impakcije donjeg trećeg molara (M3M)*
Materijal i metode: *Uključeni su ortopantomogrami i lateralni cefalogrami 300 pacijenata starosti 18–30 godina. Procenjena su linearna merenja kao što su visina ramusa, meziodistalna širina prvog molara donje vilice i M3M, retromolarni prostor, odnos retromolarnog prostora prema širini meziodistalnog tipa udarnog panoramskog radiografa na M3M. Ugaona merenja, kao što je gonijalni ugao, procenjena su na bočnim cefalogramima.*
Rezultati: *Srednje vrednosti studije su otkrile statistički značajne razlike između grupa sa impaktirani i neimpaktirani u smislu gore navedenih radiografskih parametara sa razlikom među polovima. Pronađene su značajne razlike između retromolarnog prostora, širine prvog molara donje vilice i odnosa retromolarnog prostora i meziodistalne širine M3M u sva tri nivoa Pell i Gregori klasifikacije, kao i značajne razlike u širini M3M u sva četiri tipa Vinterove klasifikacije.*
Zaključak: *Studija identifikuje ključne anatomske faktore kao što su odnos retromolarnog prostora i meziodistalne širine M3M retromolarnom prostoru, visinom ramusa i gonijalnim uglom da bi značajno uticali na rizik od M3M impakcije. Ovi nalazi povećavaju sposobnost stomatologa da predvide impaktaciju i poboljšaju ishode lečenja.*

Ključne reči: *impakcija trećeg molara, visina ramusa, retromolarni prostor, gonijalni ugao, mezodistalna širina, mandibularni treći molar, prvi molar*

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Abstract

Introduction: *Factors like mismatches between tooth and jaw sizes, the width of the ramus, and alignment of lower back teeth are thought to play significant roles inmandibular third molar impaction (M3M).*
Aim *of the study was to evaluate the radiographic differences in angular and linear measurements between various types of impacted and erupted M3Ms.*
Material and Methods: *Orthopantomographs and Lateral cephalograms of 300 patients aged 18–30 were included and linear measurements such as ramus height, mesiodistal width of mandibular first molar and M3M, retromolar space, the ratio of retromolar space to mesiodistal width of M3M, type of impaction were assessed on panoramic radiographs. Angular measurements, such as gonial angle, were assessed on Lateral cephalograms.*
Results: *The study's mean values revealed statistically significant differences between impacted and non-impacted groups in terms of the above-mentioned radiographic parameters and were also significant across genders. Significant differences were found between retromolar space, mandibular first molar width, and retromolar space to M3M mesiodistal width ratio across all three levels of Pell and Gregory classification, as well as significant differences in M3M width across all four types of Winter's classification.*
Conclusion: *The study identifies key anatomical factors such as retromolar space to M3M mesiodistal width ratio followed by retromolar space, ramus height and gonial angle to significantly influence the risk of M3M impaction. These findings enhance the ability of dental professionals to predict impaction and improve patient outcomes.*

Key words: *third molar impaction, ramus height, retromolar space, gonial angle, mesiodistal width, mandibular third molar, first molar*

Introduction

Peterson defined the impaction of teeth as "Fail in eruption within anticipated timeframe"[1]. The function of M3Ms in the oral cavity has been the subject of extensive research over the years. M3Ms are the teeth most often susceptible to incomplete eruption, often resulting in impaction[2]. Clinically, impacted M3Ms result in issues such as pain, swelling, caries, and root resorption[2,3]. Even though devoid of noticeable symptoms, M3M impaction is capable of being linked to various pathological conditions, ranging from pericoronitis to cysts and neoplastic lesions[4]. Prophylactic removal is estimated to be performed in 54% of mandibular M3Ms, even in the absence of subjective symptoms, which may aid in preventing the above-mentioned complications[2,3].

The complexity of surgical removal of M3Ms depends largely on their position within the jaw. Numerous classification systems have been developed to categorize the positions of mandibular M3M teeth, with Winter (1926) and Pell and Gregory (1933) classifications being the most commonly followed[2]. These classification systems might provide valuable insights into potential challenges associated with these prophylactic extractions.

Despite this, in most cases, M3Ms are not directly considered in orthodontic treatment planning, but they may play a crucial role while framing an orthodontic treatment plan. By prophylactic extraction, we can eliminate anterior teeth crowding. As the etiology of M3M impaction is complex, no precise predictive method has been developed[4].

Prediction of impaction or eruption of M3Ms would offer significant clinical benefits in dentistry. Various methods for predicting the eruption of M3Ms have been introduced since Henry and Morant's initial data in 1936. Most of these studies rely on lateral cephalographic measurements, while other techniques, such as anteroposterior views, periapical films, and bitewings are also utilized. Additionally, panoramic tomograms have been employed in studies by Ganss et al.[5] and Venta[6]. As panoramic tomograms become increasingly accessible to most practicing dentists and they are also cost-effective and easily obtained, utilizing such projections for predicting the future development of M3Ms could prove advantageous[7]. The pitfall of panoramic radiography includes distortion and magnification[8].

The exact causes of M3M impaction remain unclear, but factors such as differences in jaw and tooth sizes, the width of the ramus, and alignment of mandibular back teeth are believed to contribute[9]. Several parameters, including the width of the mandibular first molar, ramus height, gonial angle and retromolar space to the width of M3M ratio, have been investigated in various studies. However, there is inconsistency among these studies regarding the predictive value of these parameters for the eruption or impaction of M3Ms.

Due to limited documentation on the usefulness of all radiographic parameters in our population, a study was designed to evaluate the radiographic differences in angular and linear measurements between various types of impacted and erupted M3Ms.

Material and Methods

This study contained Orthopantomo-graphs and Lateral cephalograms of 300 individuals aged 18–30, equally distributed by gender. The study respondents were divided into two groups: 150 respondents with impacted (75 males, 75 females) and 150 of them with erupted (75 males, 75 females) M3Ms. The study design was thoroughly scrutinized and got approval from the Institutional Review Board [IRB] and Ethical Committee IECVDC/2022/PG01/OMR/IVT/04. The following inclusion and exclusion criteria were met:

Inclusion Criteria

- Radiographs of patients under the age group of 18–30 years
- Orthopantomograph (OPG) and LC (Lateral Cephalograph) with impacted and erupted M3Ms
- OPG and LC with permanent mandibular first molars without proximal caries and any restorations
- Radiographs with complete mandibular permanent dentition and without any impactions of remaining tooth other than M3Ms
- OPG and LC should have to meet the standard radiographic quality

Exclusion Criteria

- Panoramic images without mandibular M3Ms
- Subjects with any developmental anomalies or syndromes
- Subjects with any pathologies and fractures in the region of interest
- Panoramic images with absence of mandibular permanent first molars

• Individuals who were undergoing or previously had undergone any orthodontic treatment or surgical orthognathic surgeries

Study Procedure

All panoramic and lateral cephalometric images were taken for each individual with an Orthopantomogram machine (Satellec X-Mind-Panoceph) using photostimulable phosphor plates (PSP, Soredex) along with standard exposure parameters as recommended by the manufacturer by a single operator and head position was standardized to the greatest extent possible. By using Scanora, and accompanying software final images were obtained in DICOM format. Impacted M3Ms were categorized based on the Pell and Gregory (Figure 1) and Winter classifications (Figure 2). The below listed linear measurements were performed on panoramic radiographs and angular measurements were performed on Lateral cephalograms. The obtained data were statistically analyzed using SPSS software version 22.0.

Linear measurements:

The following linear measurements were done in OPG:

1. Ramus height (O1–O2)—the edge point of the condyle on the lateral aspect (O1) and edge point of the ramus on the lateral aspect (O2) were identified on OPG. O1–O2 was measured and defined as ramus height1 (Figure 1)

2. Retromolar space (Figure 2)—distance from the second molar distal contact point to the line at right angles to the Z plane (A tangent drawn along the descending anterior border of the mandibular ramus)2

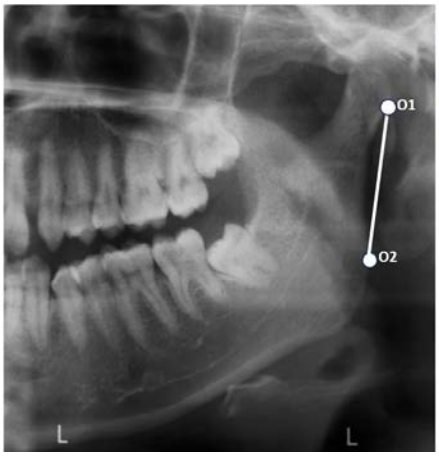
3. Mesiodistal width of permanent mandibular first molar (Figure 3A)1

4. Mesiodistal width of M3M (Figure 3B)2

5. Retromolar space to mesiodistal width of M3M ratio2

Angular measurements:

7. Gonial angle (Figure 4)—gonial angle was measured on lateral cephalograms. It is the angle obtained by joining articular, gonion and menton points1



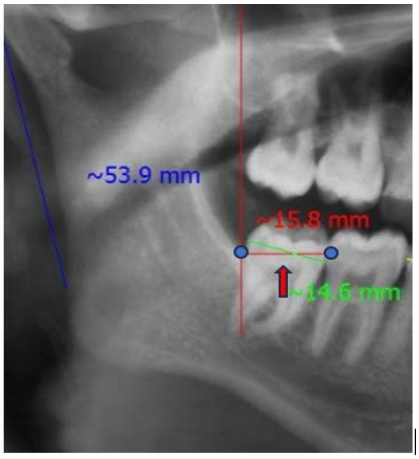


Figure 1*:** Ramus height ***Figure 2: Retro-molar space (marked in red color)

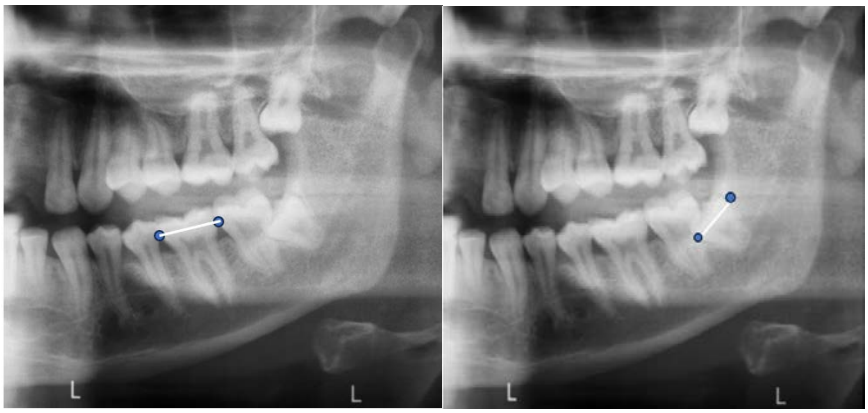


Figure 3: Mesio distal width of mandibular (A) First molar (B)M3M

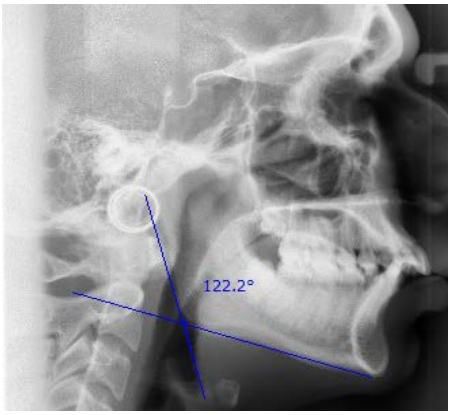


Figure 4. LC showing Gonial angle

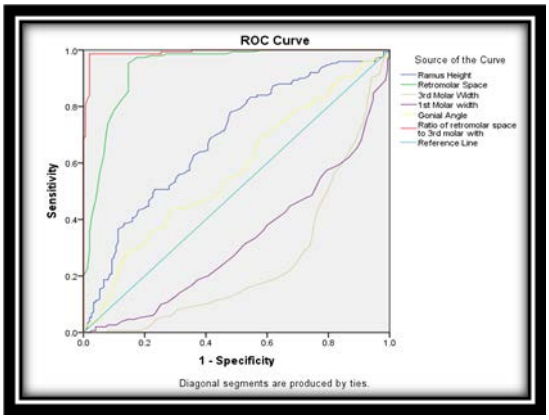


Figure 5. ROC ANALYSIS

Statistical analysis

The obtained data were compiled and analysed statistically by using SPSS software (version 22). Data analysis was done by using Mann–Whitney U test to draw inter-group comparisons among the non-impacted and impacted groups and to calculate mean values for ramus height, retromolar space, mesiodistal width of the mandibular permanent first molar, mesiodistal width of M3M, the ratio of retromolar space to mesiodistal width of mandibular permanent M3M. Kruskal–Wallis test and one-way ANOVA were used to calculate intra-group (impacted) comparison of the mean values of ramus height, retromolar space, mesiodistal width of mandibular first molar, mesiodistal width of M3M, retromolar space to mesiodistal width of permanent M3M ratio of the Winter classification (horizontal, mesioangular, vertical and others group) and Pell and Gregory classification (levels of impaction A, B, C). A p-value of < 0.05 was considered statistically significant.

The receiver operating characteristic curve (ROC) curve was plotted with a 95% confidence interval.

Results

The mean values of ramus height, retromolar space, mesiodistal width of M3M, mesiodistal width of the mandibular first molar, the ratio of retromolar space to mesiodistal width of permanent M3M width, and gonial angle showed a statistically significant difference between the impacted and non-impacted groups where ramus height, retromolar space, gonial angle, ratio of retromolar space to mesiodistal width of M3M were greater among the non-impacted group when compared with the impacted group and mesiodistal width of the mandibular permanent first molar, mesiodistal width of permanent M3M were comparatively less for the impacted group than the non-impacted group (Table 1).

The mean values of ramus height, retromolar space, mesiodistal width of

permanent M3M width showed statistically significant differences where all three parameters were greater in males when assessed with females (Table 2).

A statistically significant difference between retromolar space, mesiodistal width of the mandibular permanent first molar, and the ratio of retromolar space to mesiodistal width of mandibular permanent M3M width was observed between all three levels of Pell and Gregory classification groups where the three parameters were more for level A type of impaction followed by level B and C (Table 3).

The mean value of mesiodistal width of M3M showed a significant difference among all four types of the Winter classification groups, where the vertically impacted group has smaller mesiodistal width compared to other impacted groups (Table 4).

A receiver operating characteristic (ROC) analysis was performed to appraise reliable marker for impaction by plotting sensitivity versus specificity for the results obtained in between non-impacted and impacted groups in terms of gonial angle, ramus height, mesiodistal width of M3M, mesiodistal width of the first molar, retromolar space, ratio of retromolar space to mesiodistal width of M3M (Figure 5).

According to ROC analysis performed in the present study, the ratio of retromolar space to 3rd molar width covers the highest area of the graph and is a reliable marker to distinguish between impacted and non-impacted groups followed by retromolar space, ramus height and gonial angle.

Discussion

Under normal circumstances, M3Ms eruption takes place between the ages of 18 and 24 years. By this age, growth typically reaches completion, and the M3Ms reach complete root formation[10]. So, individuals aged 18–30 years in our study group were included for this reason.

To prevent bias and ensure a balanced representation, an equal gender distribution was implemented, with an equivalent number of male and female samples considered. This approach aimed to achieve a meaningful comparison between the parameters utilized in the study.

The impaction of M3Ms persists as a significant concern in dental practice due to its frequent and potential clinical implications.4 They are also implicated in various issues including crowding in the lower arch, temporomandibular joint (TMJ) disorders, as well as neuralgias and vague orofacial pain[11,12].

There are limited data pertaining to the relationship between M3M impaction and the mesiodistal width of the first molar, it is believed that a larger mesiodistal width of the first molar could create limited space within the dental arch, potentially hindering the natural eruption pathway of the M3M.

Table 1: Mean values of linear and angular measurements between impacted and non-impacted groups

Radiographic parameters	IMPACTION	No.	Mean ± ST deviation	P-value
Ramus height	IMPACTED NON-IMPACTED	150 150	44.19 ± 4.75 47.14 ± 5.38	0.000*
Retromolar space	IMPACTED NON-IMPACTED	150 150	8.6 ± 3.15 14.24 ± 1.86	0.000*
Mesiodistal width mandibular of M3M	IMPACTED NON-IMPACTED	150 150	14.13 ± 1.25 13.07 ± 1.08	0.000*
Mesio-distal width of mandibular first molar	IMPACTED NON-IMPACTED	150 150	14.87 ± 1.17 13.42 ± 1.16	0.000*
Gonial angle	IMPACTED NON-IMPACTED	150 150	120.46 ± 6.5° 122.03 ± 6.5°	0.030*
Ratio of retromolar space to mesiodistal width of mandibular M3M	IMPACTED NON-IMPACTED	150 150	0.60 ± 0.21 1.09 ± 0.12	0.000*

Table 2 Mean values of linear and angular measurements between genders

	IMPACTION	No.	Mean ± ST deviation	P-value
Ramus height	MALE FEMALE	150 150	47.17 ± 5.55 44.16 ± 4.54	0.000*
Retromolar space	MALE FEMALE	150 150	11.89 ± 3.61 10.95 ± 3.99	0.026*
Mesiodistal width of M3M	MALE FEMALE	150 150	14.57 ± 1.81 13.43 ± 1.33	0.029*
Mesiodistal width of mandibular first molar	MALE FEMALE	150 150	14.59 ± 1.28 13.67 ± 1.2	0.06
Gonial angle	MALE FEMALE	150 150	120.4 ± 7.05^{o} 122.07 ± 5.9^{o}	0.055
Ratio of retromolar space to mesiodistal width of M3M	MALE FEMALE	150 150	0.86 ± 0.28 0.82 ± 0.31	0.33

Table 3: Mean values of linear and angular in all Pell and Gregory Classification groups

	Level	Mean ST deviation	P-value
Ramus height	A	45.24 ± 5.18	0.191
	B	43.56 ± 4.52	
	C	43.28 ± 4.09	
Retromolar space	A	9.43 ± 3.1	0.004*
	B	8.66 ± 2.95	
	C	7.41 ± 3.05	
Mesiodistal width of M3M	A	14.21 ± 1.37	0.806
	B	14.09 ± 1.15	
	C	14.07 ± 1.18	
Mesiodistal width of mandibular first molar	A	14.44 ± 1.15	0.044*
	B	14.06 ± 1.07	
	C	13.9 ± 1.22	
Gonial angle	A	120.58 ± 6.81	0.495
	B	120.8 ± 5.94	
	C	120.01 ± 6.61	
Ratio of retromolar space to mesiodistal width of M3M	A	0.66 ± 0.21	0.005*
	B	0.61 ± 0.2	
	C	0.52 ± 0.22	

Table 4: Mean values of linear and angular radiographic parameters for all Winter Classification groups

	Type	Mean ST deviation	P-value
Ramus height	Horizontal	44.32 ± 4.95	0.979
	Mesioangular	44.23 ± 4.67	
	Vertical	44.13 ± 4.86	
	Others	43.2 ± 1.3	
Retromolar space	Horizontal	8.34 ± 3.07	0.276
	Mesioangular	8.89 ± 3.75	
	Vertical	8.68 ± 2.72	
	Others	5.83 ± 1.5	
Mesiodistal width of M3M	Horizontal	14.98 ± 1.12	0.001*
	Mesioangular	13.98 ± 1.18	
	Vertical	13.81 ± 1.25	
	Others	14.8 ± 0.91	
Mesiodistal width of mandibular first molar	Horizontal	14.36 ± 1.4	0.237
	Mesioangular	13.88 ± 0.97	
	Vertical	14.27 ± 1.07	
	Others	14.13 ± 2.4	
Gonial angle	Horizontal	119.7 ± 7.3^{O}	0.731
	Mesioangular	120.4 ± 6.1^{O}	
	Vertical	120.5 ± 5.6^{O}	
	Others	127.7 ± 14.02^{O}	
Ratio of retromolar space to mesiodistal width of M3M	Horizontal	0.56 ± 0.21	0.128
	Mesioangular	0.63 ± 0.26	
	Vertical	0.62 ± 0.19	
	Others	0.39 ± 0.11	

Table 5: Roc analysis

Variables	Area under the graph	P-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Ramus height	.687	0.000*	.628	.747
Retromolar space	.937	0.000*	.910	.965
Mandibular 3rd molar width	.249	0.000*	.193	.305
Mandibular 1st molar width	.324	0.000*	.264	.384
Gonial angle	.572	0.030*	.508	.637
Ratio of retromolar space to 3rd molar width	.992	0.000*	.984	1.000

The current study showed considerable variation statistically among the impacted and non-impacted groups, pertaining to the first molar width with 14.8 mm among the impacted group and 13.4 mm in the non-impacted group and the current study results were in contradiction to the results of Jéssica de Fátima Segantin[13] study where they reported there was no statistical significance observed with values 9.3 mm and 9.5 mm among erupted and impacted groups respectively. In a study conducted by Hung-Huey Tsai[3] et al. in the Taiwanese population, the mesiodistal crown dimension of the mandibular permanent first molar among males was 8.4 mm in the impacted group and 7.4 mm in the non-impacted group, in females, it was 7.5 mm in impacted group and 7.2 mm in the non-impacted group, mesiodistal width of the lower permanent first molar was greater among

the impacted group when compared to the non-impacted group, which is consistent with the results of the present study.

Genetic diversity can affect tooth size and shape which can lead to different mesiodistal width of molars in different ethnic groups, Environmental and dietary factors also play a role; diets requiring more chewing can promote larger jaw sizes and teeth, leading to variations in dental measurements across different populations. M3M impaction might be due to increased width of M3M[3].

The Kaur R[14] et al. study on the Turkish population and the Hung Huey Tsai[3] study on the Taiwanese population revealed that M3Ms exhibited greater width in partially or non-erupted groups compared to fully erupted ones, which is similar to our current findings. However, the results of Talat Hasan Al-Gunaid[9] and Nur Mollaoglu[15] showed there was no significance in M3M width between subjects with erupted and impacted M3Ms, which was contradictory to the present study.

Quiros's[16] panoramic study of 300 individuals found the M3M's mesiodistal width (MDW) to be about 15.8 mm, which is slightly more than in the present study. This difference may stem from using a conventional panoramic machine, which magnifies images by 15% to 20%. These variations could potentially account for differences in measurements in other studies too.

The development of the retromolar space involves several factors, including thinning of the anterior margin of the ramus. The anteroposterior dimension of the retromolar spaces expands, allowing for the accommodation of permanent molars due to the posterior repositioning of the ramus[17]. Ganss[5] et al. found that the likelihood of M3M eruption reaches 70% when measurements of retromolar space were 13.9 mm for women and 14.3 mm for men and E. S. J. Abu Alhaija[18] et al.'s observation on the Arabian population revealed significant difference among gender, which was consistent with current study results.

In a study performed by Selmi Yilmaz[19] on the Turkish population, the retromolar space was categorized according to Pell and Gregory as levels A, B, and C with measurements of 14.7 mm, 11.1 mm, and 10.3 mm, respectively. These results were statistically significant and consistent with the findings of the present study.

In studies conducted by Talat Hasan Al-Gunaid[9] and Nur Mollaoglu[15], the average ratio of retromolar space to mesiodistal width of M3M was higher amongst the non-impacted group compared to the impacted group and there was a considerable disparity between the non-impacted groups and the impacted. The findings of the above-mentioned studies were similar to those of the present study, with ratios of 0.60 ± 0.21 for the impacted group and 1.09 ± 0.12 for the non-impacted group respectively. Earlier research by Mollaoglu[15] indicated that 69% of M3M eruptions occurred when the ratio of retromolar space to M3M width was at least one.

Gonial angle measurements are typically conducted using Lateral cephalograms. Studies suggest that measurements taken from panoramic radiographs are comparable to those from lateral cephalograms (Radhakrishnan et al.[20], 2017). However, some research indicates that there are significant differences between the two methods (Kundi and Baig, 2018)[2]. So, in the study, a lateral cephalometric radiograph was chosen for angular measurements. Björk et al.[21] (1956) suggested that individuals with a large jaw angle might possess greater posterior space within the dental arch. They hypothesized that this could result from predominantly condylar growth in a sagittal direction, consequently elongating the distance from the interdental area to the anterior border of the mandibular ramus[22].

In the present study, a notable distinction was observed between the impacted and non-impacted groups with the values of 120.46o and 122.03o, respectively. Studies by Kaur R et al.[14] and Al-Gunaid et al.[9] reported a more acute gonial angle in the impacted group compared to non-impacted group. These findings are similar to the findings of the present study. However, our results are contradictory to those of Al-Gunaid et al., who found no association between gonial angle magnitude and M3M impaction[9]. These variations could be due to the geographical distribution of the population or sampling differences in the study group.

The current study revealed no substantial association between positions and levels of M3M impaction classified according to Pell and Gregory as Level-A, Level-B, Level-C for gonial angle with values of 120.5o, 120.8o, 120.01o, respectively, which is similar to that of Oğuzhan Demirel et al.[23].

Lower facial height results in impaction and pattern of agenesis in M3M[24,25]. A decline in gonial angle and facial height was linked to an ascending rotation of the mandible due to decreased alveolar height. This increased rotation rate may be attributed to the faster growth in the condyle in vertical compared to the alveolar bone and some of the facial sutures[26]. The present study revealed that the

mean values of ramus heights classified according to Pell and Gregory classification were ranked as A > B > C. This observation indicating the increase of depth among vertical impaction correlates with ramus height reduction, supporting the aforementioned theory. These findings are consistent with the results of Gumrucku[2] et al.

In the non-impacted group, it was found that ramus heights were higher (47.14 ± 5.38) compared to the impacted group (44.19 ± 4.75), with statistical significance observed between both groups. Additionally, males exhibited greater ramus height (47.17 mm) in comparison to females (44.16 mm), with a significant difference noted between genders. These findings closely align with those reported by Talat Hasan Al-Gunaid et al.[9], i.e., 46.22 mm in the non-impacted group and 44.32 mm in the impacted group with males having a ramus height of 47.25 mm and females 40.17 mm in the Saudi population.

According to ROC analysis performed in the present study, the ratio of retromolar space to 3rd molar width covers the highest area of the graph and could serve as a reliable marker to distinguish between the impacted and non-impacted groups followed by retromolar space, ramus height and gonial angle.

Racial variation, dietary patterns, masticatory habits, and genetic inheritance all influence the size of the jaw and teeth. The variability in facial growth, jaw and tooth size, across various ethnic groups and inhabitants, demonstrates distinct inheritance patterns. The differences in the above-mentioned features lead to variations in results. When predicting M3M eruption or impaction, it is crucial not to rely solely on one or two variables. Therefore, it is advisable to conduct longitudinal studies to validate the effectiveness of this method.

Limitations

The sample was derived from a single orthodontic practice, which may not represent the broader population. The study focused exclusively on panoramic and cephalometric radiographs which have inherent limitations. Moreover, it did not differentiate between bilateral and unilateral impactions which may have distinct characteristics and predictive factors. One of the limitations is reliance on a classification system based solely on observation of radiographs. Additionally, participants who did not have M3Ms and were missing other molars were excluded, raising the possibility that some of the missing M3M might be due to agenesis. The inability to explore this factor represents another limitation of the study.

Conclusion

The study identifies key anatomical factors—lower retromolar area to M3M mesiodistal width ratio, insufficient retromolar area, shorter ramus height, larger gonial angle, wider first molar, wider M3M in order of importance according to ROC analysis and significantly influence the risk of M3M impaction. Understanding these factors is essential for effective diagnosis, treatment planning, and patient management, aiding in space management and early intervention strategies.

These findings enhance the ability of dental professionals to predict impaction, improve patient outcomes, and reduce complications, providing a strong basis for clinical guidelines.

Conflicts of Interest

The authors have no conflicts of interest to declare pertinent to this investigation.

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EFIKASNOST OZONIZOVANE VODE I 0,2% HLORHEKSIDIN GLUKONATA U LEČENJU HRONIČNOG PARODONTITISA

EFFCACY OF OZONISED WATER AND 0,2% CHLORHEXIDINE GLUCONATE IN THE MANAGEMENT OF CHRONIC PERIODONTITIS

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Sažetak

Cilj: *Proceniti efikasnost irigacije parodontalnih džepova korišćenjem ozonizovane vode i 0,2% hlorheksidin glukonata (CHKS) u lečenju hroničnog parodontitisa.*
Materijal i metod: *U studiju je uključeno 40 pacijenata sa hroničnim parodontitisom podeljenih u dve grupe od po 20 pacijenata. Indeks zubnog plaka, indeks upale gingive, dubina parodontnog dzepa i klinički gubitak epitelnog pripoja bili su mereni na početnom pregledu i nakon iperioda od 4 nedelje. Tokom i nakon tretmana čišćenja i poliranja korenske površine, prva grupa je irigirana ozonizovanom vodom, a druga grupa sa 0,2% hlorheksidin glukonatom tokom dva minuta. Prikupljeni podaci su podvrgnuti statističkoj analizi.*
Rezultati: *Ova studija je pokazala značajne rezultate u pogledu poboljšanja kliničkih parametara u obe grupe. Poređenjem između grupa, ozoniyovana voda je pokazala nešto bolje poboljšanje u odnosu na grupu sa hlorheksidinom. statistički značajna razlika je uočena za Indeks upale gingive (IGI).*
Zaključak: *Subgingivalna irigacija ozonizovanom vodom se pokazala kao novi metod lečenja koji pacijentima nudi značajne prednosti. Ozonizirana voda ograničava stvaranje zubnog plaka i smanjuje broj subgingivnih patogena. Njena jaka antimikrobna moć, sposobnost da stimuliše cirkulacijski sistem i modulira imunološki odgovor je čini lekom izbor kao sredstvo za irigaciju u kombinaciji sa terapijom prve faze u lečenju parodontitisa.*

Ključne reči: *ozonirana voda, irigacija, hlorheksidin glukonat, hronični parodontitis*

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Abstract

Aim: *To evaluate the efficacy of irrigation of periodontal pockets by using ozonated water and 0.2% chlorhexidine (CHX) gluconate in the management of chronic periodontitis.*
Materials and methods: *40 patients suffering from chronic periodontitis were involved in the study. They were divided into two groups with 20 patients. Dental Plaque Index, Gingival Inflammation Index, Periodontal Pocket depth and Clinical Attachment Level were recorded for both groups at the baseline visit and after 4 weeks interval, when they were subsequently recalled . During and after treatment of scaling and root planning, the first group was irrigated with ozonated water and the other group was irrigated with 0.2% chlorhexidine gluconate for two minutes. Collected data was compiled to statistical analysis.*
Results: *The present study showed significant results regards to the improvement in the clinical parameters in the both groups. When the parameters were compare between the groups, ozonated water showed slightly better improvement than the chlorhexidine group. However, a statistically significant difference was seen for Index of gingival inflammation (IGI).*
Conclusion: *Subgingival irrigation with ozonized water is proving to be a new useful treatment modality which offers great benefits to the patients. Ozonated water restricts the formation of dental plaque and reduces the number of subgingival pathogens. The strong antimicrobial power of ozone, its ability to stimulate the circulatory system and modulate the immune response, makes it a remedial agent of choice as an irrigant in conjugation with first phase therapy in the treatment of periodontitis.*

Key words: *ozonated water, irrigation, chlorhexidine gluconate, chronic periodontitis*

Introduction

Periodontal diseases are among the most common conditions, affecting more than 90% of the global population[1]. Today, it is well known that in the etiology and pathogenesis of these diseases, alongside other local and general factors, the accumulation and maturation of dental biofilm, or the presence of certain specific microorganisms within it, play a dominant role[2]. Therefore, the elimination of periodontal pathogens is the primary goal of periodontal therapy.

Conservative treatment in periodontology (ultrasonic instrumentation and root surface treatment) is considered the gold standard, but it does not always achieve the desired effect. Factors such as variations in the depth of periodontal pockets, as well as the ability of some specific bacteria to invade tissues, suggest the need for additional antimicrobial agents, either systemically or locally, to complement conservative treatment.

Systemically administered antimicrobial agents achieve low concentrations in periodontal pockets and, on the other hand, have several unwanted side effects. Therefore, locally applied antimicrobial agents are preferred, as they provide a longer-lasting concentration of the medication in the affected area, reducing the potential for the development of resistant bacterial strains[3].

Chlorhexidine gluconate (CHX) is considered the gold standard in the fight against bacterial agents, with a broad antimicrobial spectrum, used for supra- and subgingival irrigation[4]. The molecules of chlorhexidine, due to their cationic nature, can bind to the molecules of the oral mucosa, enamel, the biofilm on teeth, proteins in saliva, and bacterial cell walls, thus exerting a negative effect on bacterial development and activity dynamics[5]. These molecules are released gradually but retain their potency. It is effective against gram-positive and gram-negative bacteria, as well as fungi and some viruses. In lower concentrations, it destabilizes and destroys the microbial cell membrane (bacteria), acting bacteriostatic, while in higher concentrations, it affects the cytoplasm of the organism (bacteria), thus having a bactericidal effect[6].

Recently, as a possible alternative antiseptic to this common treatment, the benefits of ozone, in its three available forms—ozonated water, ozone gas, and ozonated olive oil are increasingly being mentioned[7]. Ozonated water and ozonated olive oil provide an ideal system for delivering ozone to tissues, as they can trap and then release oxygen molecules, thereby altering the subgingival environment, which is highly anaerobic, and exert their antibacterial effect against the present periodontal pathogens[8].

The powerful antimicrobial action of ozone, without the development of drug resistance and without side effects, together with its capacity to stimulate the circulatory system and modulate the immune response, makes it a therapeutic agent of choice[9,10,11]

The aim of this study was to compare the effectiveness of subgingival irrigation of periodontal pockets with ozonated water and 0.2% chlorhexidine (CHX) as an adjunct to conservative periodontal treatment.

Materials and Methods

The study was performed at the Faculty of Dentistry in Skopje, Clinic for Periodontology and Oral Medicine, University "Ss Cyril and Methodius" – Skopje.

The study involved 40 patients aged 30-60 years, diagnosed with chronic periodontal disease. The patients were divided into 2 groups of 20 participants each. During the first examination, clinical periodontal indices (DPI, IGI, PPD, and CAL) were recorded for each patient. During and after the conservative treatment, selected periodontal pockets with the deepest depths were irrigated. In the first group, irrigation was done with ozonated water, using a direct irrigation method with a syringe for 2 minutes. In the second group, irrigation was done with 0.2% chlorhexidine gluconate, using a properly sized needle for 2 minutes. Patients were simultaneously trained and motivated for proper and regular oral hygiene using the modified Bass technique. One week after the initial treatment, the patients were recalled for control and re-motivation for proper oral hygiene, and irrigation was repeated in the selected periodontal pockets with either ozonated water or 0.2% chlorhexidine gluconate. After one month, the periodontal index parameters were recorded.

The results were analyzed using descriptive statistical analysis with the SPSS statistics program. Differences in means were analyzed as statistically significant using the Student's t-test. The difference between treatment modalities was assessed using the Wilcoxon Signed-Ranks test.

Resluts

The first group of patients, treated with conservative therapy and irrigation of the periodontal pockets with ozonated water,

consisted of 20 patients, 8 women and 12 men, with an average age of 48 years. (Table 1).

The second group, treated with conservative therapy and irrigation with 0.2% chlorhexidine, consisted of 7 women and 13 men, with an average age of 52 years. (Table 2)

DPI in the first group, treated conservatively and supplemented with ozonated water irrigation, showed a statistically significant reduction from an initial value of 2.05 to 0.25 after one month. $p < 0.00001$. (Table 3)

Similarly, IGI in this group showed a significant decrease from 2.05 to 0.2. $p < 0.00001$. (Table 4)

For PPD, there was a reduction in the depth of periodontal pockets from an initial value of 3.3 to 2.6, but this was not statistically significant. (Table 5)

For CAL, there was a reduction from 3.45 to 3.05, but this difference was also not statistically significant. (Table 6)

In the second group treated with 0.2% chlorhexidine, DPI showed a statistically significant reduction from 2.3 to 0.75 after one month of treatment. $p < 0.00001$ (Table 7)

IGI also showed a significant decrease from 2.15 to 0.7. $p < 0.00001$ (Table 8)

For PPD, there was a reduction in depth from 3.95 to 3.75, but this was not statistically significant. (Table 9)

Similarly, for CAL, the values were identical to those of PPD, showing a reduction from 3.95 to 3.75, but this difference was also not statistically significant (Table 10)

The Wilcoxon Signed-Ranks test for the difference between treatment modalities (ozonated water vs. 0.2% chlorhexidine) showed statistically significantly better results only for IGI in the group treated with ozonated water. ($p = 0.011$). For the other parameters (DPI, PPD, and CAL), no statistical significance was found. (Table 11)

Table 1. Average age of I group (Irrigation with ozonated water)

Average age	Mean	Median	Mode
8 Female	48	48,5	58
12 Male			

Table 2. Average age of II group (Irrigation with 0,2% chlorhexidine gluconate)

Average age	Mean	Median	Mode
7 Female	51,95	54	54
13 Male			

Table 3. DPI - I group - Irrigation with ozonated water (before and after treatment)

	DPI - I group (irrigation with ozonated water, before and after treatment)					
	1	2	Total			
N	20	20	40			
∑X	41	5	46			
Mean	2.05	0.25	1.15			
$\sum X^2$	89	5	94			

Std.Dev.	0.5104	0.4443	1.0266			
Source	***SS***	***df***		***MS***		
Between-treatments	32.4	1		32.4	$F = 141.51724$ $p < 0$ .00001	
Within-treatments	8.7	38		0.2289		
Total	41.1	39				

Table 4. IGI - I group- Irrigation with ozonated water (before and after treatment)

	IGI - I group (irrigation with ozonated water, before and after treatment)					
	1	2	Total			
N	20	20	40			
∑X	41	4	45			
Mean	2.05	0.2	1.125			
$\sum X^2$	91	4	95			
Std.Dev.	0.6048	0.4104	1.0667			
Result Details						
Source	***SS***	***df***		***MS***		

Between-treatments	34.225	1	34.225	$F = 128.13301$ $p < 0\ .00001$
Within-treatments	10.15	38	0.2671	
Total	44.375	39		

Table 5. PPD - I group - Irrigation with ozonated water (before and after treatment)

	PPD - I group (irrigation with ozonated water, before and after treatment)					
	1	2	Total			
N	20	20	40			
∑X	66	52	118			
Mean	3.3	2.6	2.95			
$\sum X^2$	230	154	384			
Std.Dev.	0.8013	0.9947	0.9594			
Result Details						
Source	***SS***	***df***	***MS***			
Between-treatments	4.9	1	4.9	$F = 6.00645$ $p < 0.018967$		
Within-treatments	31	38	0.8158			
Total	35.9	39				

Table 6. CAL - I group - Irrigation with ozonated water (before and after treatment)

	CAL - I group (irrigation with ozonated water, before and after treatment)					
	1	2	Total			
N	20	20	40			
∑X	69	61	130			
Mean	3.45	3.05	3.25			
$\sum X^2$	269	223	492			
Std.Dev.	1.2763	1.3945	1.3349			

Result Details

Source	***SS***	***df***	***MS***	
Between-treatments	1.6	1	1.6	*F* = 0.89543 *p* < 0.349988
Within-treatments	67.9	38	1.7868	
Total	69.5	39		

Table 7. DPI - II group - Irrigation with 0,2% chlorhexidine gluconate (before and after treatment)

	DPI - II group (irrigation with chlorhexidine, before and after treatment					
	1	2	Total			
N	20	20	40			
∑X	46	15	61			
Mean	2.3	0.75	1.525			
$\sum X^2$	110	21	131			
Std.Dev.	0.4702	0.7164	0.9868			

Result Details

Source	***SS***	***df***	***MS***	
Between-treatments	24.025	1	24.025	$F = 65.44444$ $p < 0\ .00001$
Within-treatments	13.95	38	0.3671	
Total	37.975	39		

Table 8. IGI - II group - Irrigation with 0,2% chlorhexidine gluconate (before and after treatment)

	IGI -II group (irrigation with 0,2% chlorhexidine, before and after treatment)					
	1	2	Total			
N	20	20	40			
∑X	43	14	57			
Mean	2.15	0.7	1.425			
$\sum X^2$	97	18	115			
Std.Dev.	0.4894	0.6569	0.9306			
Result Details						
Source	***SS***	***df***	***MS***			
Between-treatments	21.025	1	21.025	$F = 62.66275$ $p < 0$ .00001		
Within-treatments	12.75	38	0.3355			
Total	33.775	39				

Table 9. PPD - II group - Irrigation with 0,2% chlorhexidine gluconate (before and after treatment)

	PPD - II group (irrigation with chlorhexidine, before and after treatment)					
	1	2	Total			
N	20	20	40			

∑X	79	75	154			
Mean	3.95	3.75	3.85			
$\sum X^2$	323	295	618			
Std.Dev.	0.7592	0.8507	0.8022			

Source	***SS***	***df***	***MS***	
Between-treatments	0.4	1	0.4	*F* = 0.61539 *p* < 0.437631
Within-treatments	24.7	38	0.65	
Total	25.1	39		

Table 10. CAL - II group - Irrigation with 0,2% chlorhexidine gluconate (before and after treatment)

	CAL II group (irrigation with chlorhexidine, before and after treatment)					
	1	2	Total			
N	20	20	40			
∑X	79	75	154			
Mean	3.95	3.75	3.85			
$\sum X^2$	323	295	618			
Std.Dev.	0.7592	0.8507	0.8022			

Source	*SS*	*df*	*MS*	
Between-treatments	0.4	1	0.4	$F = 0.61539$ $p < 0.437631$
Within-treatments	24.7	38	0.65	
Total	25.1	39		

Table 11. DPI, IGI, PPD, CAL differences between two treatments (irrigation with ozonated water and chlorhexidine gluconate) (Wilcoxon Signed-Ranks Test)

Among the groups	Positive sign count	Negative sign count	Total count	*Z - score*	*P - value*
DPI	3	10	13	1.94145	0.052
IGI	1	9	10	2.529	0.011
PPD	3	10	13	1.94145	0.052
CAL	5	11	16	1.5	0.133

Discussion

The onset and progression of periodontal disease is caused by various bacterial accumulations in the subgingival pockets. The elimination of pathogenic subgingival microflora can be achieved mechanically. However, the chronic course of the disease requires additional treatment, necessitating the use of various antimicrobial agents, either systemically or locally, to complement the conservative treatment, in order to maintain the results of the initial therapy for a longer period.[9]

Subgingival irrigation is the most common method of applying antimicrobial agents, whether performed by professionals or patients themselves. Antiseptics can deactivate bacteria in two ways: physical-chemical damage to the components of the cell surface, followed by damage to intracellular constituents and disruption of their function, or direct disruption of intracellular functions without damaging surface structures.

Both, chlorhexidine and ozone act on the same principle, disrupting the integrity of the microbial cell wall, thereby damaging cell components. Chlorhexidine gluconate is a cationic biguanide with a broad spectrum of already proven antibacterial effects against both gram-positive and gram-negative bacteria, as supported by numerous studies. However, its use is burdened with some side effects (brown staining of dental structures, taste sensitivity, allergic reactions, etc.).

On the other hand, the use of ozone is a new option for periodontal pocket irrigation with antimicrobial action, without the tendency to develop side effects, due to its ability to oxidize microbial cell components. Ozone becomes highly reactive and quickly decomposes when it contacts water, generating hydroxyl radicals, which are among the most active oxidizing species.

Water ozonates show high biocompatibility with fibroblasts, cementoblasts, and epithelial cells. Its biological effects include immune stimulation, immunomodulation, anti-inflammatory action, biosynthetic, bioenergetic, anti-hypoxic, analgesic, and hemostatic effects.

Various studies confirm the positive effects of irrigation with both chlorhexidine and ozone. Our study aimed to compare the effects of 0.2% chlorhexidine, as a well-established subgingival antibacterial irrigant, with the effects of subgingival

irrigation with ozonated water in the treatment of chronic periodontal disease.

Conclusion

Irrigation of gingival tissue with ozonated water leads to changes in plaque composition, resulting in reduced inflammationand faster regeneration of gingival tissue, confirming its antimicrobial and anti-inflammatory effects. The use of ozone as a subgingival irrigant is a simple and painless adjunct in non-surgical periodontal treatment. However, there is still a need for high-level evidence, such as well-designed double-blind randomized clinical studies, to justify its routine use. Therefore, clinical application of ozone has not yet achieved its effectiveness, and its cost-effectiveness remains to be proven.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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REGULATORNI ASPEKTI PREPARATA ZA ISPIRANJE USTA: SLUČAJ REPUBLIKE SEVERNE MAKEDONIJE

REGULATORY ASPECTS OF MOUTHWASHES: THE CASE OF REPUBLIC OF NORTH MACEDONIA

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Sažetak

Uvod: *S obzirom na to rastvori za ispiranje usta mogu izazvati neželjene efekte, pacijenti i zdravstveni radnici treba da prijave neželjene događaje nacionalnim institucijama. Da bi se osigurala bezbednost ovih proizvoda i olakšalo prijavljivanje neželjenih događaja, neophodno je da pacijenti i zdravstveni radnici budu svesni regulatornog statusa proizvoda koji je odgovoran za neželjeni događaj.*
Cilj *ovog rada bio je da se ispita regulatorni status preparata za ispiranje usta dostupnih na tržištu u Republici Severnoj Makedoniji.*
Materijali i metode*: Istraživanje tržišta je sprovedeno u Republici Severnoj Makedoniji, pokrivajući i tradicionalna i onlajn tržišta. Preparati za ispiranje usta su kupljeni direktno od prodavaca, Imena robnih marki proizvoda i regulatorne informacije naznačene na njihovoj ambalaži su dokumentovane.*
Rezultati: *U vreme sprovođenja ovog istraživanja na tržištu Republike Severne Makedonije bilo je dostupno ukupno 76 preparat za ispiranje usta. Većina njih (n=71, 93,43%) je klasifikovana kao kozmetički proizvodi, dok su 3 (3,94%) kategorisani kao lekovi, a 2 (2,63%) kao medicinski proizvodi. Utvrđena je statistički značajna razlika između broja preparata za ispiranje usta klasifikovanih kao kozmetički proizvodi i onih registrovanih kao lekovi ili medicinski uređaji.*
Zaključak: *Bez obzira na njihovu klasifikaciju, sve preparate za ispiranje usta moraju biti u skladu sa nacionalnim i međunarodnim bezbednosnim standardima pre stavljanja na tržište i moraju biti podvrgnute budnosti nakon stavljanja na tržište tokom normalne ili razumno predvidive upotrebe.*

Ključne reči: *preparati za ispiranje usta, regulacija, medicinski uređaji, kozmetika, bezbednost*

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Abstract

Background: *Considering that mouthwashes can cause side effects, patients and healthcare professionals should report adverse events to national authorities. To ensure the safety of these products and facilitate the reporting of adverse events, it is essential for patients and healthcare professionals to be aware of the regulatory status of the product responsible for the undesirable event.*
The aim *of this paper was to examine the regulatory status of mouthwashes available on the market in the Republic of North Macedonia.*
Materials and Methods: *A market survey was conducted in the Republic of North Macedonia, covering both traditional and online markets. Mouthwashes were purchased directly from vendors. The brand names of the products and the regulatory information indicated on their packaging were documented.*
Results: *A total of 76 mouthwashes were available on the market in the Republic of North Macedonia at the time of conduction of this research. Most of these (n=71, 93.43%) were classified as cosmetic products, while 3 (3.94%) were categorized as medicines, and 2 (2.63%) as medical devices. A statistically significant difference was found between the number of mouthwashes classified as cosmetic products and those registered as medicines or medical devices.*
Conclusion: *Regardless of their classification, all mouthwashes must comply with national and international safety standards prior to market placement and must be subject to post-market vigilance during normal or reasonably foreseeable use.*

Key words: *mouthwashes, regulation, medical devices, cosmetics, safety*

Introduction

Oral hygiene plays a crucial role in the prevention of many oral diseases, including periodontitis, tooth decay, and oral candidiasis. To prevent oral diseases, proper oral hygiene must be practiced ensuring the mouth, gums, and teeth are healthy[1]. Many scientific studies show a connection between oral health and cardiovascular diseases, diabetes, and even death[2,3]. To prevent caries formation and periodontal disease, effective oral hygiene should be performed, plaque should be removed and plaque formation should be prevented[4].

Throughout history, various products have been used to maintain oral hygiene. These include toothbrushes and toothpaste, mouthwashes, dental floss, miswak (chewing sticks), and toothpicks[5]. Patients and dentists are faced with different oral hygiene products. A consumer's choice regarding the appropriate product may be influenced by personal motives or advice from healthcare professionals, media advertisements, brand, the credibility of the company manufacturing the product, ingredients, availability of product information, and physical properties of products, such as their taste, flavor, color, and appearance, which are also influencing factors [6–10].

In the last few decades, mouthwashes and rinses have significantly expanded and developed as a category of oral care products [11]. A mouthwash is defined as a non-sterile aqueous solution used mostly for its deodorant, refreshing, or antiseptic effect. Mouthwashes or rinses are designed to reduce oral bacteria, remove food particles, temporarily reduce bad breath, and provide a pleasant taste[12].

The first known reference for using mouthwashes for the treatment of diseases of the gums is found in Chinese medicine, around 2700 BC[13]. The Egyptians were the first to put emphasis on a clean and healthy body and mixed water with honey to maintain good breath[14]. Later, in the Greek and Roman periods, mouth rinsing following mechanical cleaning became common among the upper classes, and Hippocrates recommended a mixture of salt, alum, and vinegar, while Pythagoras recognized the freshening effect of anise. Different products have been used for mouth rinsing over the centuries. In the 1500s, wine or beer was used; in the late 19th century, around 1890, the use of essential oils was introduced among dental care habits[15].

Today, on the market, there are numerous mouthwashes. There are many ingredients in mouthwashes, including oral health substances, solvents, surfactants and thickeners, sweeteners, plants (extracts, waters, and oils), preservatives, colorants, flavoring or cooling agents, and others. Some of the ingredients are not associated with medical benefits but are necessary for the creation of formulas, while some mouthwashes contain one or more active ingredients, like fluorine compounds, cetylpyridinium chloride, chlorhexidine, benzydamine hydrochloride, etc.[16,17]. The complex compounds of modern oral health products, including mouthwashes, make them one of the most sophisticated pharmaceutical products on the market today [11].

Mouthwashes can be used for therapeutic, diagnostic, and cosmetic purposes. Examples of therapeutic mouthwashes include allopurinol for treating stomatitis, pilocarpine for xerostomia, and nystatin for oral candidiasis. Toluidine blue mouth rinse is used as an adjunct tool for the detection of oral malignant and premalignant lesions[18]. Cosmetic mouthwashes (e.g., phenol and mint mouthwashes) may be used for refreshing purposes. Other topical mouthwashes include antiplaque (e.g., cetylpyridinium chloride) and fluorinated mouthwashes[19].

However, mouthwashes can be associated with undesirable effects or adverse events[20–22]. The most frequently reported adverse events were local morphological (oral mucosa and dental crown staining, mucosal lesions) and functional (taste modifications, abnormal oral sensation) alterations[22].

Considering that mouthwashes can cause side effects, patients or healthcare professionals must report adverse events to national authorities. To report adverse events and guarantee the safety of the products, it is necessary for patients and healthcare professionals to know the regulatory status of the product that caused the undesirable event, as well as the national competent authorities responsible for the vigilance of specific products. Specifically, depending on the regulatory status of the product, there are differences in terms of post-marketing surveillance of the products.

Aim

The aim of the paper was to examine the regulatory status of mouthwashes available on the market in the Republic of North Macedonia.

Materials and Methods

Between January 1, 2024, and July 1, 2024, market research was conducted in the Republic of North Macedonia. This research encompassed traditional markets (pharmacies, cosmetic chains, and consumer goods markets)

as well as the online market. Four researchers (VK, KI, SS, and BP) carried out this research aiming to identify all available mouthwashes. One to three packs of each mouthwash were purchased directly from vendors without requesting free samples from manufacturers or importers. Mouthwashes were selected based on the following inclusion criteria: intended for maintaining oral hygiene, preventing oral diseases, or having a therapeutic effect; available over-the-counter; and in the pharmaceutical forms of either a solution intended for direct use or a concentrate to be dissolved in water, regardless of their regulatory status (medicine, medical device, cosmetic product). The exclusion criteria included: tablets that dissolve in water or other liquids, chewing tablets, and saliva substitutes; products containing antibiotics, steroids, parasympathomimetic saliva stimulants, topical local anesthetics, and other prescription drugs; liquids taken orally but not intended for maintaining oral hygiene; liquids in the form of sprays, toothpastes, gels, powders, foams, homeopathic products, and products without a fully available composition.

Two researchers (VK and SS) recorded the brand names of the products and labeled the packaging information regarding regulatory status in an Excel spreadsheet. The authors considered national legislation related to the labeling of medicinal products, medical devices, and cosmetic products. Additionally, a review of the Register of Medicinal Products and Medical Devices maintained by the Agency for Medicines and Medical Devices of the Republic of North Macedonia (MALMED) was conducted. The other two authors (KI and BP) validated the data provided by VK and SS.

Frequency analysis of the regulatory status was performed using Microsoft Excel v. 2016 (Microsoft Corporation, Redmond, Washington, United States) and SPSS Statistics v. 23 for Windows (IBM Corp., Armonk, NY), while the difference between the proportions of means was analyzed using the Difference Test in StatSoft STATISTICA v. 12.5 (StatSoft, Inc., Tulsa, Oklahoma, United States).

Results

There were 76 mouthwashes available on the market in the Republic of North Macedonia at the time of the conduction of this research. A comprehensive list of these mouthwashes with their regulatory status is shown in Table 1:

Most of the available mouthwashes (n = 71, 93.43%) were cosmetic products, while 3 were classified as medicine (3.94%) and 2 as a medical device (2.63%) (Table 2).

There was a statistically significant difference between the available mouthwashes classified as cosmetic products compared to those registered as medicines and medical devices, Difference test ($p < 0.001$).

Table 1. List of available mouthwashes and their regulatory status

	Commercial name	**Regulatory status**
1	Alkmene Tea Tree Mouthwash	Cosmetic product
2	Alur Care Mouthwash Cool Mint	Cosmetic product
3	Alverde Pro Climate 5 in 1 Mundspülung	Cosmetic product
4	Aquafresh Big Teeth Mouthwash	Cosmetic product
5	Aquafresh Fresh & Minty	Cosmetic product
6	Astera Total All-in-One	Cosmetic product
7	Ben & Anna Natural Mouthwash Sensitive	Cosmetic product
8	Betadine Gargle	Medicine product
9	Bilka Dent Expert Classic Parodont Protect	Cosmetic product
10	Bilka Homeopathy Grapefruit Mouthwash	Cosmetic product
11	Colgate Cool Mint	Cosmetic product
12	Colgate Max White	Cosmetic product

13	Colgate Plax ICE	Cosmetic product
14	Colgate Plax Soft Mint	Cosmetic product
15	Colgate Plax White + Charcoal	Cosmetic product
16	Cosmos Organic People Mouthwash Coconut & Mint	Cosmetic product
17	Curaprox Perio Plus + Protect CHX 0.12	Cosmetic product
18	Curaprox Perio Plus Balance CHX 0.05	Cosmetic product
19	Curaprox Perio Plus Forte CHX 0.20	Cosmetic product
20	Curaprox Regenerate CHX 0.09	Cosmetic product
21	Doctor's Anti-Tartar Mouthwash	Cosmetic product
22	Doctor's Herbal Mouthwash	Cosmetic product
23	Doctor's Mint Mouthwash	Cosmetic product
24	Doctor's Propolis Mouthwash	Cosmetic product
25	Doctor's Smokers Mouthwash	Cosmetic product
26	Dontodent Junior Lerneffekt - spülung	Cosmetic product
27	Dontodent Junior Mund - spülung	Cosmetic product
28	Dontodent Neue Rezeptur Mundwasser Konzentrat	Cosmetic product
29	Dontodent Protect & Care 10 in 1 Rundumschutz	Cosmetic product
30	Dontodent Sensitive Intensiv - Schutz	Cosmetic product
31	Dontoent Zahnfleisch Intensiv - Pflege	Cosmetic product
32	Dr. Silver Mouthwash Total Care	Cosmetic product
33	Eco Denta Refresh & Protect Mouthwash	Cosmetic product
34	Edel+White Fresh+Protect	Cosmetic product
35	Elmex Caries Protection	Cosmetic product
36	Elmex Sensitive	Cosmetic product
37	ESI Aloe Fresh Collutorio	Cosmetic product
38	FrezyDerm Plaque & Tartar Mouthwash	Cosmetic product
39	FrezyDerm Sensitive Teeth Mouthwash	Cosmetic product
40	Gengigel Oral Solution	Medical device
41	Green Fresh Concentrate Mouthwash	Cosmetic product
42	Intermed Chlorhexil 0.12% Mouthwash	Cosmetic product
43	Intermed Chlorhexil Extra 0.20% Mouthwash	Cosmetic product
44	Intermed Kids Mouthwash	Cosmetic product
45	Intermed Unisept Mouthwash	Cosmetic product
46	Lacalut Aktiv	Cosmetic product
47	Lacalut Flora	Cosmetic product
48	Lacalut Micellar Sensitive Mouthwash	Cosmetic product

49	Lacalut Micellar Tartar Protection Micellar Water	Cosmetic product
50	Lacalut Micellar Whitening Mouthwash	Cosmetic product
51	Lacalut Multi-Effect Micellar Mouthwash	Cosmetic product
52	Lacalut Sensitive	Cosmetic product
53	Lacalut white	Cosmetic product
54	Limes Rosa Fresh Concentrate	Cosmetic product
55	Listerine Advanced Defence Sensitive	Medical device
56	Listerine Advanced White Mouthwash Mild Taste	Cosmetic product
57	Listerine Cool Mint	Cosmetic product
58	Listerine Fresh Burst	Cosmetic product
59	Listerine Green Tea Mild Taste	Cosmetic product
60	Listerine Natural Enamel protect	Cosmetic product
61	Listerine Naturals Sabor Suave	Cosmetic product
62	Listerine Smart Rinse	Cosmetic product
63	Listerine Teeth & Gum Defence	Cosmetic product
64	Listerine Total Care Clean Mint 6 in 1	Cosmetic product
65	Listerine Total Care Clean Mint 6 in 1 Mild Taste	Cosmetic product
66	Listerine Total Care Tartar Protect	Cosmetic product
67	Maxlab Silver Water	Cosmetic product
68	Natura Siberica Plaque Control & Fresh Breath	Cosmetic product
69	Natura Siberica Strong Teeth & Gums	Cosmetic product
70	Natura Siberica Whitening & Enamel Protection	Cosmetic product
71	Oral-B Gum & Enamel Care Fresh Mint	Cosmetic product
72	Oral-B Pro-Expert	Cosmetic product
73	Oralsept	Medicine product
74	Parodont Active	Cosmetic product
75	Parodontax Active Gum Health	Cosmetic product
76	Stomatidin	Medicine product

Table 2. Regulatory status of available mouthwashes

Regulatory status	**Number (percent)**
Cosmetic products	71 (93.43%)
Medicine products	3 (3.94%)
Medical devices	2 (2.63%)
Total	**76 (100%)**

Discussion

The term *oral hygiene product* is relatively new and describes mechanical devices and chemical compounds designed to provide the user with oral health and cosmetic benefits. The potential major health value of such oral hygiene products is the prevention of plaque-related diseases, such as caries, gingivitis, and periodontitis. The primary cosmetic benefits are breath refreshing and extrinsic stain control. Given the long-term history of oral hygiene products, control over the chemical compounds (products) and scientific evaluation of efficacy are very recent matters. Medicine laws in many countries demand extensive toxicological data on the ingredients used in oral hygiene products[23].

The cosmetics industry is one of the most dynamically developing sectors globally [24] and together with the pharmaceutical industry, they have a major contribution to human well-being[25].

As a result of many incidents throughout history, regulatory bodies have introduced new laws and guidelines that improve the quality, safety, and efficacy of medical products[26]. Their goal is to ensure that the products deliver their intended benefits without causing harm, which requires a meticulous and multifaceted approach to regulatory control[27].

The qualification of a substance-based product as a medicinal product, a medical device, or a cosmetic product can be challenging, with several products being considered borderline. Different regulatory authorities have their own specific set of regulations for the registration, approval, and control of the ingredients of these products[28–30].

Our study shows that most of the available mouthwashes on the market in the Republic of North Macedonia are classified as cosmetic products, which is consistent with national legislation where dental and oral care products are considered cosmetic products[31]. The National Law on Safety of Cosmetic Products defines a cosmetic product as any substance or product intended to be applied to various external parts of the human body (epidermis, hair, nails, lips, and external genital organs, or to the teeth and the mucous membranes of the oral cavity), for cleaning, perfuming, altering appearance, correcting body odors, and/or protecting or maintaining them in good condition[32].

A similar definition is given by Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, where a cosmetic product is defined as any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair, nails, lips, and external genital organs) or with the teeth and the mucous membranes of the oral cavity, with the exclusive or primary aim of cleaning, perfuming, altering appearance, protecting, maintaining them in good condition, or correcting body odors[33]. The Regulation defines an oral product as a cosmetic product intended to be applied to the teeth or the mucous membranes of the oral cavity[33]. This act recognizes mouthwashes as oral products.

To ensure compliance through the single market regarding the categorization of products, the European Commission has published a series of guidelines and guides for the demarcation of products between cosmetic products and other product categories, to determine whether a product falls within the definition of Regulation 1223/2009 on cosmetic products. Namely, sometimes it is unclear whether a certain product, based on its characteristics and function, can be categorized as a cosmetic product according to the regulations governing cosmetic products or if it falls under other sectoral regulations. The European Commission published certain guidelines to facilitate the application of EU legislation, which include Guides on the scope of application of Regulation 1223/2009 on cosmetic products and Guides between the legislation of cosmetic products and biocides and medicines. While these guidelines are not legally binding, they serve to help categorize products. According to some documents, a mouthwash that presents antibacterial or antiseptic claims can be qualified as a cosmetic product, a biocidal product, or a medicinal product. A decision on the qualification of the products must be made by the national competent authorities on a case-by-case basis, taking into account all relevant elements, such as the presentation of the products, the ingredients, the mode of action, and the claims [34].

Sometimes, mouthwashes can be qualified as medical devices[35]. Our study shows that two of the commercially available mouthwashes (Gengigel Oral Solution, and Listerine Advanced Defense Sensitive) are classified as medical devices. The Regulation 2017/745 on medical devices (MDR) determines that devices composed of substances or combinations of substances intended to be introduced into the human body via a body orifice or applied to the skin, and

that are absorbed by or locally dispersed in the human body, are classified as class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, achieving their intended purpose in those cavities[36]. These mouthwashes found in the Macedonian market are also classified as medical devices in Serbia[37], Croatia[38], Bosnia and Herzegovina[39], and other regional countries.

Three out of the 76 mouthwashes were classified as medicinal products. These mouthwashes contain one of the following active substances: povidone-iodine, benzydamine, or hexetidine. According to the drug register maintained by the Agency for Medicines and Medical Devices (MALMED), these products are available without a prescription[40]. Povidone-iodine has antiseptic properties[41], while benzydamine possesses anti-inflammatory properties[42], and hexetidine also possesses antiseptic properties[43]. Marketing authorizations for medicines and medical devices intended for human use are fundamentally granted by a competent regulatory authority in the form of an official approval (license) for a specified time period. This authorization is based on a rigorous and comprehensive evaluation process that assesses scientific, clinical, quality, and cost-effectiveness factors[44].

In the USA, the Federal Food, Drug, and Cosmetic Act defines two main categories of products: cosmetics and drugs. The latter includes a sub-category of over-the-counter (OTC) drugs, which can be sold without a prescription[45]. The United States Food and Drug Administration has established guidelines indicating that mouthwashes with potential therapeutic properties should be registered as drugs rather than cosmetics[46]. The American Dental Association employs a dichotomous approach to mouthwash usage, classifying them as either cosmetic or therapeutic based on the presence or absence of a chemically active ingredient. Cosmetic mouthwashes are those that lack bactericidal or bacteriostatic properties and are primarily used for temporarily masking symptoms such as bad breath. These products are typically sold over the counter (OTC) and do not require a prescription for purchase, including some of the previously mentioned natural mouthwashes. Essential oil-containing antimicrobial mouthwashes are recognized as clinically effective against plaque and gingivitis and are also available OTC. Therapeutic mouthwashes, in contrast, contain active ingredients such as cetylpyridinium chloride, chlorhexidine, fluoride, or hydrogen peroxide, which provide antimicrobial effects. These mouthwashes must be dispensed by prescription, are intended for short-term use, and are designed to treat specific conditions. Research indicates that therapeutic mouthwashes can be effective in managing oral health issues[47,48].

Similarly, in Canada, products can be categorized as either cosmetics or over-the-counter (OTC) drugs, with natural health products (NHP) considered a subset of drugs. Japan features a unique categorization system, where beauty products are divided into two categories: cosmetics and quasi-drugs. In Australia, toothpaste and oral hygiene products are regulated as either therapeutic goods or cosmetics, depending on factors such as how the product is advertised, the claims made, its intended use, and its ingredients[49].

Nevertheless, regardless of their categorization, all cosmetic products, medicinal products, and medical devices placed on the market must be safe. In the Republic of North Macedonia, according to the Law on Medicines and Medical Devices, the Agency for Medicines and Medical Devices (MALMED) is mandated to establish and maintain a pharmacovigilance and materiovigilance system. The current law defines materiovigilance as a system designed to detect, collect, monitor, evaluate, and ensure the appropriateness of new safety data concerning medical devices and potential incidents of use. Pharmacovigilance is defined as a system applied to detect, collect, monitor, evaluate, and ensure the appropriateness of new safety data regarding medicines and their interactions. The Agency for Medicines and Medical Devices (MALMED) is responsible for establishing and maintaining the pharmacovigilance and materiovigilance systems. The pharmacovigilance and materiovigilance system for the holder of the marketing authorization for a medicine or medical device is organized by the responsible personnel of the marketing authorization holder[50]. Additionally, the rulebook on the method of reporting side effects during the use of medical devices outlines the types of reactions they can cause, the actions required from health professionals and suppliers, and the organization of the system for monitoring side effects and reactions from medical devices [51]. For cosmetic products, national regulations stipulate that only cosmetic products that fully meet safety requirements can be placed on the market. Cosmetic products that are imported must meet the safety requirements established

by law. The manufacturer placing the product on the market is responsible for the safety of the cosmetic product. The legal or physical entity conducting the marketing of the product is responsible for maintaining the product's safety in terms of storage methods and shelf life. Oversight of the application of the law is conducted by the Ministry of Health, while the State Sanitary and Health Inspectorate performs the inspection oversight regarding the implementation of the law[32].

EU law mandates that every marketing authorization holder, national competent authority, and the European Medicines Agency (EMA) establish and maintain a pharmacovigilance system. The overarching EU pharmacovigilance system functions through cooperation among EU Member States, the EMA, and the European Commission. In certain Member States, regional centers operate under the coordination of the national competent authority[52]. The Medical Device Regulation (MDR) was established as a new certification framework that imposes additional requirements, such as the obligation for manufacturers to designate a specific role within their organization responsible for regulatory compliance. It also introduces stricter measures, including enhanced post-market surveillance and vigilance, reflecting the evolving global medical device market. Specifically, these new requirements are designed to ensure user safety through improved transparency and better traceability of medical devices[53]. In addition, cosmetic products marketed in the European Union (EU) are held to high standards of safety and quality. Undesirable effects arising from the normal or reasonably foreseeable use of cosmetic products are rare, typically mild, and completely reversible. Companies have established procedures to respond effectively to reports of undesirable effects, which include recording, assessing, and understanding their nature to prevent future occurrences. This process is crucial for companies as it enhances post-marketing surveillance of cosmetic products and their performance in the marketplace. The primary objective of post-marketing surveillance is to protect consumer health by monitoring the incidence of undesirable effects (UE) and minimizing the risk of their reoccurrence. The evaluation of Serious Undesirable Effects (SUEs) includes the dissemination of information that can be utilized to prevent their recurrence or to mitigate the consequences of such effects. The EU Cosmetovigilance System aims to ensure a direct, prompt, and harmonized implementation of these actions across EU Member States, as opposed to addressing issues on a country-by-country basis. This system enhances the ability to manage and respond to undesirable effects effectively throughout the European Union[54].

Considering that the majority of mouthwashes available on the market in the Republic of North Macedonia are classified as cosmetic products, the question arises whether this classification is accurate and if their safety is guaranteed. In our view, the cosmetics industry has been striving for global regulatory harmonization over the past few decades. Mouthwashes are deemed safe and, thus, should be classified as cosmetic products. However, with the increasingly demanding and evolving global regulatory landscape, there is a pressing need for heightened vigilance among companies and manufacturers to ensure compliance. The significance of post-market surveillance, reporting adverse effects, addressing non-compliance, and implementing enforcement measures against responsible parties (such as withdrawing non-compliant products from the market or imposing financial penalties) cannot be overstated.

Conclusion

Most of the mouthwashes available on the market in the Republic of North Macedonia are classified as cosmetic products. Regardless of their classification, it is essential for mouthwashes to meet both national and international safety standards before being placed on the market. Additionally, ongoing vigilance is required following normal or reasonably foreseeable use of these products.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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SPECIFIČNOSTI ORALNOHIRURŠKE REHABILITACIJE PACIJENATA SA POSEBNIM POTREBAMA U OPŠTOJ ANESTEZIJI

SPECIFICITIES OF ORAL SURGICAL REHABILITATION OF PATIENTS WITH SPECIAL NEEDS UNDER GENERAL ANESTHESIA

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Sažetak

Uvod: *Osobe sa posebnim potrebama imaju dugotrajna fizička, mentalna, intelektualna ili senzorna oštećenja koja mogu ometati njihovo puno i efektivno učešće u društvu. Visoka učestalost oralnih bolesti je veoma česta kod ove populacije i oni posećuju stomatologa kada je potrebno hitno lečenje.*
Cilj: *Ova studija je imala za cilj da izvrši analizu stomatoloških tretmana osoba sa posebnim potrebama u opštoj anesteziji na Klinici za stomatološku medicinu u Nišu u roku od tri godine, sa posebnim osvrtom na njihovo oralno-hirurško lečenje.*
Materijali i metode: *Retrospektivnom studijom obuhvaćeni su pacijenti sa posebnim potrebama kojima je urađena restauracija zuba u opštoj anesteziji na Klinici za stomatološku medicinu u Nišu u periodu od tri godine od 1. decembra 2021. do 1. decembra 2024. Prikupljeni su demografski podacima o pacijentima, kao i oni o njihovom zdravstvenom stanju uz datum obavljanja.*
Rezultati: *U datom periodu, u opštoj anesteziji je lečeno 124 pacijenata sa posebnim potrebama, uzrasta 29,31 ± 5,59 godina i oba pola skoro podjednako zastupljena. Kod 74,2% njih istovremeno su rađene i konzervativna restauracija i oralna hirurška restauracija zuba, 4,03% je podvrgnuto samo konzervativnoj restauraciji, a 21,77% samo oralno-hirurškom lečenju. Svaki pacijent je imao u proseku 9,04 ± 5,56 popravljenih zuba sa stopom koja je značajno veća za ekstrahovane nego konzervativno popravljene zube (p = 0,007).*
Rezultati: *Stomatološki tretman pacijenata sa posebnim potrebama se uglavnom obavlja u zdravstvenim ustanovama na tercijarnom nivou, u opštoj anesteziji i praćen je višestrukim vađenjem zuba.*
Zaključak: *Uključivanje ovih pacijenata u sisteme stomatološkog monitoringa bi znatno olakšalo upravljanje njihovim stomatološkim problemima i smanjilo broj urgentnih stomatoloških tretmana, kao i rehabilitaciju u opštoj anesteziji.*

Ključne reči: *posta anestezija, osobe ometene u razvoju, stomatoloska zastita*

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Abstract

Introduction: *People with special needs have long-term physical, mental, intellectual or sensory impairments that can hinder their full and effective participation in society. A high frequency of oral diseases is very common in this population and they visit the dentist when it is necessary to provide urgent treatment.*
Aim: *This study aimed to perform an analysis of the dental treatments among people with special needs provided under general anesthesia at the Clinic for Dental Medicine in Niš within three years, with special reference to their oral surgical treatment.*
Materials and methods: *The retrospective study involved patients with special needs who underwent a tooth restoration under general anesthesia at the Clinic for Dental Medicine in Niš within three years from December 1, 2021 to December 1, 2024. Demographic data on patients as well as the ones on their health status along with the date of dental intervention, type and reference number of dental services provided under general anesthesia were collected.*
Results: *During the given period, 124 patients with special needs, within the age range 29.31 ± 5.59 and both genders nearly equally represented were treated under general anesthesia. In 74.2% of them, both conservative restoration and oral surgical restoration of teeth were performed at the same time, 4.03% underwent only conservative restoration and 21.77% only oral surgical treatment. Each patient had an average of 9.04 ± 5.56 repaired teeth with rate which is significantly higher for extracted than conservatively repaired teeth (p = 0.007).*
Results: *Dental treatment of patients with special needs is mainly provided in health care institutions at the tertiary level, under general anesthesia and is accompanied by multiple tooth extractions.*
Conclusion: *The inclusion of these patients in dental monitoring systems would make it much easier to manage their dental problems and decrease the number of urgent dental treatments as well as general anesthesia rehabilitation.*

Key words: *general anesthesia, developmentally disabled persons, dental care*

Introduction

Based on the United Nations Convention, people with special needs have long-term physical, mental, intellectual or sensory impairments that, in interaction with various obstacles, can hinder their full, efficient and equal participation in society[1]. It is estimated that people with special needs make up about 16% of the overall global population[2]. Unfortunately, there is no official data on their number or the official register available in our country.

People with special needs are at high risk when it comes to the occurrence of all oral diseases. Numerous epidemiological studies indicate that people with special needs have an extremely high prevalence of untreated caries and gingival periodontal diseases, which inevitably lead to numerous complications such as pain, swelling, and early tooth loss[3–6]. The aforementioned complications have a negative impact on the performance of the masticatory apparatus of these people, whose basic diseases are often accompanied by changes in the level of the orofacial region, such as macroglossia, the structure and number of teeth disorders, severe orthodontic irregularities. As a result, such changes create a very negative impact on qualityof life of these people; furthermore, it affects quality of life of their family members/guardians[7,8].

People with special needs encounter numerous barriers when it comes to providing adequate dental care. These barriers related to providing dental care are divided into physical and non-physical[9] based on the dentist's point of view, guardian's perspective and finally, the perspective of the patients themselves. As a rule, this population functions within its primary families, even though a significant number reside in specialized institutions and custody; unfortunately some of them live alone[10]. In the literature, what seems to be the main obstacles for people with special needs are the dentists' insufficient preparedness to help these people, structural problems related to accessibility to dental offices, difficulties in communication, lack of awareness to conduct dental treatments and insufficient number of specialized dental services. Moreover, due to the inadequate cooperation with the patients in a regular dental office, it is very often impossible to diagnose mouth and dental diseases using standard dental procedures as well as diagnostic imaging of the teeth. For this reason, these patients visit the dentist when urgent dental treatment is indicated, which, due to the impossibility of adequate cooperation with the patient as well as numerous associated ailments, is carried out in dental health care units of the tertiary level. In Serbia, one such institution is The Clinic of Dental Medicine in Niš, a highly-specialized, stationary, specialist and consultancy-oriented healthcare unit in the Serbian healthcare system for the territory of south Serbia and as such it provides healthcare dental services on the tertiary level. Based on the population census conducted in 2022, this institution provides services for the population of 1,406,050 from south and east Serbia but also for patients coming from other parts of the country.

Aim

Having in mind all the above mentioned facts, this study aimed to analyze the dental treatment of people with special needs provided under general anesthesia at the Clinic for Dental Medicine in Niš during a period of three years, with special reference to the oral surgical treatment of these patients.

Materials and Methods

A retrospective study was conducted at the Dental Clinic in Niš during the three months from December 1, 2021 to December 1, 2024, and included patients with special needs who underwent tooth restoration under general anesthesia. The study involved only adults with special needs treated under general anesthesia during the specified period (Aproval of Ethical Comitee 14/7-2023-2 EO). Based on the patients' dental records, their demographic data (gender, date and place of birth, permanent residence), as well as the data on patients' health status along with the date, type and number of dental interventions provided under general anesthesia were collected.

Statistical data processing was conducted in the MC Excel program. Within the framework of descriptive statistics, numerical data are presented with measures of central tendency (mean value) and measures of variability (standard deviation). Attributive features are presented in the form of absolute and relative numbers. The comparison of numerical variables was performed with the T-test, and the results were considered significant for $p < 0.05$. The obtained results are presented through charts and graphs.

Results

During the analyzed period, a total of 124 patients with special needs of approximate gender representation (52.4% male and 47.6% female) underwent dental treatment under general anesthesia at the Clinic for Dental

Medicine in Niš. The average age of the respondents for the analyzed three-year period was 29.31 ± 5.59. The biggest portion of rehabilitated patients was within 20 to 30 age range. Also, the biggest portion of rehabilitated patients came from related institutions while smaller number was settled in primary families. Basic demographic characteristics of patients are shown in Table 1.

All analyzed patients with special needs had a mental disorder of varying degrees of severity accompanied by cerebral paralysis, epilepsy, diseases of the cardiovascular system or some syndromes such as Down's syndrome.

The biggest portion of people with special needs, 56 of them, was rehabilitated in the period from December 1, 2022 to November 30, 2023 which is 45.16% of the total number of patients included in the analysis (Figure 1). X-ray imaging as part of the pre-operational preparation of the patients was only possible in 24% of the examined patients.

December 1, 2021–November 30, 2024
December 1, 2023–November 30, 2024
December 1, 2022–November 30, 2023
December 1, 2021–November 30, 2022

Table 1. Basic demographic characteristics of patients

	Male N (%)	Female N (%)	18–20 age range N (%)	21–30 age range N (%)	Over 31 age range N (%)
Dec. 1, 2021–Nov. 30, 2022	15 (48.4%)	16 (51.6%)	2 (6.5%)	17 (54.8%)	12 (38.7%)
Dec. 1, 2022–Nov. 30, 2023	33 (58.9%)	23 (41.1%)	2 (3.6%)	38 (67.8%)	16 (28.6%)
Dec. 1, 2023–Nov. 30, 2024	17 (46%)	20 (54%)	6 (16.2%)	25 (67.6%)	6 (16.2%)
Total	65 (52.4%)	59 (47.6%)	10 (8.1%)	80 (64.5%)	34 (27.4%)

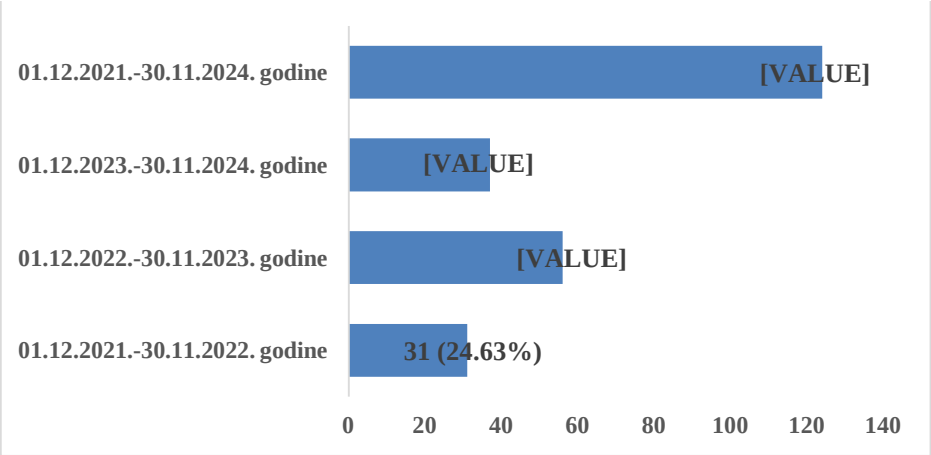

Figure 1. Distribution of the number of treated patients during the analyzed period

As part of the dental restoration, each patient underwent the removal of soft and hard dental deposits using standard methods before providing the indicated dental interventions. In the biggest portion of examined patients (74.2%), both conservative tooth restoration and oral surgical tooth restoration were performed under general anesthesia. Only conservative tooth restoration was performed in 4.03 patients, while only oral surgical treatment was provided for 21.77% of analyzed patients (Figure 2).

Oral surgical rehabilitation
Conservative rehabilitation
Conservative and oral surgical rehabilitation

In each patient, an average of 9.04 ± 5.56 teeth were rehabilitated (Table 2). There were significantly more extracted than conservatively rehabilitated teeth (p = 0.007). In each patient, on average, 3.09 ± 3.24 teeth were rehabilitated conservatively, and 5.23 ± 5.05 teeth were extracted. The biggest portion of patients had between 5 and 10 teeth for

conservative restoration and extraction—44.71% of them, while 31.72% of the examined patients had more than 10 teeth for conservative and surgical restoration. Twenty-three point fifty-seven percent of examined patients had up to 5 teeth for rehabilitation (Table 3). When it comes to oral surgical interventions, three patients underwent surgical removal of impacted teeth, while one patient had apicectomy of two teeth and the other patients underwent tooth extraction (Figure 4).

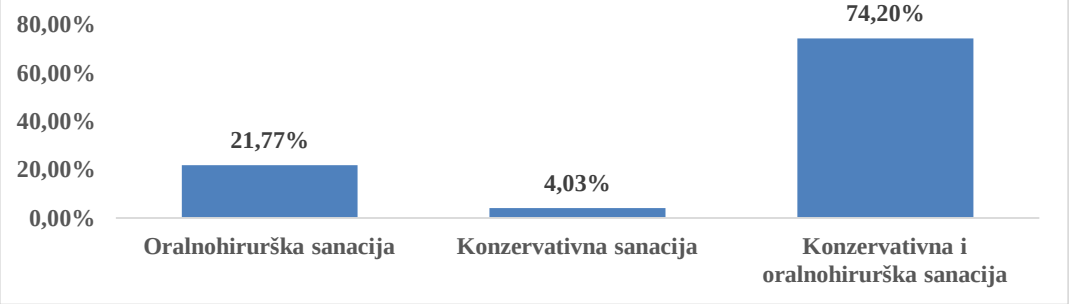

Figure 2. Dental interventions performed under general anesthesia in the analyzed group of patients

	Average number of repaired teeth **AS ± SD***	Average number of extracted teeth **AS ± SD***	Average number of conservatively repaired teeth **AS ± SD***
Dec.1, 2021–Nov. 30, 2022	8.64 ± 5.91	4.64 ± 5.23	3.71 ±. 61
Dec.1. 2022–Nov.30. 2023	8.82 ± 6.06	5.49 ± 5.32	3.68 ± 3.04
Dec.1. 2023–Nov. 30. 2024	9.48 ± 4.77	5.18 ± 4.41	4.29 ± 3.20
Total	9.04 ± 5.56	5.23 ± 5.05**	3.09 ± 3.24

*AS ± SD—arithmetic mean ± standard deviation;
** significantly more than the average number of conservatively repaired teeth (p = 0.007)

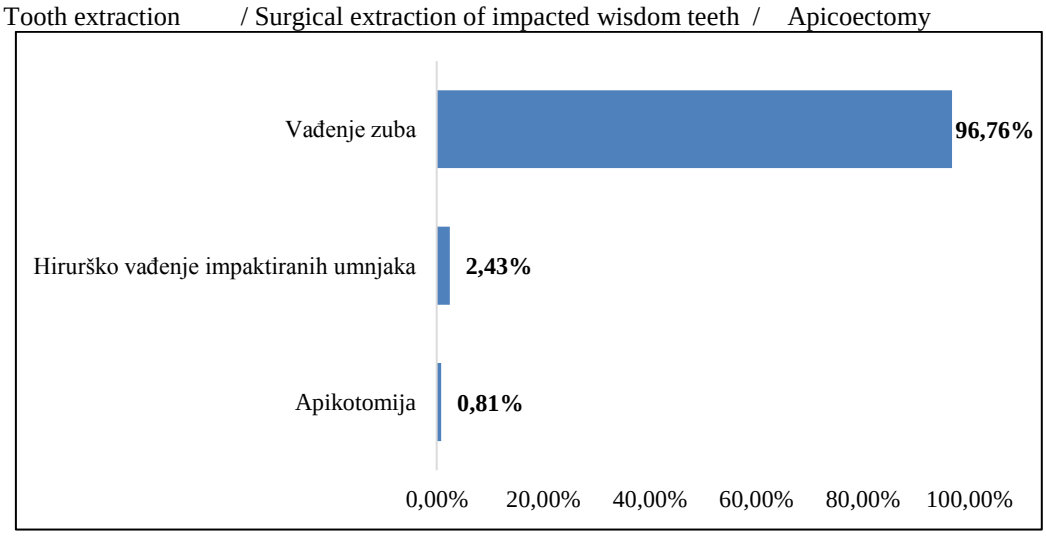

Figure 3. Oral surgical interventions performed under general anesthesia

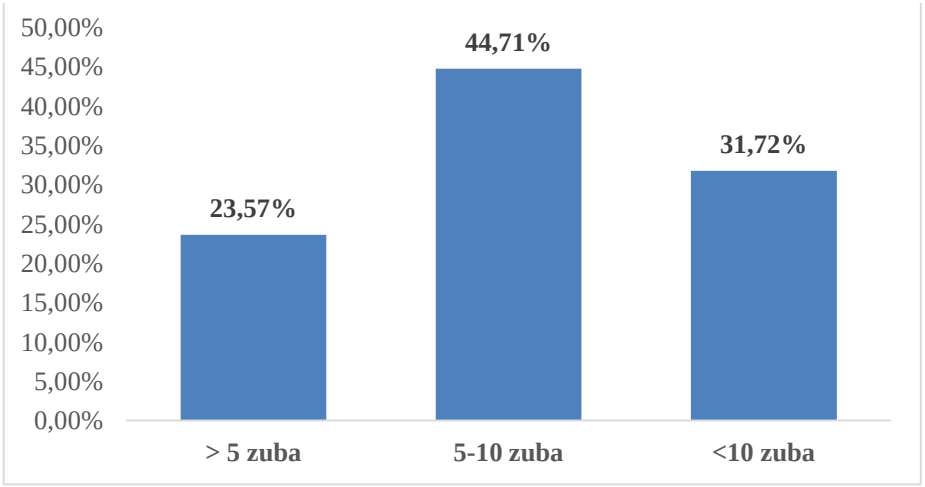

Figure 4. Distribution of the number of teeth for rehabilitation under general anesthesia in analyzed group of patients

Discussion

It is not a rare case that dental treatments for people with special needs is a big challenge in dental practice. Due to the numerous barriers that dentists encounter in working with this population, it is often impossible to perform a dental examination of the patient and radiological imaging to establish a diagnosis and determine and provide adequate therapy. On the other hand, these patients seek help from a dentist in the stage of advanced oral diseases, accompanied by numerous complications including pain and swelling and at the point where emergency treatment is the treatment of choice. When this is the case, restoration of a larger number of teeth is generally indicated. Due to the nature of the underlying disease, a tooth restoration in outpatient settings is often impossible, and these patients are treated dentally under general anesthesia, which entails a radical approach to the therapy of oral diseases, and tooth extraction is often the only therapeutic option. For the above-mentioned reason, the aim of this study was to analyze the dental treatment of people with special needs, provided under general anesthesia at the Clinic for Dental Medicine in Niš during a period of three years, with a special focus on the oral surgical treatment of these patients.

The results obtained in this study indicate a poor state of dental health within the population involved in the study, where each analyzed patient had an average of 9.04 ± 5.56 teeth restored under general anesthesia, with significantly more extracted than conservatively restored teeth. In addition, in as many as 21.77% of patients, only tooth extraction was performed without conservative rehabilitation. About 31% of the examined patients had more than 10 teeth repaired under general anesthesia. Such results confirm that even in our community, the help of a dentist is sought at the moment when urgent surgical treatment is indicated, when tooth extraction is the only therapeutic option and when it is necessary to restore a large number of teeth.

The study found that the average age range of the examined patients was 29.31 ± 5.59 and that the largest number of subjects belonged to the age group between 21 and 30. Taking into account the results obtained by the study that a high percentage of extracted teeth were registered in this group of respondents, it can be concluded that people with special needs face significant teeth loss very early and/or often are completely toothless, with poor chances for an adequate prosthetic rehabilitation. Some other authors also came to this cnclusion[11−13]. Generally speaking, such results do not come as a surprise; on the contrary, they are expected. In the group of patients with special needs, a high plaque index and solid dental plaque index are often present as the main indicators of poor oral hygiene as the main etiological factor of caries and gingival-periodontal diseases[14,15].

On the other hand, orthodontic anomalies in this group are very frequent[16]. Apart from this, numerous factors such as the impossibility of performing oral hygiene, the use of various drugs that affect the flow of saliva, the specifics of the diet and lifestyle of these people, the fact that their guardians are mainly focused on dealing with basic health problems explain the fact that oral health care remains neglected[17–20]. To all this, we should add the above-mentioned barriers regarding the adequate assessment of these patients at the primary level of dental health care and the unavailability of specialized services that would prevent the occurrence of oral diseases, i.e., timely therapeutic action to preserve the oral health of this group of patients. Furthermore, a significant problem is the patients with special needs' incapacity to cooperate with the dental team, which makes it difficult to carry out a routine examination and diagnosis of oral diseases. One more fact that should be mentioned is the radiological imaging of these patients which is difficult or even impossible. Therefore a tooth extraction is the therapeutic procedure of choice even when it comes to teeth in the frontal region[21]. In this study, only two teeth required apicoectomy during the observed period. However, it is likely that this number would have been significantly higher if orthopantomogram imaging had been performed for each subject.

Notwithstanding previously mentioned, there is some optimism in the fact that many dentists believe that the dental treatment of people with special needs is difficult, but worthy, and that a prevailing percentage of dentists show emotional concerns during the dental treatment of people with special needs[22,23]. Therefore, it is very important that at the primary level people with special needs have access to dental care and to insist on early diagnosis of oral diseases in this population and timely therapy of oral diseases. This seems to be the only way to avoid the early loss of a large number of teeth people with special needs often face and to improve their quality of life related to oral health.

Conclusion

Very few people with special needs have access to primary dental care. In addition, there is a lack of specialized dentists and dental practices that would provide dental services to this population without any obstacles. Moreover, in our region, the biggest portion of these people are in institutional custody. For this reason, people with special needs undergo dental care mainly in the institutions at the tertiary level of dental health care, where, due to the patient's incapacity to cooperate and the large number of associated diseases they have, a tooth restoration is performed under general anesthesia followed by the extraction of a large number of teeth. Therefore, one of the optimal solutions that could be considered is the inclusion of these people in dental monitoring systems and programs, which would significantly facilitate the management of dental problems among these patients and reduce or nearly completely exclude the possibility of urgent dental treatments and dental rehabilitations of these patients under general anesthesia.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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BISFOSFONATIMA IZAZVANA OSTEONEKROZA VILICA POZNATA PATOLOŠKA POJAVA ILI NE?

BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAW – KNOWN PATHOLOGYCAL ENTITY OR NOT?

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Sažetak

Uvod: *Pojava novih terapijskih mogućnosti za onkološke, autoimune i reumatološke pacijete, dovela je do značajnog poboljšanja kvaliteta njihovog života. Ipak, kako su ovi paciejnti na dugoročnoj terapiji lekovima koji pokazuju neželjena dejstva, uporedo sa prevencijom pogoršanja osnovne bolesti, javlja se novi patološki prblem u vilicama, takozvana bisfosfonatna osteonekroza viličnih kostiju(BRONJ).*
Cilj *ove epidemiološke studije bio je da se utvrdi koliki je procenat stomatologa u Severnoj Makedoniji upoznat sa pojavom, problemima i komplikacijama koje prate pacijente koji koriste terapiju koja može izazvati bisfosfonatne lezije vilica, kao i mogćnost prepoznavanja bisfosfonatne osteonekroze vilica.*
Materlijal i metode: *Istraživanje je sprovedeno u Republici Severnoj Makedoniji, u ukupno 100 stomatoloških ordinacija u periodu od jula do avgusta 2024.godine. Anketa je sardžala 10 pitanja o informisanosti i načinu informisanosti lekara, kao i sposobnostima prepoznavanja osteoneekroze vilica i lečenja bisfosfonatima izazvane osteonekroze vilica.*
Rezultati: *Od ukupno 100 podeljenih anketa, 35 stomatologa je vratilo popunjene upitnike, odnosno, 35% stomatologa je želelo da učestvuje u anketiranju. Od tog broja 68,5% nije do sada čulo za pojavu bisfosfonatne osteonekroze vilica. Od 31,5% koji su imali saznanja o ovoj patološkoj pojavi, 60% saznalo od kolega, 25% na kontinuiranoj medicinskoj edukaciji,15% iz literature. 88,5% stomatologa ne zna da li i koji lekovi mogu da dovedu do BRONJ, dok 68,5% ne postavlja anamnestička pitanja vezano za stanja u kojim se ovi lekovi korite. Osamdeset procenata stomatologa ne poznaje bilo kakve preventivne niti terapijske mere za BRONJ.*
Zaključak: *Mali procenat stomatologa Severne Makedonije ima znanje o BRONJ-u. Informisanost o pojavi, preventivi i lečenju trebalo bi da se poveća, kroz programe kontinuirane medicinke edukacije, kao i kroz ostale vidove dobijanja stručnih saznanja.*

Ključne reči: *osteonekroz**a**, BRONJ, edukacija*

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Abstract

Introduction: *The appearance of new therapeutic options for oncologycal, and rheumatological patients has led to a significant improvemen in their quality of life. These patients are on long-term therapy with drugs that show unwanted effects, along with the prevention of worsening of the underlying disease, a new pathological problem in the jaws appears, the so-called bisphosphonate related osteonecrosis of the jaw bones (BRONJ).*
The aim *of this epidemiological study was to determine the percentage of dentists in North Macedonia who are aware of the occurrence, problems and complications that accompany patients BRONJ as well as the ability to recognize it.*
Material and methods*: The research was conducted in the Republic of North Macedonia, in a total of 100 dental practices. The survey included 10 questions about the information and the way doctors were informed, as well as the ability to recognize osteonecrosis of the jaws and treatment of osteonecrosis of the jaws caused by bisphosphonates.*
Results: *Out of a total of 100 distributed surveys, 35 dentists returned completed questionnaires, i.e., 35% of dentists wanted to participate in the survey. Of the total of 35 processed questionnaires, 68.5% have not heard of the occurrence of bisphosphonate osteonecrosis of the jaws. Of the 31.5% who had knowledge of this pathological phenomenon, 60% learned from colleagues, 25% during continuing medical education, 15% from the literature. 88.5% do not know whether and which drugs can lead to BRONJ, while 68.5% do not ask anamnestic questions about the conditions in which these drugs are used. troughs. Eighty percent of dentists do not know any preventive or therapeutic measures for BRONJ.*
Conclusion: *A small percentage of dentists in North Macedonia have knowledge about BRONJ. Awareness of occurrence, prevention and treatment should be increased, through programs of continuous medical education, as well as through other ways of obtaining professional knowledge.*

Key words: *osteonecrosis**,** BRONJ, education*

Introduction

For the first time, osteonecrosis of the jaws as a consequence of therapy was definitively associated with radiotherapy, with the initial paper on radioosteonecrosis published in 1922.[1]. Nearly a century later, in 2003[2], studies began to emerge regarding the negative effects of bisphosphonate therapy. This phenomenon has since been termed Bisphosphonate-Related Osteonecrosis of the Jaws -BRONJ[3].

Bisphosphonates are potent antiresorptive agents. The primary objective of antiresorptive therapy is to prevent pathological fractures in bones weakened by primary and secondary bone diseases, most commonly osteoporosis and oncological conditions. First documented in the literature in 2003[2], Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) was characterized as avascular, aseptic necrosis of the jaw resulting from pharmacological agents that disrupt normal bone metabolism. Interestingly, a similar condition, historically known as "Phosphorus jaw," was observed in the nineteenth century among match factory workers[4].

Bisphosphonates were first synthesized in 1865 in Germany for use in the agricultural industry[5]. Their role in bone resorption became widely recognized in the 1960s. More than fifty years have passed since the biological effects of bisphosphonates in thet period termed as diphosphonates—were first described in Science and Nature in 1969[6]. Bisphosphonates possess two key characteristics: a strong affinity for bone minerals and the ability to inhibit osteoclast activity. Extensive evaluation of nitrogen-containing bisphosphonates during the 1980s and 1990s led to a pivotal discovery: the antiresorptive effects of these advanced analogues primarily result from their potent inhibition of the enzyme farnesyl diphosphate synthase[7].

Bisphosphonates (BPs) are classified into two main groups based on their chemical composition and mechanism of action. Nitrogen-free bisphosphonates (low potency), such as etidronate and clodronate, disrupt ATP-dependent intracellular pathways, leading to osteoclast apoptosis. In contrast, nitrogen-containing bisphosphonates (high potency), including pamidronate, alendronate, ibandronate, and zoledronate, exert their effects by inhibiting key enzymes in the mevalonate biosynthetic pathway. The elucidation of the enzyme's crystal structure has demonstrated that nitrogen-containing bisphosphonates bind to its active site via their critical nitrogen atom, effectively inhibiting key enzymes in the mevalonate biosynthetic pathway. This inhibition disrupts osteoclast function and survival, leading to a substantial reduction in bone resorption. As a result, nitrogen-containing bisphosphonates have become highly effective therapeutic agents in the management of osteoporosis, metastatic bone disease, and other conditions associated with excessive bone turnover[3].

Bisphosphonates form a strong bond with osteoclasts, initially inhibiting their apoptosis. However, once apoptosis occurs, these agents remain embedded in the bone matrix, integrating into the surrounding bone and exerting cumulative effects that can persist for 5 to 12 years[8]. The retention of bisphosphonates in the skeleton is closely linked to bone turnover, as their release is dependent on the rate of bone remodeling.

Pathological remodeling arises when there is an imbalance between bone resorption and formation, or when both processes occur excessively. Notably, jawbones have a significantly higher metabolic turnover compared to long tubular bones, rendering them particularly vulnerable to the effects of bisphosphonates. Consequently, the majority of bisphosphonate-related osteonecrosis of the jaw (BRONJ) cases occur following tooth extraction or minor surgical interventions, poorly adapted prosthesis that causes pressure on the soft and bone tissue, poor dental fillings that can create periodontal pockets.

All these facts highlight the extremely potent effects of bisphosphonates, surpassing even the impact of radiation therapy on bone metabolism. Due to their strong affinity for bone and prolonged retention in the skeletal system, bisphosphonates play a crucial role in the management of various pathological conditions affecting bone health. Bisphosphonates are widely used in the treatment of osteoporosis, osteomalacia, osteogenesis imperfecta, and Paget's disease, as well as endocrine disorders that influence bone metabolism. Additionally, they are employed in oncology for both primary bone malignancies (e.g., multiple myeloma, sarcoma, and thyroid cancer) and metastatic bone disease arising from cancers such as prostate, breast, and lung cancer. The reported prevalence of BRONJ varies significantly, ranging from 3% to 20%, depending on factors such as dosage, duration of therapy, and patient-specific risk factors[9].

Certain criteria must be met to classify a condition as Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)[10]. According to established definitions, the diagnosis requires the following conditions to be fulfilled: History of bisphosphonate use (either oral or intravenous administration); Presence of non-healing intraoral or extraoral fistula or exposed necrotic bone in the maxillofacial region persisting for more than 8

weeks; No history of radiation therapy in the head and neck region; Absence of metastatic tumors or other malignancies affecting the jaw.

These criteria help distinguish BRONJ from other osteonecrotic conditions, such as radiation-induced osteonecrosis or tumor-related bone destruction.

The appearance of BRONJ can be staged in four stages from 0 to 3.[10] dependant of bone exposure, symptoms and infection.

Stage 0 represents an asymptomatic phase during which there is no clinically visible bone exposure; In approximately 50% of patients, bone exposure subsequently occurs within 1–7 months, most commonly around 4–5 months[9,10]. Stage 1 is characterized by the presence of an area of exposed necrotic bone or a fistula. Generally, patients in this phase remain asymptomatic and do not exhibit any signs of inflammation or infection. Stage 2 is characterized by clearly exposed necrotic bone, accompanied by an intraoral fistula, pain, and impaired oral function. This stage is invariably associated with inflammatory signs and infection in the surrounding soft tissues. Stage 3 is advanced stage, the necrotic area extends beyond the alveolar ridge to involve the base of the mandible; alternatively, it may extend into the maxillary sinus or affect the zygomatic process of the maxilla. Typically, extraoral fistulas, as well as oroantral or oronasal communications, are observed. Additionally, spontaneous detachment of small fragments of necrotic bone may occur,as well as pathological bone fractures[10].

Factors influencing on appearance of BRONJ are :the dose, type and length of therapy; oral health enlightenment – awareness of the importance of oral hygiene; geographical area - Scandinavian countries have more patients with osteoporosis due to lack of sunny days[11]; socioeconomic status - regulation of the health system in the country and knowledge of medical doctors and dental doctors about the possibility of appearance of BRONJ.

The aim of this study was to assess the awareness of dentists in the Republic of North Macedonia regarding the potential development of osteonecrosis of the jaw as a consequence of bisphosphonate therapy.

Materials and Methods

The study was conducted from 1 July to 1 August 2024 in 100 private dental practices in the Republic of North Macedonia. The assessment of knowledge regarding BRONJ was carried out using a questionnaire comprising 10 questions addressing the occurrence of osteonecrosis of the jaw in relation to bisphosphonate therapy.

Questionnaire Content:

1. How many complications related to difficult wound healing after tooth extraction do you experience per month/year?
2. During anamnesis, do you routinely inquire if patients are currently undergoing or have previously received treatment for malignant diseases?
3. What is the recommended minimum period before initiating radiation therapy during which it is safe to perform tooth extraction?
4. Are you aware of any oncological therapies, aside from radiation and chemotherapy, that negatively affect the healing of extraction wounds?
5. During anamnesis, do you routinely ask patients if they suffer from osteoporosis or other bone system disorders?
6. During anamnesis, do you routinely ask patients about the specific therapies they use to treat osteoporosis or other bone system disorders?
7. Are you knowledgeable about the drugs used in treating osteoporosis and bone malignancies?
8. Have you heard of bisphosphonate therapy?
9. Have you ever encountered the association between bisphosphonate therapy and lesions in the jawbones?
10. How did you first receive information regarding the relationship between jaw changes and the use of bisphosphonate therapy?

After the completion and return of the questionnaires, the data were processed and the results were presented in percentages.

The Resluts

Out of a total of 100 private dental practices where the questionnaire was administered, as many as 65 were not motivated to complete it, i.e. 35% questionares were assesed. The primary reason for dentist`s demotivation cited was a lack of knowledge regarding the answers to most of the questions.

Among the remaining 35 completed questionnaires, findings indicated that approximately 25% of tooth extractions resulted in complications related to the healing process, meaning that every fourth extraction exhibited prolonged or difficult healing (Figure 1). During patient anamnesis, 65% of dentists

reported inquiring about medication use, whereas 35% did not (Figure 2). Regarding the time considered safe for extraction wound healing, only 14% correctly identified a period of three or more weeks (Figure 3).

Concerning oncological therapies, 72% of dentists were unaware of any treatment other than radiation therapy that could affect jawbone healing (Figure 4). Additionally, 63% of dentists did not ask patients about their bone health regarding osteoporosis during anamnesis (Figure 5), while 68.5% failed to inquire whether patients were taking medications for bone diseases (Figure 6). Alarmingly, 89% of dentists could not identify which medications might impact bone metabolism (Figure 7). Furthermore, 68.5% had never heard of bisphosphonate therapy (Figure 8).

Approximately 80% of dentists were unable to recognize or manage bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Figure 9). Moreover, 58% had never heard of osteonecrosis of the jaw at all. Among the small proportion of informed dentists (35%), 60% reported learning about BRONJ from colleagues, 15% through the academic literature, and 25% via continuing medical education (Figure 10). (Green color-yes, Orange- No)

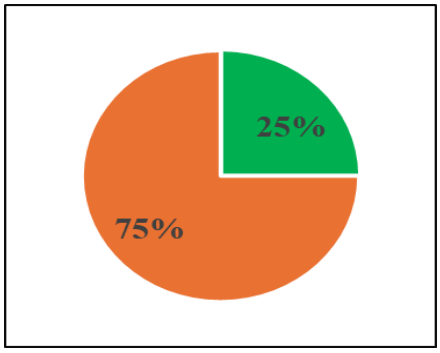

Figure 1. The presence of complications after tooth extraction

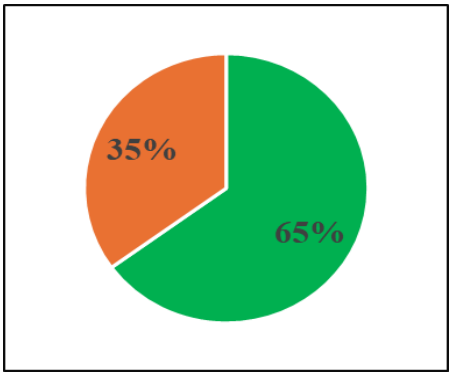

Figure 2. The percent of dentists who take data on oncology and bone diseases

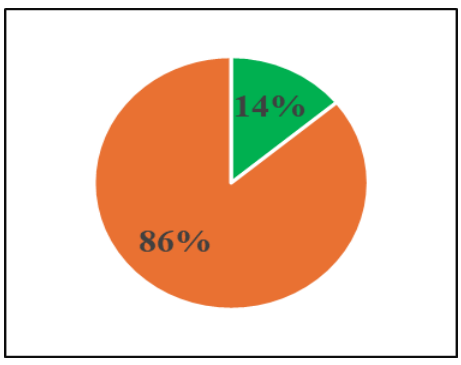

Figure 3. The knowledge of dentists about timely tooth extraction before radiation therapy

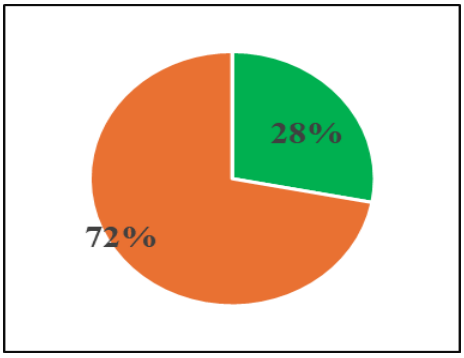

Figure 4. The knowledge of dentists about any therapy (excluding radiation) that disturbs post extraction wound healing

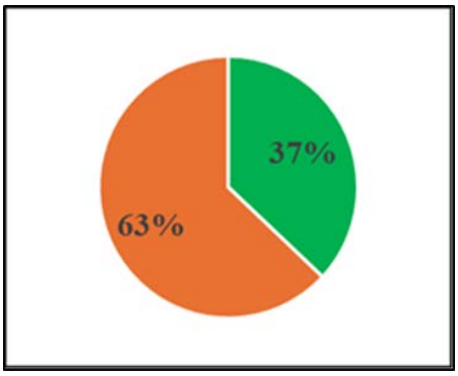

Figure 5. The percentage of dentists taking detailed data about bone diseases

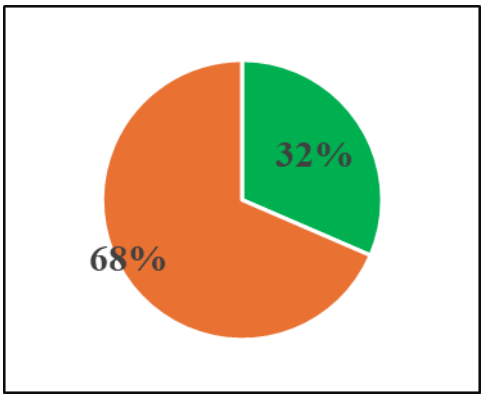

Figure 6. The percentage of dentists taking data about consuming medication for osteoporosis and bone diseases

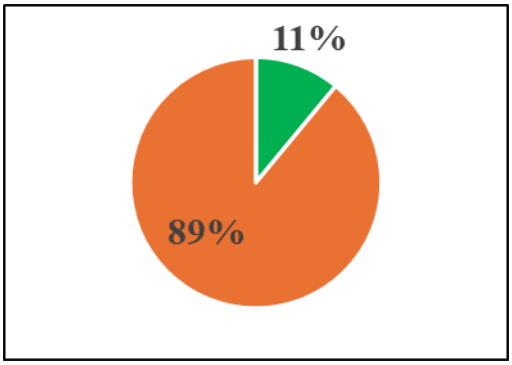

Figure 7. Knowledge about medications for osteoporosis and malignancy treatment

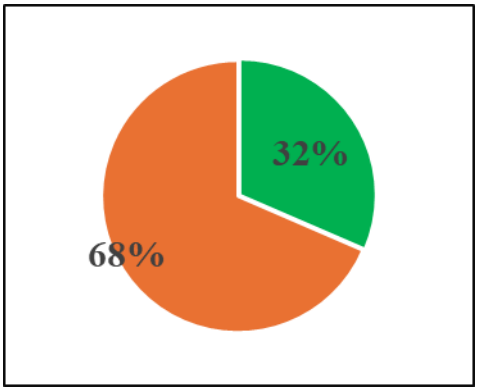

Figure 8. The percetage of dentists never heard about bisphosphonate therapy

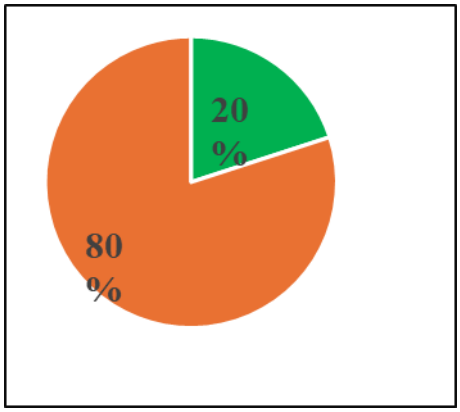

Figure 9. The percetage of dentists able to recognize BRONJ

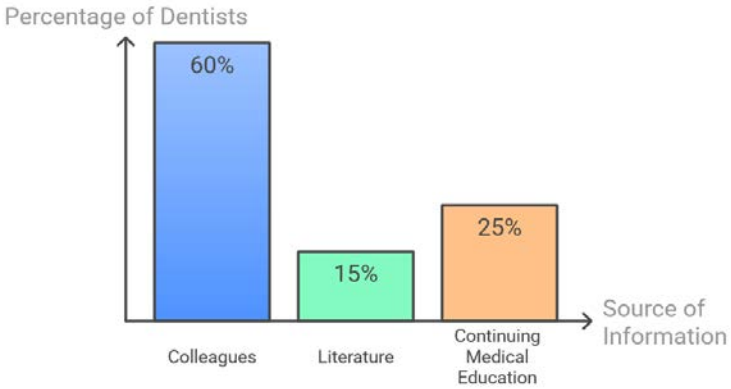

Figure 10. Sources of awareness about BRONJ among dentists

Discussion

Antiresorptive agents, specifically bisphosphonates, exhibit a high affinity for osteoclasts, influencing their differentiation and promoting apoptosis. By integrating into the bone matrix, bisphosphonates exert a prolonged cumulative effect on bone remodeling and healing. The suppression of osteoclastic activity, which is responsible for bone resorption, consequently leads to a reduction in osteoblastic function, thereby impairing bone formation. Additionally, bisphosphonates induce alterations in the microstructure of bone tissue, leading to vascular disturbances that compromise bone circulation and nutrient supply[12].

The emergence of novel therapeutic options for oncological and rheumatological patients has significantly enhanced their quality of life. Bisphosphonate therapy plays a crucial role in regulating bone conditions and resorption associated with primary or metastatic tumors, as well as advanced osteoporosis[13].

In women, the most common indications for bisphosphonate use, which may lead to

bisphosphonate-related osteonecrosis of the jaw (BRONJ), include osteoporosis and bone metastases from breast cancer (73% of cases metastasize to the bones) and uterine cancer (29%)[14]. Notably, 78% of postmenopausal women aged ≥50 years present with osteopenia and/or osteoporosis, with one in three experiencing osteoporotic fractures. In Macedonia, the female population is approximately 1,000,000 (average age ≥40). In men, bisphosphonate therapy is primarily indicated for bone metastases from malignant tumors, most commonly prostate cancer (68%), lung cancer (36%), and kidney cancer (22%)[14,15]. Additionally, around 20% of men over 50 years of age have osteoporosis. The male population of Macedonia is estimated at approximately 870,000 (average age ≥42).

The fact that 80% of dentists are not aware of the possibility of osteonecrosis of the jaw as a result of medication use, and that 69% of dentist had never heard about bisphosphonate therapy. In total of 100 examined dentists, only 35 were motivated to participate in the study. Also discouraging fact was that 35% of dentists do not take a complete medical history that includes systemic and oncological diseases, or appropriate information about their therapy. Osteoporosis can cause problems itself, even if it was not treated with bisphosphonates.

The pathophysiology of BRONJ remains incompletely understood. It is widely considered multifactorial, involving a complex interplay of mechanisms. Key contributing factors include impaired physiological bone remodeling, persistent inflammation and infection, inhibition of angiogenesis, and dysfunction of both innate and acquired immunity. These factors collectively compromise bone homeostasis and wound healing, predisposing affected individuals to osteonecrosis[16].

Interventions that contribute to the development of BRONJ include procedures that directly involve jawbone tissue, such as tooth extractions, implant placement, periodontal pocket curettage, and periapical surgeries. Additionally, interventions that result in mucosal damage, compromising the integrity of the oral soft tissues, may also increase the risk of BRONJ. To avoid BRONJ it is essential to conduct a comprehensive medical and dental history assessment, along with a thorough clinical examination and the necessary radiographic imaging.

General Medical History should obtain detailed insight into systemic diseases and ongoing pharmacological treatments, data about oncology treatment. Dentists should be aware that radiation therapy in the chest region can cause partial irradiation of the mandible and salivary glands. Xerostomia is a predisposing factor for the occurrence of BRONJ. Cytotoxic drugs induce xerostomia by directly damaging the salivary glands, whereas anticholinergic agents inhibit salivary secretion by disrupting neural stimulation. Additionally, diuretics contribute to dehydration and increased excretion of bodily fluids, further exacerbating dry mouth[17].

Dental history and examination should obtain an assessment of any changes in sensitivity, vitality, postponed wound healing, the appearance of fistula formation (onset, etiology), periodontal probing, percussion sensitivity, evaluation of the presence of periodontitis, soft tissue inflammation and infections. Cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), may contribute to the development of osteonecrosis of the jaw by exacerbating inflammation and enhancing bone resorption[18].

Bisphosphonates are anticipated to have applications beyond their conventional role as antiresorptive agents. Emerging research suggests their potential use as vectors for targeted drug delivery into the skeletal system, capitalizing on their high affinity for bone mineral[19].

The indications for the use of bisphosphonate therapy are expanding, while awareness of the risks associated with this type of therapy in some regions remains very low[20].

Conclusion

Dentists are responsible for raising awareness about bisphosphonate-related osteonecrosis of the jaw, as well as other medical doctors. Nurses can also play role in facilitating communication between physicians and dentists, ensuring coordinated patient care. This responsibility implies educating of medical stuff through continuous professional edukation, including seminars, ongoing training, and other educational opportunities.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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TRETMAN STALNOG CENTRALNOG SEKUTIĆA SA TALONOVOM KVRŽICOM: SLUČAJ POGREŠNE DIJAGNOZE I ODLOŽENOG LEČENJA

MANAGEMENT OF A PERMANENT MAXILLARY CENTRAL INCISOR WITH A TALON CUSP: A CASE OF MISDIAGNOSIS AND TREATMENT DELAY

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Sažetak

Uvod: *Prisustvo talon kvržice je važno za diferencijalnu dijagnozu jer se može pomešati sa drugim dentalnim anomalijama, kao što je fuzija zuba. Pogrešna dijagnoza može dovesti do odloženog ili neodgovarajućeg lečenja, što može izazvati dalje komplikacije.*
Prikaz slučaja*: Zdrava 7-godišnja devojčica je upućena oralnom hirurgu na lečenje zbog strukture nalik zubu u prednjoj maksilarnoj regiji. Dijagnostikovana je fuzija desnog maksilarnog centralnog sekutića sa meziodensom, ali je konačni tretman odložen dok se razvoj korena ne završi. Na snimku kompjuterizovane tomografije sa konusnim snopom (CBCT), napravljenom na kontrolnom pregledu dve godine kasnije, uočena anatomija zuba nije odgovarala početnoj dijagnozi. Pacijentkinja je prvo upućena na endodontsku terapiju, a kasnije, sa napunjenih 11 godina, na Univerzitetsku stomatološku kliniku. Desni maksilarni centralni sekutić je imao izraženu, dobro omeđenu akcesornu kvržicu na palatinalnoj površini koja se protezala do nivoa incizalne ivice, na prvi pogled, nalik na spojeni meziodens. Dodatna kvržica je stvorila okluzalnu interferenciju sa labijalnim pomeranjem zahvaćenog zuba, što je rezultiralo kompromitovanom dentalnom estetikom i povećanim rizikom od traume zuba.*
Rezultati: *Postavljena je dijagnoza palatinalne kvržice sa rogom pulpe prema unutra. Shodno tome, rog pulpe je skoro potpuno eliminisan u četiri posete u periodu od šest meseci, dajući kruni normalnu morfologiju. Ovaj tretman omogućio je adekvatan prostor za ortodontsku retrakciju zuba.*
Zaključak:*Stomatolozi bi trebalo da budu svesni kliničkih karakteristika talonove kvržice i njenog radiografskog izgleda da bi postavili tačnu dijagnozu i pružili odgovarajući tretman.*

Ključne reči*: Talonova kvržica, dentalna morfologija, dentalna anomalija, stalni maksilarni sekutić, diferencijalna dijagnoza*

Abstract

Background: *The presence of talon cusp is important for differential diagnosis as it can be confused with other dental anomalies, such as fusion of teeth. Misdiagnosis can lead to delayed or inappropriate treatment, which may cause further complications.*
Case presentation: *A healthy 7-year-old girl was previously referred to an oral surgeon to be treated for an extra tooth-like structure in the maxillary anterior region. Fusion of the right maxillary central incisor with a mesiodens was diagnosed, but definitive treatment was deferred until root development was complete. On a cone-beam computed tomography (CBCT) scan, made at a follow-up two years later, the observed tooth anatomy did not match the initial diagnosis. The patient was referred first to an endodontic office and later to the University Dental Clinic, where she was examined at the age of 11 years. The right maxillary central incisor exhibited a pronounced, well-demarcated accessory cusp on the palatal surface extending to the level of the incisal edge, on first sight, resembling a fused mesiodens. The accessory cusp had created occlusal interference with labial displacement of the affected tooth, resulting in compromised dental esthetics and an increased risk for dental trauma.*
Results: *A diagnosis of free true palatal talon with a pulp horn inside was made. Accordingly, the talon cusp was almost completely eliminated in four visits over a period of six months, giving the crown a normal morphology. This allowed adequate space for orthodontic retraction of the tooth.*
Conclusion: *Dentists should be aware of the clinical features of talon cusp and its radiographic appearance to make an accurate diagnosis and provide appropriate treatment.*

Key words: *talon cusp, dental morphology, dental anomaly, permanent maxillary incisor, differential diagnosis*

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Introduction

Talon cusp is a developmental anomaly which takes the form of an additional cusp or ridge on the lingual or labial surface of primary or permanent anterior teeth. Some authors consider talon cusp as a subset of *dens evaginatus*[1-4]; however, histological structure, geographic distribution, and lack of association with its counterpart on posterior teeth, mainly premolars, favor a hypothesis that they are independent clinical entities[5,6]. A recent meta-analytic study estimated that it affects 1,67% of the current world population[7]. The anomaly most frequently occurs on the palatal aspect of the permanent maxillary incisors[1,8]. In the permanent dentition, the talon cusp shows a preference for expression in lateral rather than central maxillary incisors whereas the reverse is true for the primary dentition [1,5,6,9-12]. Talon cusp may occur bilaterally with variable expressivity, but unilateral occurrence is predominant [6, 13]. The co-existence of labial and lingual talon cusps on the same tooth has also been observed in a small number of cases [14-18]. Epidemiological studies indicate either no sex predilection[1,6,8,13] or higher prevalence in females[5]. The etiology is multifactorial, combining both genetic and environmental factors[19]. Talon cusp's clinical implications are variable and include compromised dental esthetics, tongue irritation during speech and mastication, breast-feeding problems, advanced attrition, occlusal interference, displacement of the affected tooth with a tendency to dental traumatism, and caries lesions in developmental grooves delineating the cusp[2,20-24]. Moreover, talon cusp may occur as an isolated anomaly or coexist with numerous other dental anomalies and syndromes[3,7,8,10,17,19,20,25-27]. Noteworthy, in affected children, the frequency of supernumerary teeth in the anterior maxilla is higher[5]. Thus, treating children with talon cusp often requires a multidisciplinary approach. In light of the mentioned facts, it is not surprising that there has been a sustained research interest in this clinical entity. A case of talon cusp reported here is unique in that it shows how misdiagnosis results in treatment delay and increased clinical complications.

Case Presentation

A 7-year-old Caucasian girl was initially referred to an oral surgeon to be treated for an extra tooth-like structure in the maxillary anterior region. Based on clinical examination and periapical radiography, fusion of the right maxillary central incisor with a mesiodens was diagnosed, but definitive treatment was deferred until root development was complete. A cone-beam computed tomography (CBCT) scan, made at a follow-up examination two years later, showed that the additional structure was part of the central incisor itself and not a supernumerary tooth. The patient was referred to an endodontist who subsequently diagnosed the talon cusp and proposed reshaping the tooth with the final objective of facilitating tooth alignment. With this opinion, the patient returned to her dentist, who then decided for referral to the University Dental Clinic. Multiple referrals and adverse medical conditions during the covid-19 pandemic additionally increased the treatment delay.

When attending the University Dental Clinic, the patient was 11 years old and her chief complaint was an unsightly dental appearance. Her medical and family history was unremarkable. Intraoral examination revealed labial displacement of the right maxillary central incisor (Figure 1A), which exhibited a protrusion in the form of a pointed cusp (width 3.8 mm, length 7.6 mm) on the palatal surface, extending from the cingulum portion to the level of the incisal edge (Figure 1B). In occlusion, the cusp was in contact with the mandibular central incisor. The affected tooth was noticeably broader than its antimere. The maximum mesio-distal diameter of the crown was 8.9 mm compared to 7.8 mm for the normal left central incisor; however, both values are within the range of 7.5 mm to 9.8 mm, recently reported for a sample of morphologically normal maxillary central incisors extracted from Slovene dental patients [28]. All maxillary incisors responded adequately to cold and electric stimulation. Clinical and radiographical examination confirmed the diagnosis of unilateral talon cusp. According to the classification system recently proposed by Decaup et al. [7], it was further specified as a free true palatal talon, corresponding to a palatally located additional free cusp extending more than half the length from the cemento-enamel junction to the incisal edge. Re-examination of the CBCT scan revealed a pulp horn inside the talon (Figure 2).

A Class II molar relationship (full-cusp on the left side and half-cusp on the right side) with an increased overjet was diagnosed. Upon cephalometric analysis, the increased overjet was judged to be mainly dental in origin since the orthognathic positions of both jaws. More in detail, a clear discrepancy in the inclination of the right and left maxillary central incisors was measured, with the left central incisor

showing a mild degree of proclination (5° above the normal value), while the right maxillary incisor was severely proclined (11° above the normal value). Therefore, the elimination of the talon cusp was necessary to allow for orthodontic repositioning of the tooth. The treatment objectives included preserving pulpal vitality and meeting esthetic and occlusal requirements. A two-phase management involving gradual grinding of the talon cusp and orthodontic therapy was proposed to the patient and her parents. The informed consent was obtained, and the patient was scheduled for the first selective grinding procedure after one week.

The first step in each appointment was the fabrication of a palatal matrix from silicone impression material (Exaflex Putty, GC America, Alsip, Illinois, USA). The impression material was formed to cover the palatal and incisal aspects of the affected tooth and two adjacent incisors. The matrix was cut in a labiolingual direction at the maximum height of the talon cusp and used to assess the amount of cusp reduction (Figure 3A). In each visit, around 1.5 mm of tissue was removed from the palatal surface of the cusp using water-cooled flame-shaped and conical diamond burs in a high-speed handpiece. In four visits separated by successive intervals of one, two, and three months, the talon cusp was completely removed without exposing the pulp (Figures 3B and 3C). In the last two visits, the procedure was carried under infiltration anesthesia using mepivacaine hydrochloride and levonordefrin 1:20,000 injection (Scandonest 2% L, Septodont, Saint-Maur-des-Fossés, France). After each grinding, a protective varnish (Cervitec F, Ivoclar Vivadent, Schaan, Liechtenstein) was applied to the palatal surface, and the advice to use desensitizing toothpaste was given. The only complaint reported by the patient was mild sensitivity to cold experienced between the appointments. The responses to cold and electric pulp vitality tests remained comparable to those obtained in the contralateral central incisor. At one-year recall, the tooth was clinically and radiographically without pathological findings. The patient was referred for orthodontic treatment.

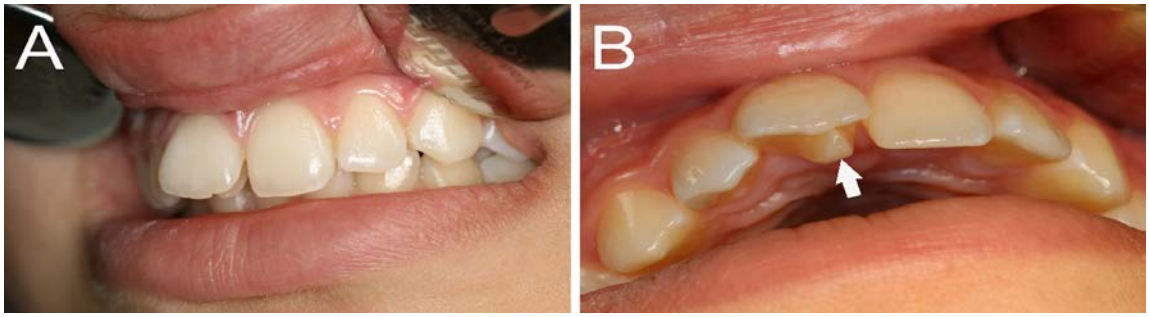

Figure 1. Maxillary anterior teeth from the left facial (A) and incisal aspects (B). The additional cusp is arrowed.

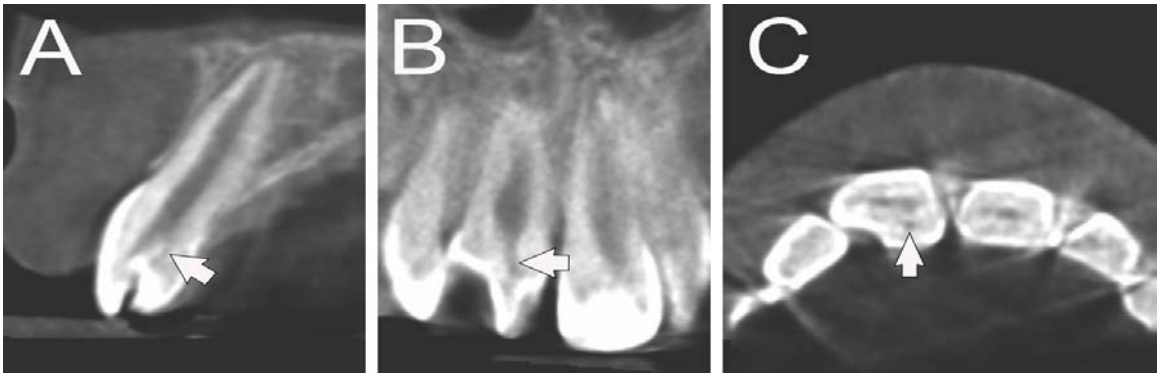

Figure 2. Cone-beam computed tomography images of the right maxillary central incisor: labiopalatal longitudinal section (A), mesiodistal longitudinal section (B), horizontal section of the crown (C). Arrows indicate a narrow extension of the pulp tissue from the pulp chamber into the cusp.

Figure 3. Palatal matrix in place before grinding (A). The amount of talon cusp reduction achieved after two (B) and four grinding sessions (C), respectively.

Discussion

A talon cusp on an unerupted maxillary incisor may mimic the radiographical appearance of a mesiodens or compound odontoma, making diagnosis challenging [10, 21, 29]. Moreover, it was noted that on examination partially erupted incisor with a talon cusp gives the illusion of a supernumerary tooth erupting palatally, particularly when an isthmus of mucosa persists between the crown and the accessory cusp [19]. As described in the present case, such diagnostic errors indeed occur and can lead to delayed or even incorrect treatment, e.g., unnecessary surgical intervention.

The presence of talon cusp may or may not cause clinical problems. In patients with clinical problems, reduction or complete elimination of the talon cusp by grinding usually represents a key part of the overall treatment. However, this procedure carries a risk of pulp exposure because a horn of pulpal tissue is usually present inside the talon cusp. Thus, the talon cusp should be reduced gradually, over several months, with 4- to 8-week intervals between subsequent visits to allow time for the deposition of reparative dentin [24, 30-32]. Moreover, grinding should not be accomplished from the cusp tip but from the palatal surface because this results in a much larger surface area of odontoblasts producing reparative dentin [31]. Application of a desensitizing agent after grinding has been recommended by virtually all authors. The amount of tissue removed from the cusp in one appointment should not exceed 1.5 mm [25, 32]. The latest step forward is a recently proposed visual method for estimating the amount of cusp reduction achieved in each visit by using a custom matrix made from impression material [32]. In the present case, we opted for a gradual reduction of the cusp for 6 months, which allowed reparative dentin formation and pulp vitality to be retained. The above guidelines were taken into account because the pre-treatment CBCT scan clearly showed the pulp extension inside the talon cusp. The use of a custom matrix proved to be a simple and time-efficient method for tracing the amount of eliminated tissue. The patient was followed up for one year without any postoperative complications.

Histological investigations revealed that pulpal tissue is not always present in the talon cusp [20, 33, 34]. In such cases, talon cusp reduction can be a one-visit procedure [35]. However, the presence and extent of the extra pulp horn are difficult to assess on conventional dental radiographs because the talon cusp is superimposed over the image of the affected tooth crown [19, 34, 36, 37]. In Turkish and Malaysian cohorts, periapical radiography revealed pulpal extension into the talon cusp in 17% and 36% of the affected teeth, respectively [6, 8]. It appears that talon cusps which are separated from the palatal surface more likely contain pulpal tissue [20-22, 34]. This is in line with findings from the present case report. Thus, gradual cusp reduction is recommended for preserving pulp integrity, except when the presence of pulp extension can be ruled out by CBCT examination or when the pulp is already irreversibly inflamed or necrotic as a result of untreated caries, trauma, or traumatic occlusion and subsequent endodontic therapy will be required [38].

In the present case, the main clinical problem associated with talon cusp was the labial displacement of the affected tooth, resulting in compromised esthetics and an increased risk of dental trauma. There is a tendency for spontaneous realignment of the affected tooth and/or its opponents after cusp reduction [19, 39]; however, no improvement

was observed in our case due to lack of space in the upper dental arch. With the same treatment approach performed shortly after tooth eruption, there would probably be no need for complex orthodontic therapy. The reasons for the mesio-distal broadening of the affected central incisor remain elusive. Mays [9] speculated that it could indicate an underlaying formation of a double tooth. Alternatively, tooth crown broadening and talon cusp may be associated via a common developmental pathway linked with the aberrant hyperactivity of the anterior end of the dental lamina [40].

Conclusion

Dentists should be aware of the clinical features of talon cusp and its radiographic appearance to make an accurate diagnosis and provide appropriate treatment. In this regard, the presence of a talon cusp should be included in the differential diagnosis of alterations associated with anterior teeth morphology and their eruption anomalies because early diagnosis and proper treatment plan might prevent the development of further clinical problems.

Disclosure of competing interest

The authors have none to declare.

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PREVENCIJA NASTANKA BISFOSFONATNE OSTEONEKROZE VILICA UPOTREBOM AUTOLOGNOG TROMBOCITNOG KONCENTARATA

PREVENTION OF BISPHOSPHONATE RELATED OSTEONECROSES OF THE JAW USING AUTOLOGOUS PLATELET CONCENTRATE

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Sažetak

Uvod: *Fibrin bogat trombocitima (PRF) se sada široko koristi u različitim oblastima medicine, uključujući regeneraciju tkiva.*
Cilj rada *je bio da se analizira efekat PRF-a na poboljšanje postoperativnog zarastanja rana kod pacijenata sa rizikom od razvoja bisfosfonatne osteonekroze vilice.*
Prikaz slučaja: *Žena, stara 71 godinu, koja je na bisfosfonatnoj terapiji, zbog generaliznove osteoporoze, javila se na kliniku sa indikacijom za hiruršku ekstrakciju impaktiranog gornjeg levog očnjaka. Oralno hirurško lečenje je sprovedeno nakon tromesečnog prekida terapije. Tokom hirurške ekstrakcije impaktiranih zuba, postavljen je fibrinski bogat trombocitima i prekriven membranom bogatom trombocitima. Zarastanje rane bilo je uspešno.*
Zaključak: *Primena PRF-a za oralne hirurške intervencije kod pacijenata koji uzimaju BP izgleda kao obećavajuće rešenje i odličan alternativni tretman za zarastanje oralnih tkiva.*

Ključne reči: *bisfosfonati, osteonekroza, osteonekroza vilice povezana sa bisfosfonatima, fibrin bogat trombocitima, oralne hirurške intervencije.*

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Abstract

Introduction: Platelet-rich fibrin (PRF) is now widely used in *various fields of medicine, including tissue regeneration.*
The aim *of the work was to analyze the effect of PRF on improving postoperative wound healing in a patient with a risk of developing bisphosphonate osteonecrosis of the jaws.*
Case report:*Case report: A 71-year-old woman, who is on bisphosphonate therapy due to generalized osteoporosis, came to the clinic with an indication for surgical extraction of an impacted upper left canine. Oral surgical treatment was performed after a three-month interruption of therapy. During the surgical extraction of impacted teeth, a platelet-rich fibrin is placed and covered with a platelet-rich membrane.The wound healing was successful.*
Conclusion*: The use of PRF for oral surgical interventions in patients taking BPs appears to be a promising solution and an excellent alternative treatment for the healing of oral tissues. Key words: bisphosphonates, osteonecrosis, BRONJ, platelet-rich fibrin, oral surgical interventions.*

Key words: *bisphosphonates, osteonecrosis, bisphosphonate-related osteonecrosis of the jaw, platelet-rich fibrin, oral surgical interventions.*

Introduction

Bisphosphonates are used for the prevention and treatment of numerous bone diseases in which there is an impairment of bone metabolism. These medications are indicated in multiple myeloma, bone metastases that develop as a result of breast and prostate cancer, as well as in Paget's disease. They are also used in patients with primary or secondary osteoporosis to prevent pathological bone fractures[1,2]. The action of these medications focuses on reducing bone resorption through the inhibition of osteoclast activity, as these cells play a central role in both physiological and pathological bone resorption[3,10]. Bisphosphonates are generally classified into two groups based on the presence or absence of an amino group:

• Bisphosphonates without an amino group (non-nitrogen-containing bisphosphonates);

• Bisphosphonates with an amino group (nitrogen-containing bisphosphonates).

Bisphosphonates that contain an amino group (alendronate, risedronate, ibandronate, zoledronate) are stronger inhibitors of osteoclast activity, meaning their potency is greater. It is particularly emphasized that amino group-containing bisphosphonates have a higher risk of causing bisphosphonate osteonecrosis[4]. It has been observed that bisphosphonate osteonecrosis can develop spontaneously or be associated with certain dental procedures, such as tooth extractions or the use of dentures[7,8].

In most clinical trials, a strong correlation has been established between the use of these drugs and the occurrence of osteonecrosis of the jaws[5,6]. Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ), is a rare but serious complication of the jawbones that can occur following therapy with antiresorptive or antiangiogenic drugs. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS)[9], BRONJ presents as an area of exposed bone in the maxillofacial region (jaws) that does not heal within eight weeks. It occurs in patients who are receiving or have received bisphosphonates or other antiresorptive drugs and who have no history of radiation therapy or metastatic disease in the jaws.

While there is considerable agreement among reports regarding the clinical presentation and risk factors associated with BRONJ, the exact etiology and pathogenesis remain unclear. Therefore, there is an ongoing effort in the literature to provide a suitable explanation for this adverse effect of bisphosphonate therapy[11]. Suggested hypotheses relate to bone turnover suppression, angiogenesis suppression, soft tissue toxicity, infection, changes in local pH values, immune system deficiency, and genetic predisposition [11].

There are numerous hypotheses for the causes of BRONJ, but the most common cause or trigger is tooth extraction[7,8]. The most widely accepted hypotheses for the occurrence of osteonecrosis are the inhibitory effect of bisphosphonates on osteoclastic activity in bone cells, as well as their toxic effect on soft tissues and their antiangiogenic effects[12,13]. The influence of bisphosphonates on the oral microflora and the formation of biofilm (microbiota) at the site of osteonecrosis is one of the possible causes of its occurrence[14,15].

Biofilm consists of numerous bacterial colonies interconnected by fibronectin fibers [17]. These colonies coat the necrotic tissue and are the most common cause of frequent and recurrent infections in these patients[15].

In a study by Hristamyan Meri A. et al. [16], among 112 cancer patients diagnosed with BRONJ, the highest proportion of patients were smokers/ex-smokers and consumed alcoholic beverages occasionally, linking them to these potential risk factors.

Aim

The use of platelet-rich fibrin (PRF) is a novel approach to tissue regeneration and is gradually becoming a valuable tool in promoting tissue healing in a wide range of oral surgical interventions. The aim of this clinical study was to confirm the influence of platelet-rich fibrin on bone and soft tissue defects during oral surgical intervention in a patient undergoing bisphosphonate therapy.

Case Report

A 71-year-old female patient was referred to the Clinic for Oral Surgery and Implantology of the University Dental Clinical Centre "St. Pantelejmon" in Skopje with a diagnosis of a fissure in the alveolar ridge mucosa. Two months before presenting to the Clinic for Oral Surgery, she had been treated by her dentist and prosthodontist for pain localized on the palatal side in the frontal region of the maxillary alveolar ridge. Her dentist treated the condition as if it were an exostosis, prescribing a gingival gel and frequent rinsing of the wound with herbal teas. According to the medical history obtained upon admission to the Clinic of Oral Surgery, it was determined that the patient was still experiencing the same

subjective symptoms, i.e., persistent pain and discomfort in the frontal maxillary region.

Objectively, the presence of an area of hyperemia in the oral mucosa of the maxillary alveolar ridge was noted (Figure 1). Additionally, the patient was receiving regular bisphosphonate therapy due to osteoporosis resulting from her primary diagnosis of osteoporosis. Following the clinical examination, the patient was instructed to obtain a retro-alveolar X-ray, which revealed the presence of impacted maxillary canines on the left and right sides (Figure 2). The patient was scheduled for an oral surgical intervention in one week, and premedication was prescribed: an antibiotic (Amoxiclav); Chlorhexil EXTRA, a wound rinsing solution; and Chlorhexil Gingival Gel, an antiseptic gel. Additionally, the patient was instructed to provide a report from a rheumatologist because of her ongoing therapy and the upcoming oral surgical intervention.

After one week, the patient was fully prepared for the intervention. The rheumatology report recommended discontinuation of bisphosphonate therapy for the next three months. The patient had discontinued the therapy for three months, and a noninvasive oral surgical intervention was then proceeded with.

Before the procedure was carried out, written informed consent was obtained from the patient. The clinical case was conducted by the ethical standards set by the World Medical Association's Declaration of Helsinki.

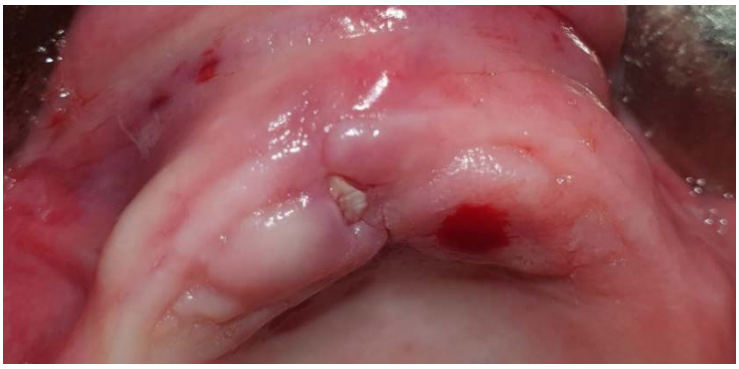

Figure 1. Situation in the mouth before oral surgical intervention (redness of the oral mucosa and apex of the impacted right maxillary canine)

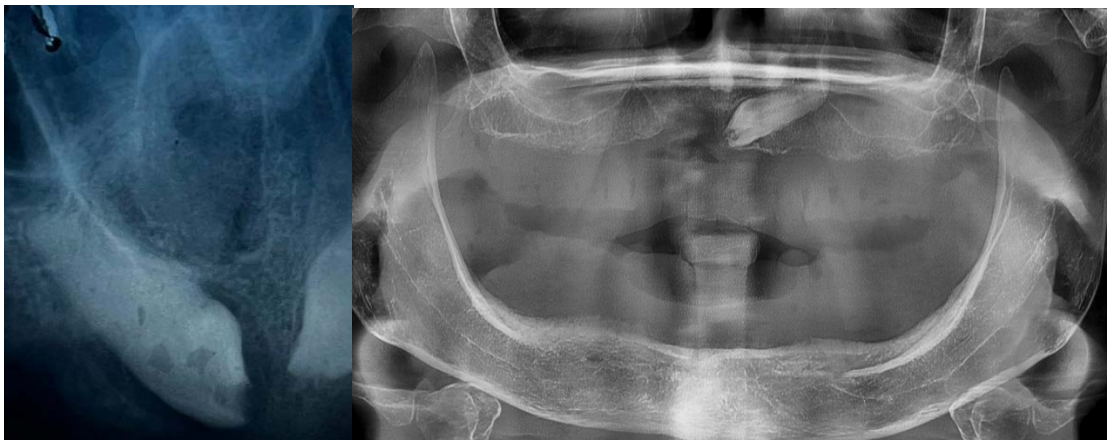

Figure 2. X-Rays show impacted left and right maxillary canines

Surgical Procedure

Under infiltrative plexus anesthesia, a horizontal incision was made along the ridge with a distal relaxing incision. The mucoperiosteal flap was created from both the palatal and vestibular sides. After the flap was raised, a gentle osteotomy was performed—circularly around the neck of the tooth—and with upper premolar forceps, the tooth was extracted. A noninvasive approach was prioritized because, in patients on bisphosphonate therapy, particular care is necessary, with minimal removal of bone tissue and constant cooling, to avoid heating the bone and reducing the additional risk of bone necrosis (Figure 3 a, b, c). Furthermore, a PRF plug was applied in the extraction wound, covered with an A-PRF membrane.

The oral surgical intervention was completed by closing the wound and stabilizing the flap with a non-resorbable silk suture to ensure primary wound healing. In these patients, the suture remains in place for a longer period, approximately 10 days, before being removed.

Blood Collection Procedure for PRF and Preparation of PRF Plug and Membrane

Venous blood was collected via venipuncture in 10 mL tubes (two tubes for balance in the PRF centrifuge) without the addition of an anticoagulant and was immediately centrifuged at 1300 rpm for 14 minutes. In this way, a fibrin clot formed in the middle of the test tube, between the red blood cells which settled at the bottom and the acellular plasma on the surface. The formed fibrin clot was removed from the tubes and separated from the red cell base at the bottom of the tube using closed scissors.

The PRF membrane and plug were prepared in the PRF Box developed by Dr. J. Choukroun. The PRF clot from the first tube was placed in the Teflon cylinder and then pressed using the piston from the PRF box, forming the PRF plug. The PRF clot from the second tube was placed on the perforated tray in the PRF box and left for a few minutes, covered. The resulting PRF membrane was then used for the oral surgical intervention (Figure 4 a, b).

Our choice to use PRF plugs was based on the inherent benefits of PRF: its anti-inflammatory, anti-edematous, and regenerative effects.

Results

When the patient returned for follow-up, one week after the surgical intervention, it was possible to observe the presence of fibrin deposits on the suture, which indicates the formation of new keratinized gingiva without signs of infection or inflammation (Figure 5 a).

After 10 days, the suture was completely removed, and healthy, pinkish soft tissues were observed. According to the Landry, Turnbull, and Howley healing index, the healing was rated as excellent with a score of 5, indicating no exposure of connective tissue and complete closure of the gingival margins. There was no granulation tissue and no pain or bleeding upon palpation.

One month after the surgical intervention, the patient returned for another follow-up. She was in good health, with an excellent condition of the supporting soft tissue apparatus (Figure 5 b).

As a result of the treatment, the wound showed complete epithelialization without infection. Four months after the intervention, an oral examination and control X-ray revealed the formation of new bone tissue and keratinized gingiva. The prosthodontist created new full dentures that fit the alveolar ridge without causing irritation or trauma to the soft and bone tissues.

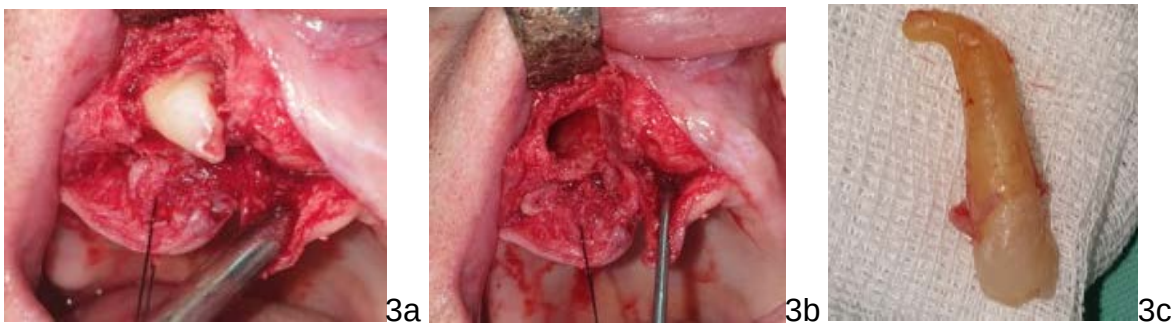

Figure 3 a, b, c. Noninvasive approach: horizontal incision and gentle osteotomy was performed—circularly around the neck of the tooth


4a

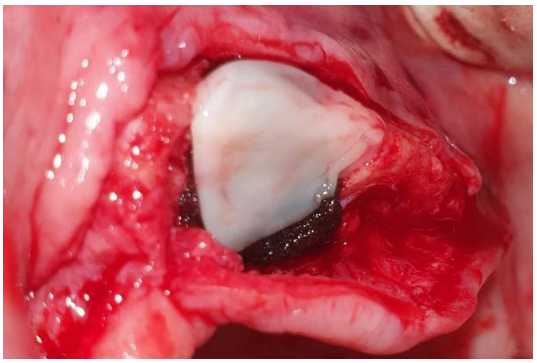
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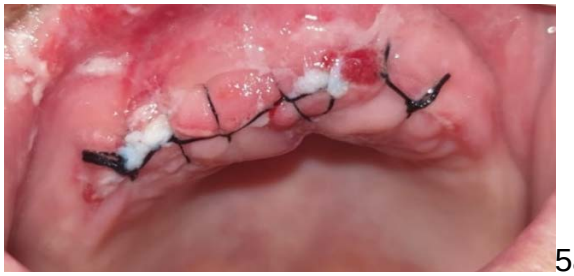
Figure 4 a, b. a) Venous blood taken in 10 mL tubes and preparation of PRF plugs and PRF membranes; b) PRF plugs applied in the extraction wound, and covered with PRF membranes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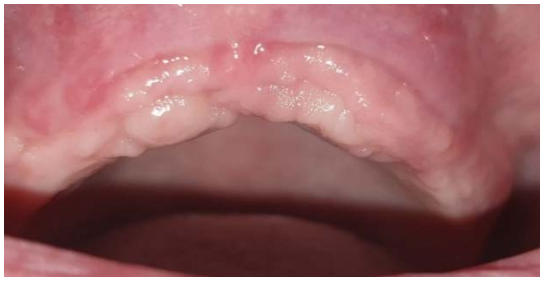
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Figure 5 a, b. a) Presence of fibrin deposits around the sutures;
b) Removed suture after 10 days with presence of healthy, pinkish soft tissues.

Discussion

Since it has been observed in dental practice that the number of patients receiving bisphosphonate therapy is constantly increasing[5,6], certain preventive measures are strongly recommended for these patients before starting bisphosphonate therapy. The preventive approach focuses on eliminating all dental infections, which helps to avoid the need for further tooth extraction after starting this therapy[3].

According to the generally accepted protocol for patients on bisphosphonate therapy, specialists in oral and maxillofacial surgery primarily recommend avoiding invasive oral surgical procedures[18]. However, if such procedures are necessary, it is recommended to perform a minimally invasive, atraumatic intervention. The standard surgical procedure for these patients includes the preparation of a mucoperiosteal flap to allow primary intraoperative closure and promote wound healing, thereby avoiding infection of the exposed bone[19].

In addition to a strictly defined and controlled surgical procedure, prophylactic antibiotic therapy is prescribed. Several antibiotic protocols have been suggested for this high-risk patient group. Broad-spectrum antibiotics, such as amoxicillin (1 g, three times a day) with or without clavulanic acid, in combination with metronidazole (500 mg, twice a day), are standard. In cases of penicillin allergy, erythromycin (600 mg, three times a day) or clindamycin (600 mg, three times a day) is administered. The therapeutic protocol proposed by Lodi et al. is based on combined antibiotic and antiseptic therapy[20]. This therapy starts three days before the oral surgical intervention and continues for at least one week postoperatively, though it may be extended depending on the wound healing progress[19].

In addition to antibiotic prophylaxis, ozone gas insufflation can be applied preventively several days before the oral surgical intervention and also after suture removal, to help prevent bisphosphonate-related osteonecrosis of the jaws[20].

Furthermore, several studies suggest a protocol for oral surgical interventions with the use of platelet-rich fibrin (PRF) in patients undergoing bisphosphonate therapy[21,22]. These

guidelines are based on the following steps: anesthesia; preparation of a mucoperiosteal flap; excision of the osteonecrotic lesion; hemostasis; application of platelet-rich fibrin (PRF); and primary closure (suturing) of the surgical wound.

After completing the minimally invasive oral surgical intervention, the application of autologous biomaterials is essential for faster and safer healing of the surgical wound, without the risk of complications.

Specifically, the growth factors present in platelets are significant for directing regenerative cells to the healing site[23,26]. These platelet growth factors include: PDGF (Platelet-Derived Growth Factor) - promotes cell growth, angiogenesis, and collagen synthesis; EGF (Epidermal Growth Factor) - stimulates the growth of epithelial cells, promotes angiogenesis, and accelerates wound healing; VEGF (Vascular Endothelial Growth Factor) - supports angiogenesis; TGF-β (Transforming Growth Factor Beta) - stimulates the growth of epithelial and endothelial cells and accelerates wound healing; IGF (Insulin-Like Growth Factor) - stimulates the differentiation and proliferation of mesenchymal cells; FGF (Fibroblast Growth Factor) - accelerates wound healing and collagen synthesis.

The application of platelet-rich fibrin (PRF), an autologous biomaterial rich in these growth factors, promotes faster and safer healing of the surgical wound in patients on bisphosphonate therapy by stimulating angiogenesis, cell proliferation, and tissue regeneration while reducing inflammation and edema.

Platelet degranulation leads to the release of cytokines, which stimulate the migration and proliferation of cells within the fibrin matrix, initiating the early phases of healing[24,25]. The platelet half-life is 8 to 14 days, which supports the idea of using platelets as a therapeutic tool to enhance tissue regeneration[26].

Since PRF supplements the natural wound healing process, it has the following effects when used in oral surgical interventions: The fibrin clot acts as a scaffold, providing mechanical support, protecting graft materials, and serving as a biological connector between bone particles. The fibrin network supports cell migration, especially of endothelial cells necessary for neoangiogenesis, vascularization, and graft survival.

3.The healing process is further enhanced by the sustained release of various growth factors (PDGF, TGF-β, IGF-1).

4.The presence of leukocytes and various cytokines enables self-regulation of infectious and inflammatory processes.

5.PRF has a platelet concentration 10 times higher than normal blood, making this biomaterial a true physiological concentrate with excellent immunogenic and regenerative properties[27].

Conclusion

The encouraging results obtained suggest that the use of PRF in oral surgical interventions for patients taking BPs is a promising solution and an excellent alternative treatment for the healing of oral tissues. We recommend that PRF be applied as a preventive measure for BRONJ after tooth extraction, especially in high-risk patients. Introducing a unified protocol for oral surgical treatment in patients receiving bisphosphonate therapy is necessary.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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PRIKAZ SLUČAJA
CASE REPORT
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UČINAK TERAPIJE OZONOM U LEČENJU BISFOSFONATNE OSTONEKROZE VILICA

THE EFFECT OF OZONE THERAPY IN THE TREATMENT OF BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAWS

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Sažetak

Uvod: *Bisffosfonatna steonekroza vilica, ili BRONJ (Bisphosphonate related osteonecrosis of the jaws), definiše se kao izložena kost vilice (deo vilične kosti) u usnoj duplji sa ekspozicijom duže od osam nedelja , koja ne reaguje na terapiju, kod pacijenata koji nnisu na radioterapiji i nemaju metatstske promene u viličnim kostima.. Uticaj ozona (ozonirano ulje i ozon gas) zbog antibakterijskog, antivirusnog i antifungalnog dejstva, dovodi do poboljšanja oksigenacije tkiva, kao i njegovog uticaja na epitelizaciju rane, stimulaciju lokalnog imuniteta.*
Cilj *ovog istraživanja bio je da se utvrdi efekat ozona u lečenju bisfosfonatne osteonekroze vilica nakon njegove primene u obliku gasa i ozonskog ulja u osteonekrotičnom području.*
Prikaz slučaja: *Kroz prikaz dva slična slučaja, prikazujemo uticaj ozona, u obliku gasa ozona i ozonskog ulja, na zarastanje rana kod BRONJ kod dva pacijenta starija od 60 godina. Oba pacijenta su primala bisfosfonatnu terapiju više od 2 godine i imaju eksponiranu kost koja je nastala nakon vađenja zuba. Pacijentima je urađena hirurška intervencija (sekvestrotomija) u kombinaciji sa konzervativnim lečenjem antibioticima i ozonom terapijom.*
Zaključak: *Upotreba gasa ozona i ozonskog ulja u lečenju osteonekroze vilice izazvane bisfosfonatima ima pozitivan efekat na zarastanje rana u predelu osteonekrotičnog tkiva, kod pacijenata koji su primali ili su još uvek na terapiji bisfosfonatima.*

Ključne reči: BRONJ, bisfosfonatna terapija, ozon, osteonekroza

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Abstract

Introduction: *The osteonecrosis of the jaws, or bisphosphonate-related osteonecrosis of the jaws (BRONJ), is defined as the exposed jawbone (part of the jawbone) in the oral cavity that persists for more than eight weeks despite a given therapy in the patient with no history of undergoing radiotherapy, and there is no evidence of bone metastases. The influence of ozone (as ozone gas and ozone oil) is due to its antibacterial, antiviral and antifungal effect, improving the oxygenation of tissues, as well as its impact on wound epithelialization, and the stimulation of local immunity.*
Aim: *This study aimed to determine the effect of ozone in the treatment of bisphosphonate-related osteonecrosis of the jaws after its application in the form of gas and ozone oil in the osteonecrotic area.*
Case report: *Through the presentation of two similar cases, we presented the influence of ozone, in the form of ozone gas and ozone oil, on wounds healing in two BRONJ patients over 60. Both patients have been receiving bisphosphonate therapy for more than 2 years and experienced exposed bone following tooth extraction. The patients underwent surgical intervention (sequestrotomy) in combination with conservative treatment with antibiotics and ozone therapy, after which tissue epithelization was stimulated.*
Conclusion: *The use of ozone gas and ozone oil in the treatment of bisphosphonate-related osteonecrosis of the jaws has a positive effect on wound healing in the area of the osteonecrotic tissue.*

Key words: *bisphosphonate-related osteonecrosis of the jaws, bisphosphonate therapy, osteonecrosis*

Introduction

The osteonecrosis of the jaws, or bisphosphonate-related osteonecrosis of the jaws (BRONJ), is characterized by the exposed jawbone (part of the jawbone) in the oral cavity that persists for more than eight weeks despite a given therapy in the patient who had no history of undergoing radiotherapy, and there is no evidence of bone metastases[1]. This is a serious complication in patients receiving bisphosphonate therapy, especially in patients who receive the therapy intravenously[2]. Bisphosphonates as a therapeutic procedure are used as potent inhibitors of bone resorption in various diseases and conditions of the bones; such as malignancies, osteoporosis, and bone metastases[3,4,5,6,7,8,9]. Marx first described osteonecrosis of the jaws (ONJ) in 2003 as a result of receiving bisphosphonate therapy, therefore it is called bisphosphonate-related osteonecrosis of the jaws (BRONJ)[10]. Later, in the period from 2008 to 2011 with the increasing use of other antiresorptive drugs in therapy for malignant diseases, American Association of Oral and Maxillofacial Surgeons renamed it as antiresorptive drugs-related osteonecrosis of the jaws (ARONJ). The special committee in the position paper of AAOMS from 2014 suggests the term medication-related osteonecrosis of the jaws (MRONJ), due to the increase in cases of osteonecrosis of the upper and lower jaw following the application of other antiresorptive drugs (denosumab) and antiangiogenic drugs, besides bisphosphonates[11]. There are numerous hypotheses about the causes of BRONJ occurrence, but the most common "trigger" is tooth extraction[12]. The most commonly accepted hypotheses of osteonecrosis are the inhibitory effect of bisphosphonates on the osteoclastic activity of bone tissue cells, their toxic effects on soft tissue and their anti-angiogenic effect. The influence of bisphosphonates on the oral microflora, as well as the creation of biofilm (microbiota) at the site of osteonecrosis, is one of the possible reasons for its occurrence. Biofilm is a set of bacterial colonies that are interconnected with fibronectin. They cover the necrotic tissue, which is the commonest cause of frequent and recurrent infections in these patients[13]. In the paper by Hristamyan et al., smoking is mentioned as a risk factor in increasing the incidence of BRONJ14. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS, 2009) there are several clinical stages (Staging) of BRONJ: patients at risk, clinical stage 0, clinical stage I, clinical stage II, and clinical stage III. Numerous studies are related to the impact of medical ozone on wound healing in bisphosphonate osteonecrosis[14]. In the last update of AAOMS, it has been decided to maintain the current classification system with no modifications[15]. Several authors have shown the effect of ozone therapy on wound healing in the osteonecrosis area in patients who are receiving or have received bisphosphonate therapy. The influence of ozone is due to its antibacterial, antiviral and antifungal effect, improving the oxygenation of tissues, its impact on wound epithelialization, and the stimulation of local immunity. Basic forms of ozone application in the oral cavity are: ozone gas, ozone oil and ozone water[16].

This study aimed to determine the effect of ozone in treating bisphosphonate-related osteonecrosis of the jaws at a different stage of the disease after its application in the form of gas and ozone oil in the osteonecrotic area.

Case report 1

A 60-year-old patient came to the Clinic of Oral Surgery because he had pain in the area of the lower jaw on the left side. Clinical examination revealed partial edentulism, and exposed bone visible in the area of the lower third molar (Figure 1). The patient's anamnestic data revealed that he had undergone surgery for prostate cancer two years ago, followed by two years of bisphosphonate therapy (Zometa). After conducting a thorough anamnesis and clinical examination, the decision was made for surgical intervention which was carried out after conservative treatment of the patient.

The patient was administered antibiotic therapy and ozone therapy was performed until the local inflammation around the exposed bone subsided. Then surgery was performed under the local anesthesia with Scandonest 3%. The necrotic bone was removed (Figure 2) and curettage of the wound was performed (Figure 3).

Ozone therapy (Ozone DTA, Apoza device) was applied in the wound with a gingival and bone probe discharger (Figure 4). A suture was placed to reduce the wound (Picture 5).

The patient continued with antibiotic therapy and rinsed the wound with antiseptic solutions in the next days until the sutures were removed, which was followed by ozone retreatment. The postoperative period had an orderly course without pain or any other complications. Regular checkups were made after 2 weeks, 1 month and three months after surgery. There was complete epithelization of gingival tissue (Figure 6).

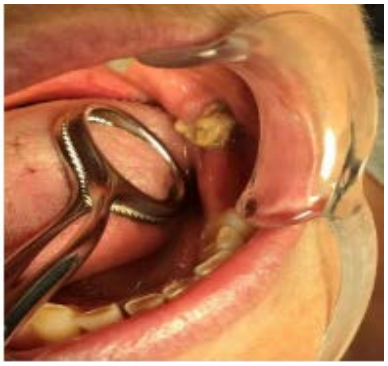


Figure 1. Exposed bone

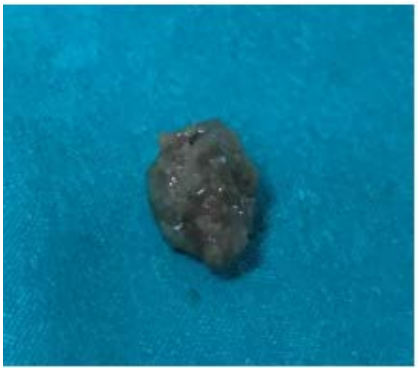


Figure 2. Necrotic bone

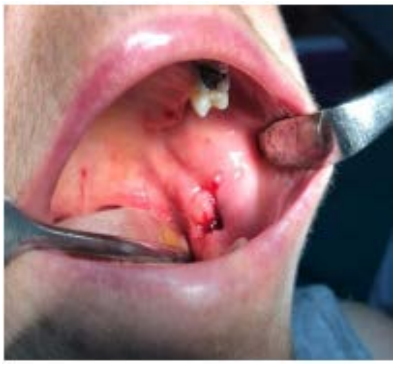


Figure 3. Wound after sequestrotomy

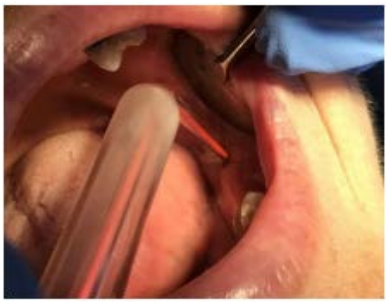


Figure 4. Application of ozone gas

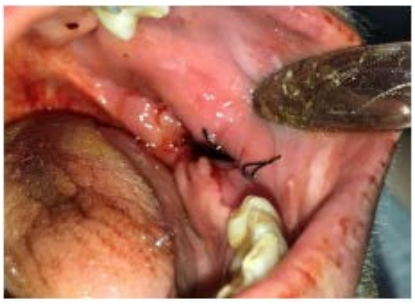


Figure 5. Suturing

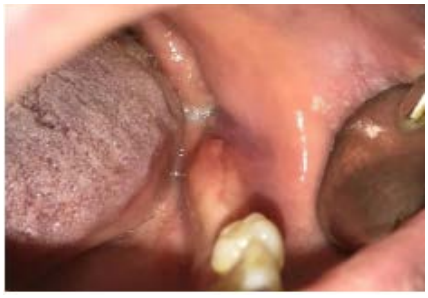


Figure 6. Wound after 2 weeks of healing

Case report 2

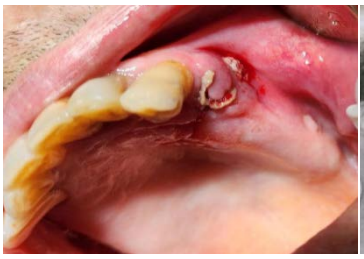
A 66-year-old patient attended the Clinic of Oral Surgery for pain in the area of the upper jaw on the left side. Clinical examination revealed partial edentulism. Exposed bone was visible in the area of the upper left first premolar (Figure 7).

The patient's anamnestic data indicated that he had undergone surgery for kidney cancer three years ago, followed by three years of bisphosphonate therapy (Zometa). The X-ray showed a small bone sequestration in the region of the first maxillary premolar (Figure 8).

We prepared the patient with antibiotic therapy determined according to a previously made antibiogram. The patient was under antibiotic therapy until the local inflammation around the exposed bone subsided and then surgery was performed under local anesthesia with Lidocain 2%. The bone sequester was removed with forceps (Figure 9), which was followed by curettage of the wound (Figures 10 and 11).

The ready-made (fabricated) ozone oil was applied to the wound and a suture was placed to reduce the wound (Figure 12).

The patient continued with antibiotic therapy and rinsed the wound with antiseptic solutions until the sutures were removed. The treatment with ozone oil was repeated in the first seven days after sequestrectomy. Ozone oil was applied for the next 7 days, after removing the suture, for complete epithelization of the wound. The postoperative period had an orderly course without pain or any other complications. Partial epithelization of the wound was visible after 10 days (Figure 13). We are still following the patient until complete epithelization of the wound.



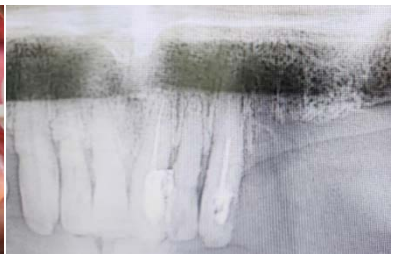
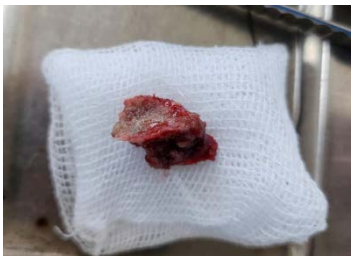
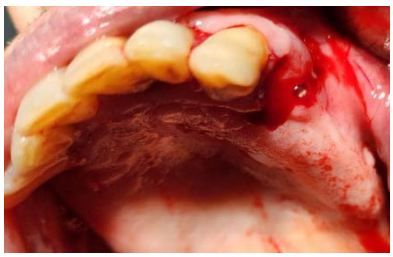


Figure 7. Exposed bone ***Figure 8.*** Rtg panoramix





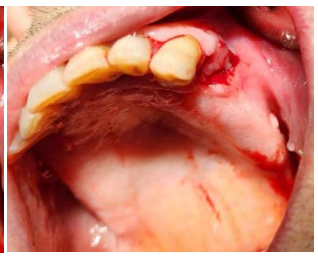
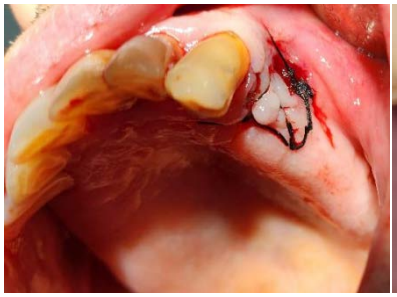


Figure 9. Necrotic bone ***Figures 10 and 11***. Wound after sequestretomy



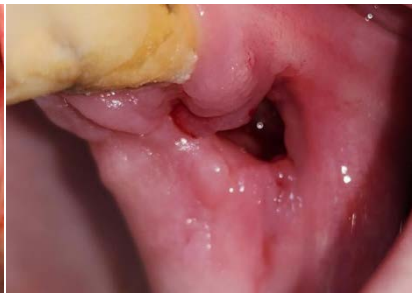


Figure 12. Suture ***Figure 13.*** 10th day after surgery

Discussion

BRONJ is a serious complication that occurs in patients receiving bisphosphonate therapy and in whom dental intervention was performed. This complication dramatically affects the quality of life of these patients and requires a serious approach to solving it. Further, patients with BRONJs suffer from various symptoms such as exposed and necrotic bone, ulceration and inflammation of the surrounding mucosa, pain, infection, as well as further loss of adjacent teeth. According to Kishimoto et al.[17], the nonsurgical management of BRONJ is aimed at improving the stage of the disease and avoiding its progression. Nonsurgical options include the use of antimicrobial mouth rinses, local disinfection/cleaning of exposed bone and fistulae, pain control, and the administration of antibiotics and nutritional support when required. In the presence of exposed bone, superficial debridement may be useful for reducing sharp edges and relieving soft tissue irritation. Even for cases in which surgery is indicated, nonsurgical management before and after surgery (i.e., during the perioperative period) is critical. As surgery is not indicated for all patients with BRONJ, further research is required to identify the most appropriate methods of nonsurgical management[17].

In both of the cases presented, we made a conservative therapy in combination with surgery.

In the treatment of BRONJ, ozone therapy can be used as an adjunctive therapy. Numerous studies are related to the influence of medical ozone on wound healing in bisphosphonate osteonecrosis. Several authors have proof of the impact of ozone therapy on wound healing in the region of osteonecrosis in patients who have received or are receiving bisphosphonate therapy. The impact of ozone is due to its antibacterial[18,19] antiviral[20,21] and antifungal action[22], improvement of oxygenation of the tissues, its influence in wound epithelization[23], what is in line with our case reports, as well as the stimulation of local immunity. In these case reports of patients having exposed bones associated with infection, the epithelialization of the wounds was evident. In the first patient, epithelization was complete after two weeks and in the second one, partial epithelization occurred over 10 days. Basic application forms of ozone in the oral cavity are ozone gas which we used in the first reported case, ozone oil used in the second reported case and ozone water. Bocci et al.[24] investigated the impact of medical ozone on the stimulation or suppression of the immune system and the use of ozone in small concentrations with its oxidative influence.

Agrillo et al.[25] applied ozone therapy as gas insufflations in five-year research as a conservative treatment or as an additional therapy in minimal sequestrotomy in patients with bisphosphonate osteonecrosis of the jaws, as same as our case report. They also describe the reduction of the pain, as well as the reduction of the secretion from the osteonecrotic lesion.

In our cases we used ozone therapy in two different forms, ozon gas and ozone oil, as an adjuvant therapy in combination with surgery and antibiotic therapy.

Nogales[26] in his review describes the impact of ozone oil in the treatment of alveolitis sicca compared with antibiotic therapy.

According to the results of Goker et al., ozone/oxygen therapy and debridement with Piezoelectric surgery for BRONJ treatment is a safe procedure with successful outcomes[27].

Di Fede et al. are using the OZOPROMAF protocol with intra-tissue injections of a 15 mL OxigenOzone (O2O3) mixture with a 26Gx 1⁄2–0.45 × 13 mm needle into the mucosal margin, surrounding the bone exposure or around the site, which had previously been highlighted by a CBCT scan[28].

Conclusion

The use of ozone gas and ozone oil in the treatment of bisphosphonate-related osteonecrosis of the jaws has a positive effect on wound healing in the area of the osteonecrotic tissue, in patients who have received or have been still receiving bisphosphonate therapy.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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PRIKAZ SLUČAJA
CASE REPORT
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UPOTREBA FIBRINA OBOGAĆENOG TROMBOCITIMA TOKOM PROTOKOLA AUTOTRANSPLATACIJE ZUBA

USE OF PLATELET-ENRICHED FIBRIN IN THE PROTOCOL FOR AUTOTRANSPLANTATION OF TEETH

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Sažetak

Uvod: *Autotransplantacija (ATT) se definiše kao hirurška transpozicija zuba sa njegovog prvobitnog mesta u alveolarnom grebenu u novo mesto. Donor zub može biti iznikao ili neiznikli zub, vitalan ili avitaln, sa završenim ili nedovršenim rastom korena. Donor mesto može biti sveža alveola načinjena posle ektrakcije zuba, sa ili bez infekcije, sa prisutna sva 4 manje od 4 koštana zida. Autotransplantacija u novu alveolu se može biti odložena (nakon par nedelja nakon ekstrakcije) ili rana – u novoformiranu alveolu.. Fibrin bogat trombocitima A-PRF definiše se kao autogeni fibrinski ugrušak obogaćen trombocitima i leukocitima, a može se koristiti kao biomaterijal u obliku čepa ili presovane membrane.*
Cilj*: Studija je imala za cilj da proceni uticaj primene A-PRF na zarastanje i razvoj mekih tkiva, kostiju i korena kod autotransplantiranih zuba kod istog pacijenta, merenjem kliničkih i radioloških parametara.*
Prikaz slučaja: *Koristeći metod split mouth, obavljene su dve procedure kod istog pacijenta. U prvom slučaju AT je izveden na klasičan način, a u drugom slučaju A-PRF je uključen u hirurški protokol.*
Zaključak*: Postoji pozitivna tendencija uticaja fibrina bogatog trombocitima na kliničke i radiološke parametre autotransplantiranih zuba. Za konkretnije zaključke o ovoj temi potreban je opsežan period praćenja i više kliničkih slučajeva.*

Ključne reči: *autotransplantacija, fibrin bogat trombocitima, proces zarastanja*

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Abstract

Introduction: *Autotransplantation (ATT) is defined as the surgical transposition of a tooth from its original place in the alveolar ridge, to a new place in the ridge. The donor tooth can be erupted or impacted, vital or non-vital, with completed or uncompleted root formation. The recipient bed can be a fresh extraction socket, with or without infection, it can have all 4 bony walls, or less than 4, ATT can be finished later (after a couple of weeks following extraction) or in a newly formed socket (prepared bed). Platelet-rich fibrin is defined as an autogenous fibrin clot enriched with platelets and leukocytes, and it can be used as a biomaterial in the form of a plug or pressed membrane.*
Aim: *The study aimed to evaluate the influence of using A-PRF on the soft tissue, bone and root healing and development in autotransplanted teeth in the same patient, via measuring of clinical and radiological parameters.*
Case report: *According to the split mouth design, two procedures were performed on the same patient. In the first case, AT was performed in a classical manner, and in the second case, an A-PRF was included in the surgical protocol.*
Conclusion: *There is a positive tendency for the influence of platelet-rich fibrin on the clinical and radiological parameters of the autotransplanted teeth. Extensive follow-up period and more clinical cases are needed for more specific conclusions about this topic.*

Key words: *autotransplantation, platelet rich fibrin, healing process*

Introduction

Autotransplantation

Autotransplantation represents the surgical relocation (transplantation) of a tooth from its original place in the alveolar ridge, to another in the alveolar ridge. The procedure is performed by intentional avulsion (removal with minimal trauma) of the donor tooth, and moving it into an already existing or newly created alveolus (place–recipient). The donor tooth can be erupted or impacted, vital or non-vital, with completed or unfinished root growth. The recipient site can be a fresh extraction alveolus with or without infection present. The recipient place can have all 4 walls intact or one of them missing. Autotransplantation can be delayed (after several weeks of extraction) or transplanted into a newly formed alveolus (prepared bearing)[1,2].

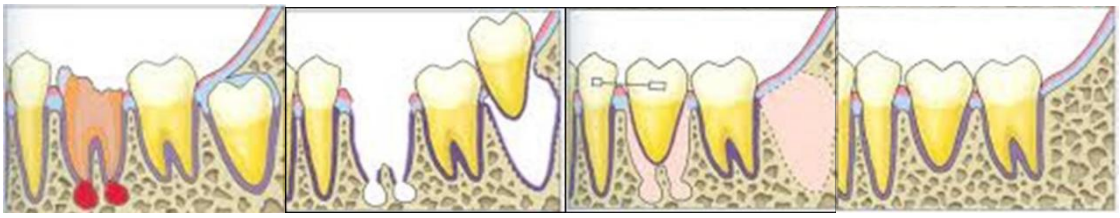

Figure 1. Autotransplantation procedure[3]

According to Bauss et al.[4], ATT is an accepted and predictable procedure for replacing an irreparable tooth. Contrary to implants, the transplant adapts to the eruption of the surrounding teeth and the developmental changes in the oral region, but it can also be orthodontically moved. It is therefore considered an ideal treatment for tooth replacement in young patients. Periodontal ligament (PDL) of autoransplanted tooth gives regenerative potential to a graft itself, stimulating the regeneration of the soft tissue attachment (epithelial and connective tissue), and leading to the restoration of a normal alveolar ridge and the preservation of the gingival architecture.

According to Tričković-Janjić O. et al.[5], preserving teeth in the dentition by replantation, even temporarily, during the child's intensive orofacial development is of great importance for maintaining the local integrity of bone structures and the proper continuation of orofacial development.

Several authors[1,2,4] give preference to other indications for ATT, emphasizing that it is a therapeutic option in cases of tooth loss due to trauma, caries, periodontopathy, and endodontic problems, but also in cases of impaction or agenesis. They emphasize that, unlike implants, transplanted teeth keep their periodontium alive, thus providing the above-mentioned advantages in terms of bone and soft tissue preservation, as well as the possibility of orthodontic or physiological movement. One of the biggest advantages of this procedure is that it can be performed in young patients who are still growing, in whom, on the other hand, the incidence of tooth loss due to trauma is relatively high.

Autotransplantation of teeth was performed many years ago but with varying degrees of success. Even in the time of the pharaohs, attempts were made to transplant teeth from the slaves to the pharaohs, but due to lack of histocompatibility, it ended in failure. This procedure can be very successful if performed carefully while respecting biological principles and using appropriate clinical techniques[6,7](Figure 1.).

Subsequently, the foundations of the modern dental AT were laid by M. L. Hale, who in 1954 documented the first AT of teeth[7], and Slagsvold and Bjercke in 1960 at the University of Oslo established the first surgical protocol for this procedure[8]. The predictability and success of this treatment have risen to a much higher level than before, which was proven by numerous long-term studies on the subject. Predictive factors for graft survival are directly related to preserving cell viability of the periodontal ligament of the donor tooth. Improper handling of the tooth during the intervention and its extraoral time can damage the ligament structure, which leads to postoperative complications of various kinds. Therefore, this procedure requires very gentle, atraumatic tooth extraction and careful handling during the procedure[9].

Several authors deal with this issue. In their paper, Yong Yoon et al.[10] state that despite the widespread use of dental implants and the

experience gained, however, ATT of teeth can be a very difficult procedure to perform. A number of factors affect the success rate, including the developmental stage of the donor tooth root, the anatomy of the tooth, surgical trauma, the time the tooth spends outside the alveolar cup, the shape and size of the recipient alveolus, the condition of the recipient alveolus (the diagnosis of the tooth being extracted) and the blood supply of the bearing. The outcome of ATT also depends on careful patient/case selection, delicate surgical technique, and understanding of the biological principles of work.

The survival and prognosis of autotransplanted teeth is similar to that of dental implants. However, it must be emphasized that certain complications can undermine the clinical outcome of these teeth. These include complications such as root resorption which can be inflammatory resorption or replacement resorption which will lead to ankylosis, pulp necrosis, impaired periodontal healing, etc.[1,2,4].

Various numerical data can be found in the literature about the percentage of survival/success/complications, but still, in the service of this paper, we decided to single out the data of a meta-study that has summarized the data of 32 other studies, considering that it shows the most objective picture. Author Evelyn C. et al.[1] found in their meta-analysis that the survival rate of these teeth, shown after 1, 5 and 10 years, was 97.4, 97.8 and 96.3 % respectively. They also show the one-year success rate of the intervention, which is 96.6%, but also the rate of complications such as ankylosis (2.0%), root resorption (2.9%) and pulp necrosis (3.3%).

Andreasen J.O. et al.[7] in their study of patients aged 7–35 years with a total of 370 autotransplanted teeth, examined root resorption in these teeth. According to their results, root resorption was observed in 52 of the examined teeth. They found that root resorption was significantly associated with the degree of root development of the donor tooth, as well as with the degree of eruption of the donor tooth. According to them, trauma to the periodontal ligament is a key factor in the development of root resorption later.

Platelet-rich fibrin (with special reference to A-PRF)

By definition, platelet-rich fibrin (PRF) is an autogenous fibrin plug enriched with platelets and leukocytes that can be used as a biomaterial in the form of a plug or pressed membrane. It belongs to the second generation of platelet concentrates obtained by simple physical procedures on autologous blood taken from the patient, as products are obtained that are proven to accelerate the healing of soft and hard tissues during water tissue and bone regeneration. The method was developed by J. Choukroun et al. in 2001[11](Figure 2.).

Figure 2. An A-PRF plug obtained from the patient's peripheral blood

The essence of the second generation is in the protocol for obtaining PRF that is created and directed to cause the accumulation of platelets and released cytokines in the fibrin plug[12]. As a result, a concentrate of multiple wound healing promoters is obtained in the wound, which is usually diluted in the initially collected blood. The slow polymerization of fibrin during the processing and obtaining of PRF leads to the incorporation of platelet-derived cytokines inside the fibrin network. This indicates that PRF, unlike other platelet concentrates (first generation), will gradually release the trapped cytokines during fibrin remodeling, which in turn explains the positive impact on the speed of tissue healing that we can clinically register.

In their study, Stojanovic S. et al.[13], conclude that isolated characterization of the respective growth factors' effects is practically impossible due to their actions being pleiotropic and mutually overlapping. Studies of physiological processes in which growth factors have a regulatory role indicate that these molecules rarely act in biological isolation.

The mechanism of action of PRF is through its structure and its composition. It represents a network of densely distributed fibrin fibers with a trimolecular and tetramolecular structure in which a large number of platelets and leukocytes are incorporated. Degranulation of platelets enables plasmin proteins, pro- and anti-inflammatory cytokines (IL-1, IL-6, IL-4, IL-8) and growth factors (TGF, VEGF, PDGF, IGF) to be released from their dense α-granules[14].

Because of such properties of PRF, it can be applied in many medical branches as an autologous biomaterial in oral and maxillofacial surgery, ear, nose and throat surgery, plastic surgery, orthopedics, etc. In oral and maxillofacial surgery it can be used alone or in combination with graft materials in: periodontal surgery, sinus floor elevation[15,16], ridge augmentation, jaw reconstruction[17], regeneration after cyst enucleation[15], guided bone regeneration[17], alveolar preservation[18], Medicine Related Osteonecrosis of Jaw—MRONJ[19], autotransplantation [20] etc.

Aim

This study aimed to evaluate the influence of the use of A-PRF on the soft tissue, bone and root healing and development in autotransplanted teeth in the same patient, via measuring clinical and radiological parameters.

Materials and Methods

Two separate cases of autotransplanted teeth, performed on the same patient at a different time interval, are shown and analyzed (split mouth study)(Figure 3).

In the first case, the ATT was performed in a classical way. The protocol of ATT includes preoperative measures (taking antibiotics one week before intervention if there is an existing infection in the surrounding tissue and measures for excellent oral hygiene and daily rinsing with antiseptic oral solution), and perioperative actions in the following order: atraumatic extraction of the damaged tooth, preparation of the extraction alveolus entailed vigorous curettage of all pathological tissues from the inside, breaking of the interdental septum if necessary, and osteotomy, if necessary, extracting the donor tooth as atraumatic as possible and fitting the tooth in the recipient alveolus in infraocclusion. Then, sutures are placed on the soft tissue, but also through the occlusal surface of the tooth, with the aim of its initial stabilization for 7–14 days. After that, an elastic splint must be placed (an elastic wire that is glued with a composite material to the vestibular surface of the tooth and two other adjacent teeth) to immobilize the transplant. The splint remains for 2–3 weeks and then is removed to prevent ankyloses.

In the second case, the procedure was performed with the application of A-PRF according to the protocol. Both interventions were performed by the same doctor and at the same place—Private Health Organization “University Dental Clinical Center Prof. Dr. Bojo Andreski", Skopje.

The entire procedure was explained to the patient and she signed a consent before the beginning. The patient’s case history parameters of importance for monitoring were recorded, pre and postoperatively.

A female patient aged 20 years, non-smoker, without any systemic diseases (ASA 1), came to the office (Private Health Organization “University Dental Clinical Center Prof. Dr. Bojo Andreski", Skopje) complaining about successive episodes of acute and chronic inflammatory reactions in the lower right quadrant of the alveolar ridge. No visible changes were observed on extraoral inspection, while during intraoral inspection extensive carious defects as well as fractures of the crowns of the first and second molars in the lower right molar region were noticed. There

was mild but firm edema with little sensitivity to pressure on that side. Both teeth reacted painfully on horizontal and vertical percussion**.** The interradicular zone showed spontaneous separation of the roots, in both cases. The presence of incomplete endodontic treatment, extensive carious lesions in the coronal and root part of the tooth, and extensive periapical lightening around the roots of both teeth were noticed in the orthopantomogram. The orthopantomogram also showed the presence of 4 unerupted wisdom teeth with incomplete root growth(Figure 3).

The following measurements were performed on the patient:

1. Clinical measurements for periodontal healing (1 and 3 months)

-depth of periodontal pocket/sulcus

-index of gingival inflammation according to Silness and Loe[21]

-wound healing index according to Morelli[22]

-luxation index according to Grace and Smales[23]

2. X-ray measurements (after 3 months)

-presence/absence of lamina dura and periodontal space

-root growth in mm

-presence/absence of periapical radiolucency.

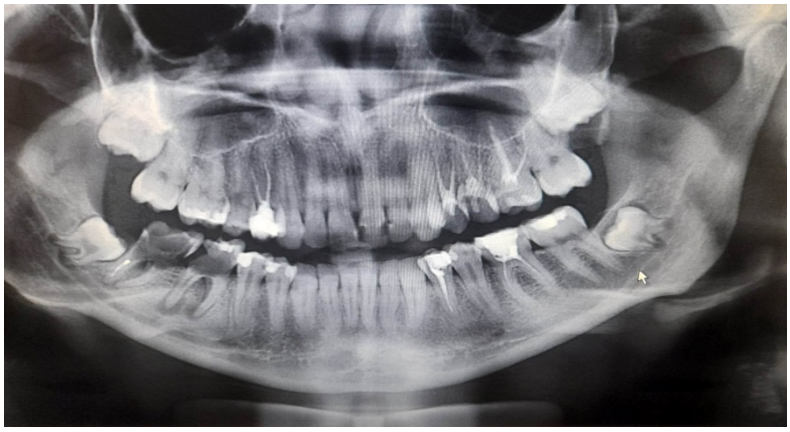

Figure 3. Preoperative OTP image of the patient

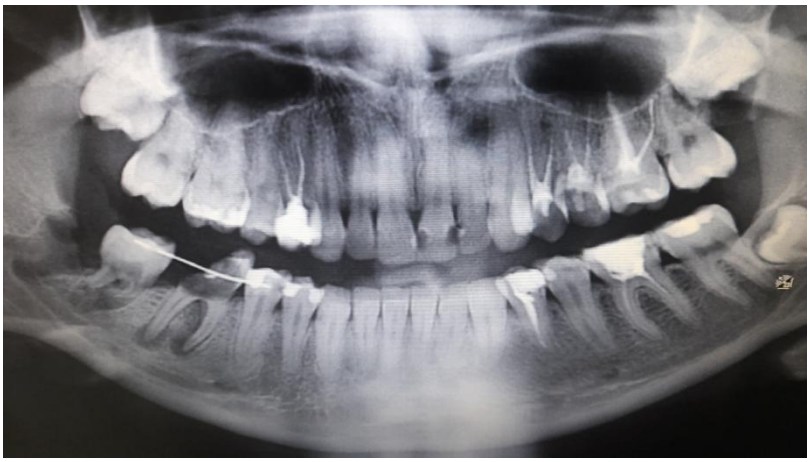

Figure 4. Postoperative OTP image immidiately after autotransplantation of tooth 48

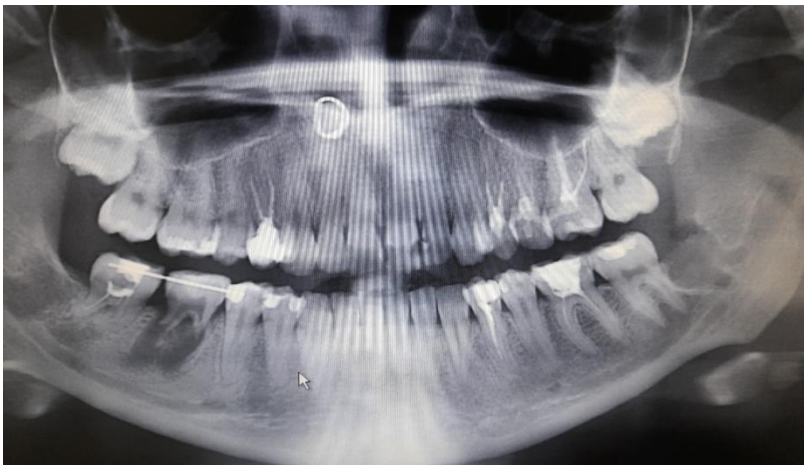

Figure 5. Postoperative OTP image after autotransplantation of tooth 38 (6 month after the autotransplantaton of tooth 48)

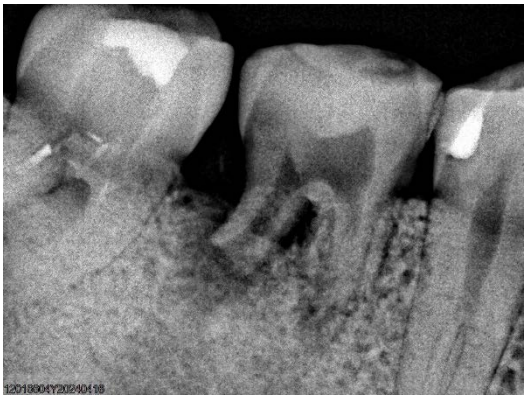

Figure 6. Postoperative OTP image several months after autotransplantation of tooth 38

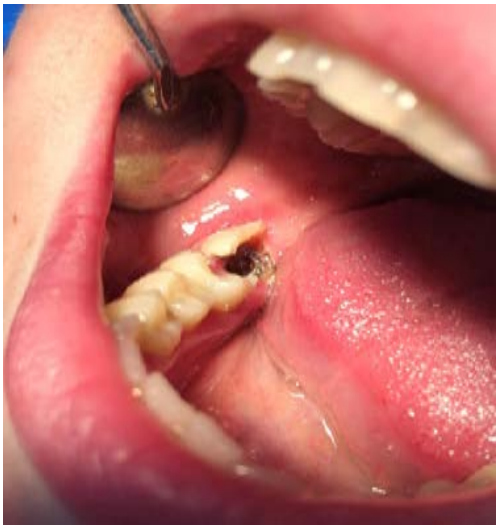

Figure 7. Preopertive evaluation

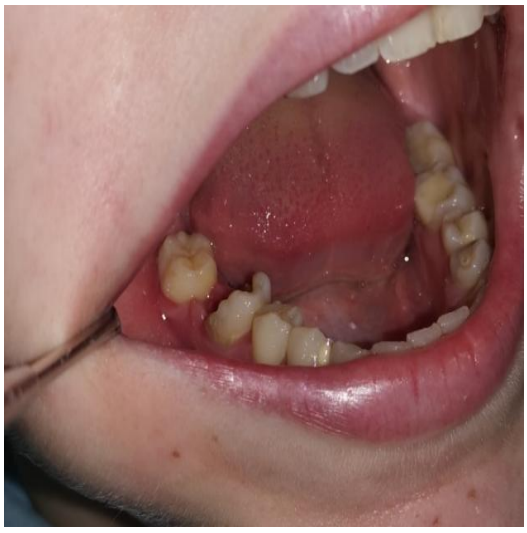

Figure 8**.** Intraoral condition 1 month after the first transplantation

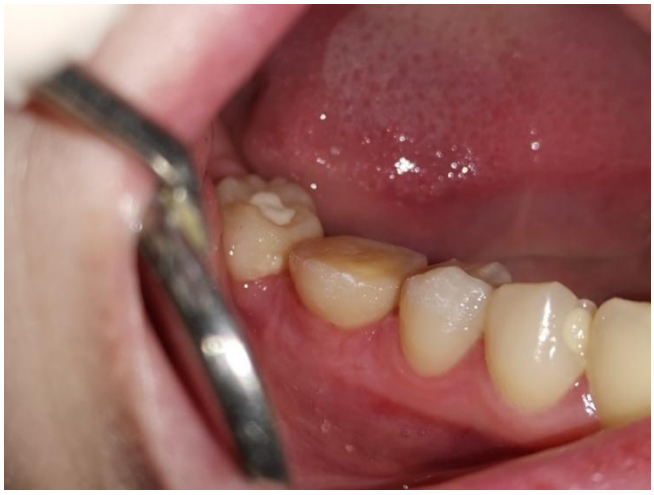

Figure 9. Intraoral condition 1 month after the second transplantation

Case 1.

Extraction tooth: 47(Figure 3 and 7**)**
Donor tooth: 48

One week before the intervention, the patient was prescribed antibiotic therapy which included Amoxicillin + Clavulanic Acid (875 + 125) to be taken twice at a dosage of one tablet a day orally, and Cetylpyridinium chloride 0.05% was recommended for rinsing the mouth twice a day.

The procedures were performed according to the principles of asepsis and antisepsis. The patient rinsed mouth with Cetylpyridinium chloride 0.05% for 2 minutes, just before the intervention. Block anesthesia with 4% Articaine HCL (Artinibsa) with 1:100000 epinephrine was applied for the branches of N.mandibularis. Dens 47 was extracted using elevators and root forceps, taking care about atraumatic extraction. Vigorous curettage of all pathological tissues from the inside of alveolus was performed, and to achieve better fitting of the donor tooth, we broke the interradicular septum. There was no need for additional adjustment and osteotomy of the alveolus.

A triangular incision was made using scalpel blade #15, and a mucoperiosteal flap was raised. Very careful osteotomy was made around the crown, and the impacted tooth was carefully extracted using elevators. The extracted tooth was immediately placed in the prepared socket without pressure and was positioned in infraocclusion before being sutured with silk, non-absorbable suture (#3/0). There was no need for occlusal adjustment in this case (Figure 10).

The extra-alveolar time of the tooth is extremely important and is related to the prognosis of the tooth. In this case, extra-alveolar time was short (15 sec). After that, an elastic splint was placed. An elastic wire was glued with a composite material (enamel was etched with 38% orthophosphoric acid, bonded with Te-econom bond, and glued with Te-econom flow composite) to the vestibular surface of the tooth and two other adjacent teeth. The splint remained for 3 weeks and then removed to prevent ankylosis. The sutures were removed after 10 days. In this case, the donor tooth had incomplete root growth and its vitality was checked after 1, 3, and 6 months. The patient was prescribed antibiotic therapy for one week postoperatively, as well as vitamin supplementation (1000 mg of Vitamin C and 2000 IU of Vitamin D) for 6 months(Figure 4, Figure 10). Additionally, the patient was advised to maintain exceptional oral hygiene and attend scheduled check-ups (Figure 8).

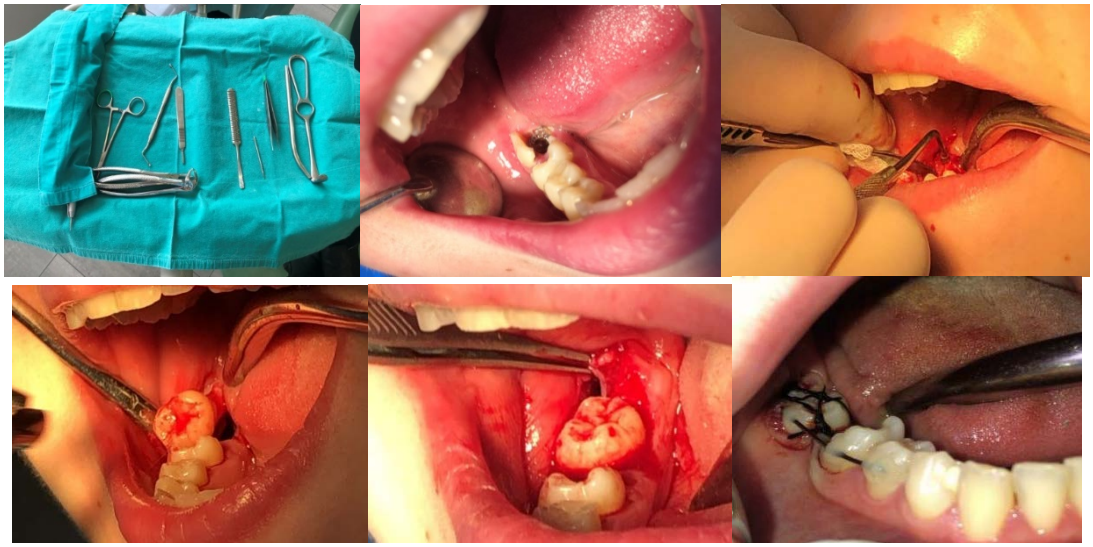

Figure 10. Surgical protocol for ATT

Case 2.

Extraction tooth: 46
Donor tooth 38(Figure 3***.)***

One week before the intervention, the patient was prescribed antibiotic therapy which included Amoxicillin + Clavulanic Acid (875 + 125) to be taken at a dosage of one tablet twice a day. Additionally, Cetylpyridinium chloride 0.05% was recommended for rinsing the mouth twice a day.

The second ATT in the patient was performed assisted by A-PRF. As the donor tooth was on the opposite side, bilateral block anesthesias were required. The first step was on the right side–preparation of the socket, and the second step was surgical extraction of the donor tooth.

In this case, A-PRF was used according to the protocol of J. Choukroun[15]. Before the start of the surgical intervention, venous blood was collected from the cubital vein using the Vacutainer method[24] in two specially designed A-PRF tubes of 10 ml each, which were placed in a BIOBASE LC-H4K centrifuge, BIOBASE, Jinjan, Shandong, China, side by side, at 1200 rpm for 8 minutes. The fibrin plug was placed in a PRF box and pressed, in order to obtain a suitable membrane, and the PRF exudate obtained during pressing was collected in a sterile container (Figure 11).

After the donor tooth was extracted, it was set to stay immersed in the collected PRF exudate for 3 minutes (it can stay as long as needed while other preparations are made).

The socket was lined with a PRF membrane and the tooth was pushed into socked, in order for the membrane to act as a physical shock absorber to protect against excessive pressure, but also as a biological substrate for assisted healing(Figure 12***).***

The rest of the procedures were identical to the first case. The surgical protocol for autotranslplantation is shown in Figure 10,11,12).

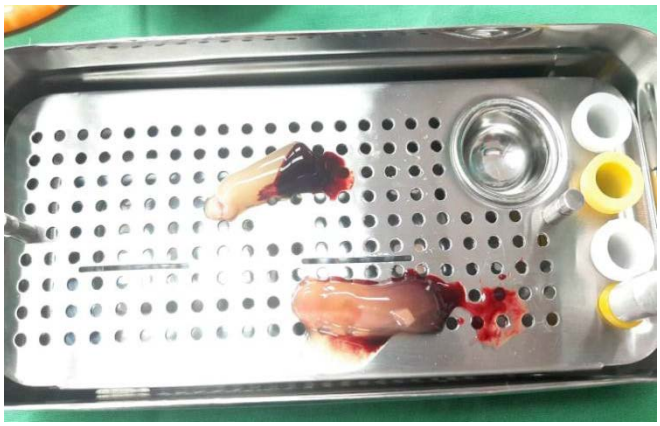

Figure 11. The obtained PRF plugs placed in a PRF box for pressing

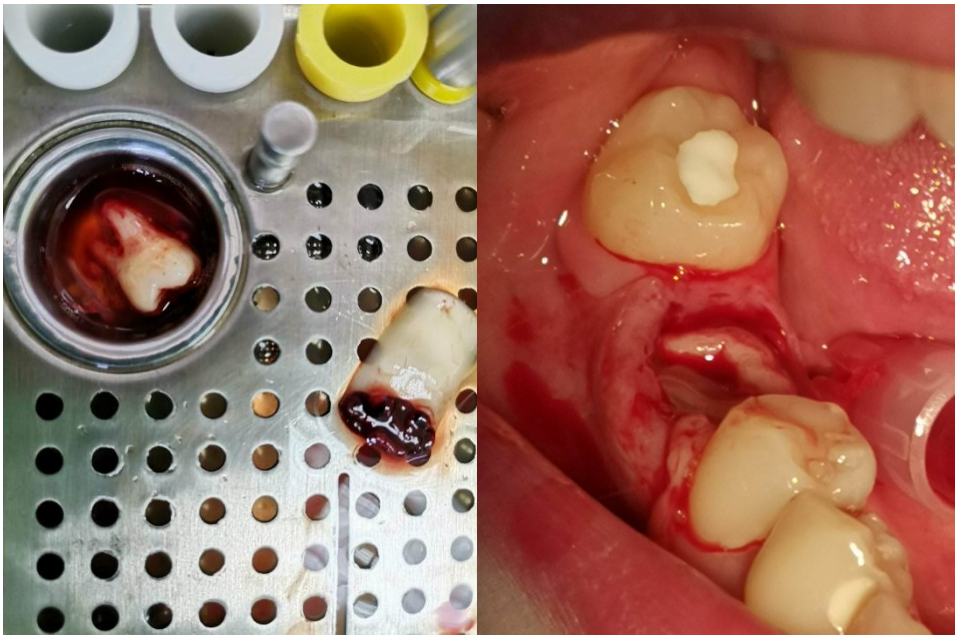

Figure 12. Use of PRF in the ATT protocol

Results

According to the performed measurements, the following results were obtained.

The depth of the periodontal pocket/sulcus in both cases in the first month postoperatively was above normal and amounted to 4 mm. After the third month, the depth of the sulcus space in the first case was 2 mm, while in the second case, it was 1 mm (Table 1).

Gingival inflammation according to the Sillnes and Loe index[21] numerically shows the state of inflammation of the tissue, where the number 0 means the absence of any signs of inflammation (redness, bleeding), while the number 3 means the presence of pronounced redness and spontaneous bleeding. In the first case, in the first month around the transplant, the presence of pronounced redness and bleeding was observed (index 3), while after the third month, the inflammation was significantly reduced, but still present (index 1). In case 2, in the first month there was also pronounced soft tissue inflammation, but with less bleeding, while after the third month, there was no inflammation at all (Table 2).

According to the wound healing index according to Morelli[22], in both cases the wounds healed successfully, there was no presence of pus and mobility and loss of the graft but there were still signs of inflammation,

which in the second case completely disappeared after 3 months (Table 3).

The luxation index, in both cases, showed significant luxation after the first month, much more pronounced in the second case (more than 2 mm), while after the third month, in both cases, the luxation was reduced to a normal, physiological luxation (Table 4).

The radiological characteristics after the first month in all cases and for all parameters remained unchanged immediately after transplantation, while after the third month, a change was observed in all of them with the formation of bone tissue, shaping of the lamina dura, reduction of periapical lightening, and most importantly, root growth of several mm (Table 5, 6 and 7).

Table 1. Depth of periodontal pocket

Depth of periodontal pocket/sulcus		
	Case 1	Case 2
After 1st month	4 mm	4 mm
After 3rd month	2 mm	1 mm

Table 2. Gingival inflammation according to the Silness and Loe Index[21]

Gingival inflammation according to the Silness and Loe Index		
	Case 1	Case 2
After 1st month	3	2
After 3rd month	1	0

Table 3. Wound healing index according to Morelli et al.[22]

Wound healing index according to Morelli et al.		
	Case 1	Case 2
After 1st month	2	2
After 3rd month	1	0

Table 4. Luxation according to the Grace and Smales Index[23]

Luxation according to the Grace and Smales Index		
	Case 1	Case 2
After 1st month	2	3
After 3rd month	1	1

Table 5. Presence of lamina dura

Presence of lamina dura		
	Case 1	Case 2
After 1st month	no	no
After 3rd month	yes	yes

Table 6. Presence of periapical radiolucency

Presence of periapical radiolucency		
	Case 1	Case 2
After 1st month	yes	yes
After 3rd month	no	no

Table 7. Root growth

Root growth		
	Case 1	Case 2
After 1st month	0 mm	0 mm
After 3rd month	2 mm	2 mm

Discussion

According to the literature, several criteria are cited as key factors in performing successful ATT. The recipient bed must be free of any infections and with a sufficient amount of bone that will provide good support and stabilization for the transplanted tooth. As for the donor tooth, the ideal candidate is the tooth with incomplete root growth, because they have the potential to form the root and preserve the vitality of the pulp. Some other prognostic factors that may influence the success rate are atraumatic tooth extraction, limited root injury and PDL, minimal root manipulation, and reduced extraoral time. All the above factors are associated with reducing the risk of PDL damage, which would lead to the most common complications of the autotransplanted tooth, such as internal/external root resorption and ankylosis[25].

Stojanović et al.[26] in their study on avulsed and replanted teeth emphasized the meaning of the extraalveolar time and the splinting method. They stated that the success of therapy and periodontal healing depended on the duration and conditions of extraoral tooth preservation, the degree of damage to the periodontal ligament, and the condition of the pulp. The age of the patient, concomitant injuries and the manner and duration of splinting are essential to the degree and manner of survival of avulsed teeth in the jaws. The splint is placed for a period of 7–10 days and physiological and mechanical cleaning should be simple. Rigid splinting should be avoided.

If we follow the criteria for ideal case for ATT, there should be no infection and inflammation in the persisting alveolus and surrounding bone. In both our cases, in the recipient bed, there was the presence of chronic inflammation. Before we decided to perform the procedure, we searched the literature for ATT in chronic infection site, but also for immediate dental implants in the presence of chronic bone infection, looking for justification for our procedure.

Tsukiboshi M. et al.[27] state that in the case of an immediate ATT, the hopeless tooth in the recipient site is extracted first. When the recipient tooth has a periapical lesion, the granulation tissue should be thoroughly removed, but care should be taken not to curettage the periodontal ligament of the extraction socket if unnecessary.

Bell C. et al.[28] state that in sockets with 3–4 intact walls, minimal periodontal resorption and good primary stability, immediate implantation is a safe procedure, despite the present chronic infection. A report by Siegenthaler and Lindeboom suggest that the complication rates with implants placed in the infected sites compared to those of non-infected sites are almost the same[29]. Novaes Jr. and Novaes[30] in their study stated success by few pre and postoperative measures including antibiotic administration, meticulous cleaning, and alveolar debridement. Hegde R. et al.[31] concluded that immediate implant placement and loading represent a viable treatment option for infected sites when combined with an antibiotic regime and complete elimination of microbiota from the infection socket.

According to the literature, we also strongly believe that the use of PRF products in infection/inflammation site has its anti-inflammatory properties. As Tanan K. G. et al.[32] state, in addition to growth factors, several pro- and anti-inflammatory cytokines

can also be produced by leukocytes in PRF membranes. It has been shown that the release of cytokines continues in the three-dimensional architecture of PRF, starting from the early inflammatory period up to 21 days. Due to these properties, PRF can regulate inflammatory processes and increase angiogenesis. In addition, the release of these substances can accelerate tissue healing and reduce the rate of postoperative complications.

The criteria for successful ATT are similarly described and divided in a large number of papers, but as the most appropriate we will take the division of Andreasen et al.[33]. Regarding the clinical examination, the division is made according to the following criteria: 1) physiological mobility; 2) no pain on percussion; 3) probing depth < 3mm; 4) no signs of inflammation; and 5) normal chewing function. The radiological criteria are: 1) normal spatium periodontale; 2) no progressive resorption of the root; and 3) presence of lamina dura. ATT is considered unsuccessful when there is a prolonged inflammation of the recipient cavity or when the transplanted tooth appears clinically unhealthy with persistent grade 3 mobility, ankylosis, or progressive root or bone resorption.

Keranmu et al.[34] in their study of 52 patients with ATT, where classic manner and PRF were compared on 26 patients, showed that initial stability of the graft in the PRF group is better immediately after the intervention, which is contrary to this case. Periapical lesions in 23 of 26 subjects with PRF healed completely with new alveolar bone within 3 months, whereas in the control group, only 9 cases showed complete lesion healing after three months. In the PRF group, all patients showed satisfactory mastication, no abnormal mobility, periodontal pockets, and root resorption or ankylosis. In the control group, deep periodontal pockets were observed in some of the subjects.

Jorge González et al.[35] in their study on 10 cases made a comparison of classical and PRF manner and showed that 10 patients had a functional and asymptomatic transplanted tooth with physiological mobility even after 1 year. All 10 had a positive vitality test and all transplants showed positive root growth (on average 2.01mm per year). The probing depth was not greater than 4 mm during the first year.

The use of A-PRF is thought to be a promoter of wound healing and angiogenesis processes. Usage in ATT cases enhances the natural revascularization process of the transplanted tooth. Also, keeping the donor tooth in a PRF exudate while outside the alveolus may have an effect on preserving the vitality of cells from both the pulp and the PDL, thus improving the clinical outcome[15].

PRF stimulates angiogenesis through migration, division and phenotypic changes of endothelial cells. It also stimulates cell mitosis and induces osteogenesis without an inflammatory reaction. These effects work through a slow process that lasts at least a week[36] and up to 4 weeks[37].

PRF can induce strong and prolonged differentiation and stimulation of osteoblasts together with fibroblasts within 14 days[38].

After 12 months of follow-up, Bakhtiar et al. showed radiological evidence of prolonged root development and closure of the apex in 4 teeth with incomplete growth and necrotic pulp[39].

These "miraculous" powers of PRF are described and explained by various authors throughout the literature. Alkofahi et al.[40] stated that this is due to the fact that PRF contains a dense network of fibrin and an abundance of growth factors such as platelet-derived growth factor and vascular endothelial growth factor. An important factor is transforming growth factor b1 (TGFb1) which is simultaneously secreted by Hertwig's coat and positively affects the differentiation of dental papilla cells to transform into odontoblasts, providing a suitable environment for PDL cell proliferation and extracellular matrix synthesis. Finally, the authors conclude that the benefit of using PRF in ATT of teeth with incomplete root growth is great in the early and late stages of the regenerative process.

The results obtained in this study show certain trends that leave an impression on the researcher who sees and follows those cases. The tendency for improved early soft tissue healing of the wound after ATT can be seen. This can be seen through the reduction of the depth of the sulcus, the reduction of the degree of inflammation of the soft tissue, and the rapid healing of the wound without early complications.

There was postoperative edema in both cases, but we have to mention that the edema was on the donor site, not on the recipient site, and it was due to surgical trauma of the tissue around the impacted teeth. There was no significant and unusual postoperative pain after the second day of surgery in both cases.

The degree of luxation of the teeth in the first month, which is higher in the tooth with the use of PRF, can be explained by the early persistence of the membrane in the alveolus, which acts as a soft tissue barrier until it is

resorbed. However, later, the degree of luxation equalizes with the tooth without PRF.

The data in this study indicate no difference in the healing of hard tissues, which means that in both cases the same goes successfully. However, the short period of follow-up in our study does not allow us to make a more detailed judgment and comparison with the literature.

Conclusion

The obtained results show a positive tendency for the influence of platelet-rich fibrin on the clinical and radiological parameters of the autotransplanted teeth. Extensive follow-up period and more clinical cases are needed for more specific conclusions about this topic. The positive results of this study encourage us to continue our research on this topic.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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EFEKTI INTERVALNOG TRENINGA VISOKOG INTENZITETA KOD ADOSLESCENATA

EFFECTS OF HIGH-INTENSITY INTERVAL TRAINING IN ADOLESCENTS

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Sažetak

Uvod: *Od kraja 20. veka, intervalni trening visokog intenziteta (HIIT) prvenstveno koriste sportisti, ali je u poslednjoj deceniji postao sve popularniji među opštom populacijom. Ovu strategiju treninga karakterišu navale aktivnosti visokog intenziteta, ispresecane periodima odmora ili vežbama niskog intenziteta za oporavak.*
Cilj: *Cilj ovog preglednog rada bio je da se utvrde efekti HIIT-a kod adolescenata i pokaže kako njegova primena u redovnoj nastavi fizičkog vaspitanja može doneti pozitivne promene u fizičkoj aktivnosti mladih.*
Zaključak: *Preporučuje se da nastavnici i profesori fizičkog vaspitanja uvek budu u stalnom kontaktu sa svojim učenicima kroz sistem obrazovanja i da im ukažu na značaj fizičkog i zdravstvenog vaspitanja u društvu*
.
Ključne reči: *ефекти, високоинтензивно интервални тренинг, адолесценти*

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Abstract

Introduction: *Since the late 20th century, high-intensity interval training (HIIT) has primarily been used by athletes, but in the past decade, it has become increasingly popular among the general population. This training strategy is characterized by bursts of high-intensity activity interspersed with periods of rest or low-intensity exercises for recovery.*
Aim: *The aim of this systematic review was to determine the effects of HIIT in adolescents and show how its implementation in regular physical education classes can positively affect young people's activity.*
Conclusion: *It is recommended that teachers and professors of physical education always be in constant contact with their students through the education system and point out to them the importance of physical and health education in society.*

Key words: *effects, high-intensity interval training, adolescents*

Introduction

Most of children and adolescents are physically active only in regular physical education classes (PE) at school[1]. Generally, they do not receive adequate health-promoting physical activity (PA)[2,3], and school PE programs should contribute to health maintenance and disease prevention[4]. PE classes[5,6,7] or other school-based activities, such as classroom exercise[8], have been shown to induce beneficial cardiometabolic[9] and neuromuscular adaptations[8], improve health-related parameters[6,8,10]and are more enjoyable than long-duration, low-intensity exercise[11,12]. Insufficient PA[13] is associated with all risks of cardiovascular disease[14,15], increasing the risk of premature mortality[16,17]. Also, overweight and obesity, poor diet, reduced cardiorespiratory fitness, hypertension, chronic infections, and dyslipidemia are evident in youth and become persistent health problems in adulthood.[18,19,20] Childhood and adolescence are, therefore, key stages in the development and adoption of healthy habits. Although regular physical activity protects against many diseases, it is estimated that the current activity level among adolescents does not meet the recommended level of exercise[21,22]. There is a strong case for future work investigating how high-intensity interval training (HIIT) can be optimized for adolescent quality of life and mental health outcomes and an important predictor of youth cardiometabolic health[23,24]. Therefore, HIIT protocols have been introduced to obtain positive psychological responses for physically inactive adolescents, and the design of the exercises is adapted to the individual[25].

Materials and Methods

Multiple databases, such as Google Scholar, PubMed, and Web of Science, were identified. For study identification in the mentioned databases, multiple keywords (combinations are separate) were used: (adolescents, high-intensity interval training, and fitness. Two authors (R.J. and M.K.) examined the study identification and data extraction separately. Furthermore, a descriptive method was used for obtained data examination, whereas all titles, abstracts, and full-text articles were reviewed for eventual study inclusion in the systematic review. After a detailed identification process, studies were considered relevant and included only if they met the pre-defined inclusion criteria.

Inclusion criteria

Each study had to meet the following inclusion criteria: year of publication (2013-2024), full-text study published in English.

Exclusion criteria

The studies were not included if they had been realized before 2013, published studies in other languages than English.

Results

The results of the analysed popers are showiv in Figure 1 and Table 1.

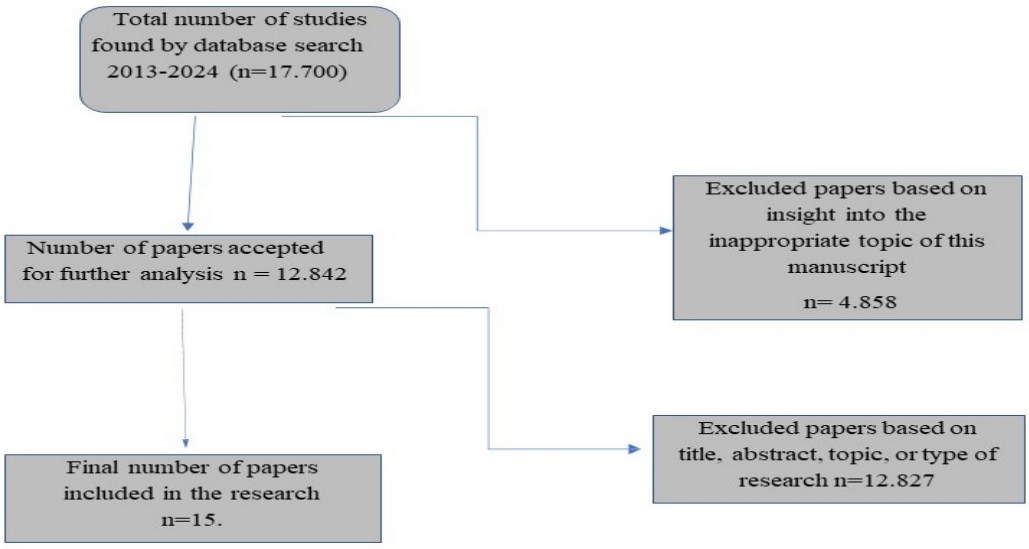

Figure 1. Flow chart of study identification

Table 1. Research on the effect of HIIT on fitness components

First author and year of publication	Examinee		Duration (weeks)	Exercise program	Measured parameters	Results	
	Age	Number and groups					
De Bourdeaudhuij et al. (2013)	10 to 12	766 girls and boys	/	E group short-term sitting exercise C group long-term sitting exercise	BMI WC	BMI E↓ WC E ↓	BMI C↑ WC C↑
Costigan et al. (2016) (5)	15,8	N-65	/	I group– aereobic exercise II group – aereobic resistance exercise III group – Control 3×HIIT per week; 8–10min	SRT MC BMI WC	I+II+III SRT MC BMI WC	SRT MC BMI WC
Muntaner-Mas et al. (2017) (2)	/	N–80 E–55 C–25	20	HIIT; 2× week on PE classes 45s exercise, 15s rest 7.5min HIIT, 2.5min rest, intensity of exercise 85%HRmax		E BMI ↑	C BMI ↑
Rey et al. (2017) (5)	14–15	N–24 Girls–14 Boys–10	5	45min HIIT, 3× недељно; diet, energy intake for girls 2000 kcal/day, for boys 2200 kcal/day; intensity of exercise >80% Hrmax	BMI W PC	Girls BMI↑ W↑ PC ↑	Boys BMI↑ W ↑ PC ↑
Larsen et al. (2018) (9)	8–10	N–295 BGG–96 CT–83 C–116	>40	HIIT; 3×40min per week; tests used to determine muscular fitness: flamingo balance test, standing long jump, 20m sprint	BM MC	BGG BM ↑ MC ↑	CT BM ↑ MC ↑
Tottori et al. (2019) (4)	/	N–56 E–28 C–28	4	(E)–3×HIIT per week/ 8–10min/4weeks	SRT ABS SLJ	(E) HIIT SRT ↑ ABS ↑ SLJ ↑	C SRT ↓ ABS ↓ SLJ ↓
Nugent et al. (2019) (4)	15,8	N–16 E–16	7	(E) HIIT; 7 weeks		(E) HIIT SP ↑	
Alonso-Fernandez et al. (2019) (4)	Adolescents	N–26 E–13 C–13	7	HIIT Tabata; 4min/8 intervals of maximum effort 20s; rest 10s	CRF BFP	(E) HIIT CRF ↑ BFP ↑	C CRF↑ BFP ↓

Plavsic et al. (2020)	13 to 19	N-44	12	E E – HIIT + nutrition C – nutrition K	BMI SBP MHR RHR	BMI ↑ SBP ↑ MHR ↑ RHR ↑	BMI ↑ SBP ↑
Ketelhut et al. (2020)	/	N-46 E-22 C-24	12	E group – first 20min of class HIIT C group – regular PE class	AFT CSP PSP APV	AFT ↑ PSP ↑ CSP ↑ APV ↑	
Fang et al. (2021) (3)	/	N-56 E-28 C-28	4	E group- HIIT; Cgroup- moderate intensity training	CF(E) ME(C)	E CF↑	C ME↑
Bogataj et al. (2021)	15.5	N-48 E-24 C-24	8	E group- 3× week HIIT and nutrition C group – regular PE class	BC CMJ YYT	BC↑↑↑ CMJ↑↑↑ YYT↑↑↑	BC↑ CMJ↑ YYT↑
Bossman et al. (2022)	11 to 15	N-121 E- 121	6	3 types of HIIT, 2xweek	BC	E BC↑	
Petrušič et al. (2022)	12 to 14	N-59	12	E group – games program (football, basketball, handball, volleyball) C group – PE classes	CMJ CMJPA SQJ MBT ABS YYT	E in relation to C CMJ (p<0.001) MBT (p<0.001) ABS (p=0,030) CMJPA (p<0.001) YYT (p=0,004)	
Popowczak et al. (2022)	Students	N-187 Boys 66 Girls- 121	10	E group-boys HIIT C group- girls, regular PE class	F S CE BF	E group – reduction of body fat and an increase in cardiovascular efficiency C group – increase in cardiovascular efficiency	

N – total number of participants; E – experimental group; C – control group; SRT – shuttle run test; ABS – abs; SLJ – standing long jump; SP – swimming performance; CRF – cardiorespiratory fitness; BFP – body fat percentage; BF- body fat; SBP – systolic blood pressure; CF – cardiorespiratory fitness; ME – muscular endurance; BMI – body mass index; S – speed; BC – body composition; MC – muscular condition; WC – weist circumference; W – weight; BGG- ball game group; PC – physical condition; CT – circuit training; BM – bone mineralization; MC – muscular condition; MHR – maximum heart rate; RHR – resting heart rate; AFT – aerobic fitness test; CSP – central systolic pressure; PSP – peripheral systolic pressure; APV – aortic pulse velocity; BC– body composition; CMJ – counter movement jumo; MBT – medicine ball test; YYT – yo-yo test; ТАК – тест аеробне кондиције; F – flexibility; CE – cardiovascular efficiency; SQJ- squat jump

Discussion

The aim of the study[26] was to identify subgroups of children based on whether they had moderate or vigorous-intensity PA (MVPA) and length of sitting time and to investigate differences in body mass index (BMI), waist circumference, and prevalence of overweight between these subgroups. A sample of 766 children aged 10 to 12 (52.9% girls, 11.6 ± 0.8 years) participated in this study. Children wore accelerometers to measure MVPA and sitting time. Cluster analysis revealed four clusters in both gender groups showing an unhealthy pattern (low MVPA/long sitting), a healthy pattern (high MVPA/short sitting), a low mixed pattern (low MVPA/short sitting), and a moderate to a high degree of mixedness (moderate to high MVPA/moderate sitting). In girls, the high MVPA/short-term sitting group had significantly lower BMI ($p \leq 0.05$), lower waist circumference ($p \leq 0.01$), and the lowest percentage of overweight ($p \leq 0.10$) compared to the other three clusters. In boys, both clusters with higher activity levels had significantly lower BMI ($p \leq 0.001$) and waist circumference ($p \leq 0.001$) than the two low-activity clusters, regardless of sitting time. The authors conclude that engaging in more MVPA and less sitting time is associated with a more favorable weight status among girls

aged 10 to 12. MVPA appears to be most important for body weight, while sitting is less relevant. In a study[27], the authors indicate that current PA and fitness levels among adolescents are low, which increases the risk of chronic diseases. The authors conducted a pilot randomized study on 65 students with an average age of 15.8 years, divided into three groups. The first group followed an aerobic exercise program, the second group followed an aerobic and resistance exercise program, and the third was a control group. The program consisted of three weekly HIIT sessions (8–10 min) held during physical education classes or lunch. Measurements were taken at the beginning and end of the exercise to detect changes in cardiorespiratory function (shuttle run test), muscle fitness (push-ups, long jump tests), body composition (body mass index (BMI)), waist circumference, and motivation for physical activity (questionnaire). Current physical activity and fitness levels among adolescents are low, which increases the risk of chronic diseases. This study indicates the need to include HIIT during mandatory PE classes to improve cardiorespiratory function and body composition among adolescents. On the other hand, the goal of the study[28] was to integrate the new HIIT method into a traditional physical education unit. The study was conducted on 80 subjects divided into two groups: an experimental group consisting of 55 subjects and a control group (25) of subjects for 5 months, twice a week in physical education classes. The program consisted of a circuit of 10 stations, each performing HIIT. Three students were at each station and stayed together for all 10 stations, exercising simultaneously. They started at one station and moved clockwise for the remaining 9. The exercise time was 45s, with a 15s rest period. The total duration of the program was 7.5 min of HIIT and 2.5 min of rest. The optimal intensity was 85 HRmax. By analyzing the results obtained, the authors indicate an improvement in body composition. The authors conclude that it is a priority to include methodological strategies during physical education classes to achieve adequate intensity. The proposed method shows a positive trend in improving health in schoolchildren, although future research is necessary to confirm or refute the results obtained. In the study[29,] the authors examined the effects of HIIT and diet in 24 obese adolescents over five weeks. Fourteen girls and ten boys (aged 14-15) participated in a pediatric rehabilitation center. The intensity of the HIIT was above 80% of the maximum heart rate (HR) and above six kilocalories per minute. The average energy intake was 2000 kcal/day (17% protein, 33% fat and 50% carbohydrates) for girls and 2200 kcal/day (17% protein, 30% fat and 53% carbohydrates) for boys. The study was conducted through three training sessions per week over five weeks, 45 minutes of different interval training consisting of playing basketball, running, cycling, and non-contact boxing and kickboxing with a similar 10-minute warm-up followed by different rest periods. The three types of training were performed: (a) in three sets of 10 min / three min passive rest in a three-on-three basketball game; (b) in two sets of three min work / three min passive rest and running at a free cadence for a maximum distance; and (c) in three sets of eight min repetitions of 10 seconds of hitting the bag / 20 seconds of passive rest. Measurements were taken before and after the intervention, including Body composition (BMI, weight, body fat percentage), physical self-perception and physical fitness (6 min walk and work), and related physiological responses (HR peak and blood lactate concentration). Significant improvements were found in body composition, physical condition and physical fitness (endurance, activity level, sports competence and appearance). This five-week HIIT program combined with diet is an effective means of improving body composition, physical condition, and physical fitness in obese adolescents, with the effects on physical fitness being greater in girls. The authors investigated[30] the effects of HIIT on musculoskeletal fitness in school children aged 8–10 years. The study included 295 Danish children, divided into small groups: a ball game group (n=96, four schools, five classes); a circuit training group (n=83, four schools, four classes); and a control group (n=116, two schools, five classes). The study lasted over 10 months, with 3×40 min/week of exercise. X-rays and absorptiometry scans were used to determine bone mineral density, bone mineral content, and body mass. The following tests were used to determine muscular fitness: flamingo balance, standing long jump, and 20m sprint. The results indicate that 3×40 min/week of HIIT including ball games or circuit training throughout the school year improves bone mineralization and several aspects of muscle fitness in children aged 8–10 years. Well organized physical education classes can positively contribute to the development and health of musculoskeletal fitness in school children.

In a study[31], the researches investigated the effects of a HIIT program on physical fitness and intelligence in children. This study involved 56 subjects, divided into an experimental and a control group. The experimental group performed three HIIT training sessions of 8 to 10 min per week for 4 weeks. Before and after the study, 20m running, sit-ups, and long jumps were assessed as a test of physical fitness. The findings of the study suggest that HIIT has positive effects on physical fitness indicators such as cardiorespiratory endurance and muscular endurance. The effect of HIIT was tested in 16 female swimmers with an average age of 15.8 years for seven weeks, and an improvement in swimming performance was shown in the experimental group that practiced HIIT[32]. In their study[33], the authors analyzed the effect of HIIT based on functional exercises on body mass index and cardiorespiratory capacity in adolescents. The study, which lasted over 7 weeks, involved 26 adolescents randomly divided into an experimental and a control group. The experimental group showed a significant increase in cardiorespiratory capacity and a significant decrease in body fat percentage. The control group showed only a significant increase in cardiorespiratory capacity. The training was based on the Tabata method. It consisted of 4 min of training, with 8 intervals of maximal effort, each interval lasting 20 s, followed by a 10 s rest period. The authors conclude that HIIT protocols represent a promising way to reduce body fat percentage and improve cardiorespiratory fitness, as well as support adolescents to reduce their sedentary lifestyle through physical education classes. The aim of the study[34] was to compare the effects of high-intensity interval training (HIIT) and dietary advice on cardiometabolic biomarkers, hormonal parameters, and cardiorespiratory fitness in adolescent girls with obesity. Adolescent girls with obesity (n=44, ages 13-19) were randomly assigned to two groups: an experimental group that performed HIIT and received dietary advice (n=22), and a control group that received only dietary advice (n=22). The study lasted 12 weeks. The concentration of inflammatory biomarkers, biochemical and hormonal tests, oral glucose tolerance test, cardiorespiratory fitness, PA level and diet were assessed. Both groups had significant improvements in body mass index (BMI), BMI standard deviation, body fat percentage, and systolic blood pressure. Positive effects on waist circumference, waist/height, diastolic blood pressure, CRP, maximal heart rate, and resting heart rate were observed only after the diet+high-intensity interval training program. There was no significant change in maximal oxygen uptake, lipid profile, and hormonal parameters between groups after intervention. Dietary advice reduced BMI, body fat, and systolic blood pressure in obese adolescent girls. In the study[35], the authors aimed to determine the effectiveness of HIIT at school on aerobic fitness and hemodynamic parameters in 46 students divided into an experimental (n=22) and a control group (n=24). During the 3-month exercise program period, students in both groups had regular physical education classes twice a week. The experimental group had HIIT during the first 20 min of physical education class. In addition to the aerobic fitness test, peripheral and central systolic blood pressure and aortic pulse wave velocity were measured. Significant differences in the effects of HIIT in the experimental group were noted for aerobic fitness ($p=0.007$), peripheral systolic blood pressure ($p=0.038$), central systolic blood pressure ($p=0.041$), and aortic pulse wave velocity ($p=0.031$). HIIT has shown positive effects on aerobic fitness and hemodynamic parameters in children. The aim of the research[36] was to examine the effect of HIIT over four weeks in 56 soccer players and showed improvements in cardiorespiratory fitness in the group of soccer players who trained with a HIIT program, while the group who worked with a moderate-intensity training program showed improvements in muscular endurance. In their study[37], the authors investigated the effects of HIIT and diet on body composition and physical fitness in obese adolescent girls (48) divided into two groups: an experimental group (24 subjects aged 15.5± 0.7 years) who received HIIT and a diet program led by a nutritionist at school; and a control group (24 subjects aged 15.7± 0.6 years) who maintained their usual activities in physical education classes. HIIT consisted of 10 sets of bodyweight exercises three times a week for eight weeks. The experimental group participated in a nutrition program led by a nutritionist twice a week. In addition to the body composition assessment, the subjects performed a prepared squat jump (CMJ), a medicine ball throw as a strength test, and a Yo-Yo test. The results show that there was a statistically significant difference between the groups in the javelin throw test ($p<0.001$) and the Yo-Yo test ($p=0.024$). A significant improvement was obtained in the

anthropometric test (p=0.004) and in the CMJ (p=0.001). This study showed that an 8-week school-based HIIT intervention and a dietary intervention, three times a week, can improve body composition, as well as muscle and physical aerobic performance in overweight adolescent girls. A study[38] in which 121 students aged 11 to 15 years at a high school in Baden-Württemberg (Germany) were tested confirmed the excellent effects of training on the aerobic fitness of adolescents in a relatively short time. The students had three different forms of HIIT training that differed in duration and content (4×4 HIIT, 12×1 HIIT, circuit), twice a week for 6 weeks (10-12 training sessions). Strength and endurance performance were determined before and after the intervention. The results confirmed that all three HIIT programs led to significant improvements in aerobic fitness ($p<0.001$). The authors[39] determined the effects of a twelve-week program of high-intensity indoor games on physical fitness in girls aged 12–14 years. The study was conducted on 59 adolescent girls aged 13.2 ± 0.3 years, randomly assigned to an experimental group that participated in a games program (football, basketball, handball, and volleyball) and a control group that participated only in mandatory physical education classes. Physical fitness was assessed using standardized tests: prepared squat jump (CMJ), free-arm squat jump (CMJ free arms), squat jump (Squat Jump), overhead medicine ball throw, 30s sit-ups, and the Yo-Yo test to assess recovery speed. There was a significant difference between groups for the standing long jump ($p<0.001$), overhead medicine ball throw ($p<0.001$), 30-s sit-ups ($p=0.030$), free-arm squat jump (CMJ) ($p<0.001$), and Yo-Yo recovery test ($p=0.004$). The results of this study indicate that after-school play significantly improved adolescent PA and fitness compared to adolescent girls who received regular physical education (PE). The authors believe that just two additional training sessions per week are enough to lead to significant changes in physical fitness in adolescent girls.

The authors conducted a study[40] on 187 students (66 boys and 121 girls), divided into two groups: an experimental group that followed a 10-week physical education curriculum supplemented with Tabata training and a control group attending classic physical education class. The intervention lasted 14 min during one physical education class per week. Before and after the intervention, anthropometric measurements were taken, and each participant was tested with tests to assess muscle strength, flexibility, speed/agility, and cardiovascular efficiency. In the experimental group, boys experienced a significant decrease in body fat (by 1.77%, $p<0.05$) and an increase in cardiovascular efficiency ($p<0.05$). Girls only increased cardiovascular efficiency ($p<0.001$). However, small changes in motor parameters were observed in all participants. The Tabata training program has shown partial effectiveness but needs to be individualized and pay attention to gender differences.

Conclusion

Physical activity plays a major role in maintaining health and improving quality of life. Adolescents who practice HIIT have improved cardiorespiratory fitness, aerobic and muscular endurance, and strength. The proven health benefits of regular physical activity in adolescents are reduced body fat, reduced risk of cardiovascular and metabolic diseases, and reduced anxiety and depression. Performing HIIT is very simple and does not require special conditions. This is a circumstance for all educational institutions to make an effort and provide appropriate requisites for the well-being of their students. It is recommended that physical education teachers and professors always be in constant contact with their students through the education system and point out the importance of physical and health education in society.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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VIŠESTRUKA ULOGA HIJALURONSKE KISELINE U STOMATOLOGIJI

THE MULTIFACETED ROLE OF HYALURONIC ACID IN DENTISTRY

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Sažetak

Uvod: *Poznato je da lokalni tretmani efikasno omogućavaju da visoke doze lekova direktno dospeju u meka tkiva gingive i parodontalni ligament, kao i u tvrde strukture kao što su alveolarna kost i cement. Pored svoje dobro utvrđene uloge u promovisanju zarastanja nakon stomatoloških procedura, hijaluronska kiselina (HA) je sada prepoznata kao održiva potporna terapija za hronična upalna stanja.*
Materijal i Metode: *Naša studija je sprovedena da bi sistematski pregledala dostupna literatura iz dveju oblasti: efikasnost HA kao dodatnog lečenja hronične upale i prednosti HA u lečenju zuba. Pretražen je PubMed, Google Scholar i Ovid koristeći kombinaciju ključnih reči i MeSH termina;*
Rezultati: *od 28 studija odabranih na osnovu naših kriterijuma za uključivanje, koje su pokrivale tri rada u vezi sa gingivitisom, trinaest za hroničnim parodontitisom, 7 sa implantološkim procedurama za oralne ulcerima.*
Zaključci: *Utvrđeno je da lokalna primena HA ne samo da značajno pomaže postoperativnom dentalnom oporavku, već je dobra i za pacijente sa hroničnom inflamacijom gingive/parodonta i onima koji pate od oralnih ulkusa.*

Ključne reči: *hijaluronska kiselina, oralno zdravlje, biokompatibilni materijal*

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Abstract

Background: *Topical treatments are known to effectively deliver high doses of drugs directly to both the soft tissues of the gums and periodontal ligament, as well as to the hard structures like the alveolar bone and cementum. In addition to its well-established role in promoting healing post dental procedures, hyaluronic acid (HA) is now being recognized as a viable supportive therapy for chronic inflammatory conditions.*
Materijal and Methods: *Our study was conducted to systematically review the available literature on two fronts: the efficacy of HA as an adjunctive treatment for chronic inflammation and the benefits of HA in dental healing. We searched PubMed, Google Scholar, and Ovid using a combination of keywords and MeSH terms;*
Results: *from the 28 studies selected based on our inclusion criteria, which covered three papers related to gingivitis, thirteen to chronic periodontitis, seven to dental surgeries (including implants and sinus lifts), and three to oral ulcers.*
Conclusions: *we found that topical HA application not only significantly aids postoperative dental recovery but also bodes well among patients with chronic gingival/periodontal inflammation and those suffering from oral ulcers.*

Key words: *hyaluronic acid, oral health, biocompatible material*

Introduction

Hyaluronic acid (HA) is not a sulphated glycosaminoglycan but a natural one. What makes it stand out is its high molecular weight which ranges from 4,000 to a whopping 20,000,000 Daltons[1]. This polymer's unique structure comprises polyanionic disaccharide segments made up of glucuronic acid and N-acetyl glucosamine linked in a complex pattern by alternating β-1,3 and β-1,4 glycosidic bonds. HA can be found all over the body— from connective tissues' extracellular matrix to joints' synovial fluid (embryonic mesenchyme, vitreous humor) — due to its presence it significantly affects other organs like skin as well as various other tissues among them dentine [1]. In dentistry it plays key roles not only in maintaining healthy soft periodontal issues (gingiva plus ligament) but also in extending into hard tissue such as alveolar bone & cementum: thus, covering different structural functions across these tissues. HA plays an indispensable role in the maintenance and health of soft periodontal tissues, the gingiva and periodontal ligament, and extends its utility to hard tissues, including alveolar bone and cementum[2,3]. The most important function of HA is its regulatory capacity in the inflammatory response. In the specific context of periodontal tissues, the gingiva, periodontal ligament and alveolar bone, HA is synthesized in high molecular weight forms by the action of hyaluronan synthase enzymes4. However, under conditions of chronic inflammation, such as gingival tissue inflammation or during post-operative recovery after implant or sinus lift surgery, high molecular weight HA is largely degraded into lower weight molecules[4]. This degradation process is accelerated by reactive oxygen species (ROS), including superoxide and hydroxyl radicals, which are predominantly produced by polymorphonuclear leucocytes and other inflammatory cells during phagocytosis of bacteria in periodontal diseases[5]. The resulting low molecular weight HA fragments play a critical function in signaling tissue damage and orchestrating the mobilization of immune cells to the site of injury or infection. In contrast, intact high molecular weight HA plays a critical role in modulating the immune response to prevent an excessive inflammatory reaction[6]. Low molecular weight HA is predominantly found in the gingival tissues of patients in the early stages of periodontitis, probably due to the action of bacterial hyaluronidases7. In addition to its role in inflammation and immune modulation, HA contributes to the structural and homeostatic balance of tissues by influencing osmotic pressure and facilitating tissue lubrication due to its exceptional hygroscopic nature[6,7] . This property of HA allows it to form hydrogen bonds with adjacent carboxyl and N-acetyl groups when incorporated into an aqueous solution, thus maintaining its conformational rigidity and retaining water. In addition, HA boasts remarkable viscoelastic properties that hinder the penetration of viruses and bacteria into tissues, emphasizing its protective function [7,8]. Furthermore, HA is an integral part of the sequential steps of the wound healing process, which includes inflammation, granulation tissue formation, epithelialization, and tissue remodeling in both mineralized and non-mineralized tissues [8]. The broad spectrum of functions attributed to HA has stimulated advances in the development and application of HA-based biomaterials for the treatment of various inflammatory conditions10. Given the multifunctional role of HA in wound healing and the similarity of biological principles governing gingival and bone healing, it is plausible that HA exerts comparable beneficial effects in the healing processes of mineralized and non-mineralized periodontal tissues [9].The use of HA spans several branches of medicine and its safety profile is further exemplified by the absence of contraindications or drug interactions. Recent years have seen the development of HA formulations for topical administration aimed at the adjuvant treatment of acute and chronic dental and gingival conditions, such as tissue healing after oral surgery, supported by abundant evidence from animal model studies on the role of HA in dentistry[10,11]. While existing literature reviews have explored the dental applications of HA, particularly in the context of treating periodontal disease, a comprehensive evaluation covering the full spectrum of HA's therapeutic effects on acute and chronic inflammatory diseases within the oral cavity remains elusive [12,13]. Our study aims to systematically review the published literature on the therapeutic impact of HA, to clarify and classify its main applications in dentistry, to demystify the pathophysiological basis and protocol for the application of HA in the post-operative setting, and to evaluate the most effective parameters for the use of HA in dentistry.[14]

Materials and Methods

The review was registered in the PROSPERO database (the International Prospective Register of Systematic Reviews hosted by the National Institute of Health Research, University of York, Centre for Reviews and Dissemination) on 25 March

2024, according to the guidelines with the identification number CRD-42024535008. To gather the necessary research for our study, we conducted a systematic search across several databases, including PubMed, Google Scholar, and Ovid. Our research, which began in June 2015, systematically examined the potential benefits of topical HA application in the management of both acute and chronic inflammatory diseases. After an initial screening of 278 articles, only 78 were reviewed, of which only 28 were selected for the above review. The PICO question was: ''Is the use of HA in randomized controlled clinical trials effective for oral health for the management of gingivitis, ulcers, wounds, and gingival recession compared with the control group?'' (Table 1). We used a combination of keywords and, for PubMed, specific medical subject headings to refine our search. These terms included combinations such as "hyaluronic acid and periodontitis," "hyaluronic acid and gingivitis," and similar phrases targeting various dental conditions and treatments involving hyaluronic acid without imposing any restrictions on the publication year. Our approach to selecting literature adhered strictly to the PRISMA guidelines. We set specific inclusion criteria for our review: articles had to be in English, involve human - controlled trials, and present either histological or clinical evaluations of hyaluronic acid effect size in dental disease contexts. We excluded a variety of document types that did not meet our criteria for primary research, such as literature reviews, technical notes, letters to editors, and instructional courses. The evaluation and selection of articles were carried out independently by two of our authors, AR and AMP, who reviewed the full texts for relevance to our topic. They excluded any paper that lacked the specific content we required for our analysis. Additionally, we examined the reference lists of all articles that passed our initial criteria to uncover any pertinent studies that our electronic search might have missed. Initially, we removed duplicates and identified articles strictly related to our topic of interest in each journal. At this point, we excluded studies conducted on animal models and in vitro studies, focusing solely on human trials. We further narrowed our selection by removing studies investigating the use of hyaluronic acid in treating oral mucositis caused by chemotherapy, radiation therapy, allogeneic hematopoietic stem cell transplantation, or in palliative care settings. After completing our meticulous selection process, we concluded with a final tally of 28 relevant publications for our review, as depicted in Figure 1 of our study documentation.

Quality Assessment and Risk of Bias

Two reviewers (A.P. and L.A.) assessed the risk of bias using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). Any disagreement was discussed until a consensus was reached with the help of a third reviewer (A.M.P.) (Figure 2). Using RoB 2, the risk of bias among the studies analyzed was estimated and is reported in Figures 2 and 3. Regarding the randomization process, 75% of studies had a high risk of bias. Regarding allocation concealment, 100% of studies had a low risk of bias. Only 25% of studies excluded performance bias, and 25% reported all outcome data; however, 85% of the included studies presented a low risk of reporting bias.

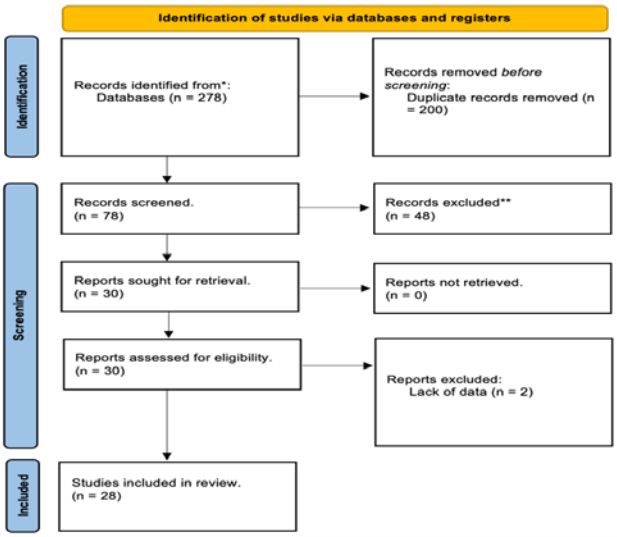

Figure 1: Search strategy flow chart from database (*Scopus, Embase, Google Scholar, Pubmed, Web of Science). **Reports excluded for lack of data

Table 1: Explication of PICO

PICO'S QUESTION	
Participants	Healthy participants with no restrictions on age and sex who were in good general health with gingival recession, periodontitis, oral ulcers, surgery wounds
Intervention	Application of HA in conjunction with surgical procedures.
Comparison	The same surgical procedures without HA or substitute
Outcomes	Pathology reduction

Table 2: Main studies included in this review

AUTHORS	MEAN AGE	HA GROUP	CONTROL GROUP	TYPE OF TREATMENT	PARAMETERS EVALUATED	CLINICAL EVIDENCE
Jentsch [15]	50 male (17 +- 39 y)	25 with use of HA	25 with placebo	Gel on gingivitis	The study evaluated oral health through clinical indices (Approximal Plaque Index, Turesky Plaque Index, Papilla Bleeding Index) and crevicular fluid markers (peroxidase, lysozyme) initially and after 4, 7, 14, and 21 days.	The test group exhibited notable enhancements in plaque indices from day 4 and in PBI from day 7, outperforming the placebo group.
Pistorius[1]	60 mixed (32 +- 41 y)	40 with use of HA	20 with reduced use of HA	Spray on gingivitis	Clinical measurements including DMF-T index, API, sulcus bleeding index, PBI, and gingival crevicular fluid were recorded at the start, then after 3 and 7 days.	Clinical parameters were assessed initially, and then at 3 and 7 days. The HA group saw decreases in sulcus bleeding index at both time points, with significant drops in PBI values and gingival crevicular fluid.
Bagde[18]	21 mixed (22 +- 34 y)	11 with use of HA	10 with placebo	Gel in periodontal pocket	A gingival biopsy for histopathological and immunohistochemical analysis, focusing on Ki-67 expression and inflammatory infiltrate evaluation, was conducted 30 days post-treatment.	Treatment with HA gel notably decreased the proliferation index of gingival epithelium and fibroblast cells.
Sahayata[13]	105 mixed	50 with use of HA	50 with reduced use of HA and short follow up	Gel in periodontal pocket	Clinical parameters (API, GI, PBI) were assessed at 1, 2, and 4 weeks from baseline; microbiological parameters were checked at 4 weeks.	Significant improvements in GI and PBI were observed in the test group compared to others. At 4 weeks, all treatment groups saw a significant decrease in anaerobic gram-negative bacilli and an increase in gram-positive coccoid cells from baseline.
Xu[22]	20 mixed (48	10 with use of	20 with placebo	Gel in periodontal	SFFR and sulcus bleeding index were	This study showed an

	+- 64 y)	HA		pocket	measured initially and weekly up to 12 weeks; probing depth and clinical attachment level were checked at the start, and at 6 and 12 weeks. Dentists collected subgingival plaque samples to identify specific bacteria at baseline, and at 6 and 12 weeks.	improvement of all clinical variables in both groups. There are not clinical and microbiological differences between test and control sites.
Johannsen[23]	11 mixed (23 +- 56 y)	10 with use of HA	11 with use of placebo	Spray in periodontal pocket	SFFR and sulcus bleeding index were measured initially and weekly up to 12 weeks; probing depth and clinical attachment level were checked at the start, and at 6 and 12 weeks. Dentists collected subgingival plaque samples to identify specific bacteria at baseline, and at 6 and 12 weeks.	There are not clinical and microbiological differences between test and control sites.
Polepalle[16]	36 mixed (30 +- 65 y)	26 with use of HA	10 with use of reduced HA and short follow up	Gel in periodontal pocket	Bleeding on probing (BOP), API, probing pocket depth (PPD), and clinical attachment level (CAL) were assessed at baseline, 1, 4, and 12 weeks. Colony-forming units (CFU) per mL were assessed at baseline, after treatment, and after 2 weeks.	There was a significant reduction in BOP, API, PPD, and CAL in the test sites than control group. In the test sites there was also a significant reduction of CFUs.
Gontiya[24]	26 mixed (25 +- 55 y)	20 with use of HA	6 with use of placebo	Gel on gingivitis	Clinical parameters GI, PBI, PPD, and Relative Attachment Level (RAL) evaluated at baseline (day 0), and weeks 4, 6, and 12.	The test sites showed statistically significant improvement in GI and PBI at 6 and 2 weeks than control sites.

Rajan[10]	Not specified	33 with use of HA	Not specified	Gel on gingivitis	The clinical parameters evaluated: GI, API, BOP, PPD, CAL at three appointments: before SRP, 4 weeks and 12 weeks after SRP.	The test sites showed statistically significant improvement in GI and PBI at 6 and 2 weeks than control sites.
Cairo[25]	19 mixed (15 +- 41 y)	15 with use of HA	4 with use of placebo	Gel and spray in mild chronic periodontitis	These clinical parameters were evaluated before treatment and repeated at 14 and 21 days: API, BOP, GI, PAL (probing attachment level).	HA gel treatment was more effective, reducing BOP by 92.7% and GI by 96.5%, compared to 75.8% and 79.0% in controls. Periodontitis reduction was significantly greater in the HA-treated area.
Eick[6]	42 mixed (41 +- 72 y)	17 with use of HA	17 with use of placebo	Gel and spray in mild chronic periodontitis	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	The test sites showed statistically significant improvement in GI and PBI at 6 and 2 weeks than control sites.

Chauhan	60 mixed (30 +- 65 y)	30 with use of HA	30 with use of reduced HA	Gel and spray in mild chronic periodontitis	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	At 3 months, change in PPD and CAL was more in Group test than Group control, but the difference was non-significant.
Engstrum[26]	15 mixed (23 +- 54 y)	8 with use of HA	7 with use of placebo	Not specified	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	After 12 months, the test and control groups in surgery showed a bone height difference under 1 mm, visible only in radiographs. Both groups experienced bone height reduction post-scaling. Probing depth decreased as anticipated following surgery and SRP.
Briguglio[8]	15 mixed (23 +- 54 y)	8 with use of HA	7 with use of placebo	Not specified	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	The use of hyaluronic acid in treating infrabony defects provided additional advantages, including improved clinical attachment levels, reduced probing depths, and enhanced predictability, compared to traditional open flap debridement methods.

Bevilacqua[27]	24 mixed (+-51 y)	11 with use of HA	13 with use of placebo	Gel in moderate-severe chronic periodontitis	Clinical variables assessed included API, BOP, CAL, PPD, calprotectin, MPO, and GCF volume on days 45 and 90. Calprotectin, MPO, and GCF quantities were measured at test and control sites on days 7 and 45.	At baseline and 45 days, the HA group showed a significant decrease in probing depth and BOP compared to the control group. Both groups experienced a notable reduction in calprotectin and myeloperoxidase per sample after 1 week, followed by an increase at 45 days.
Fawzy El-Sayed [28]	14 mixed (23 +- 34 y)	7 with use of HA	7 with reduced use of HA	Gel in Chronic periodontitis	BOP, API, PPD, and CAL were assessed at baseline, 1, 4, and 12 weeks. CFUs per mL were assessed at baseline, after SRP and after 2 weeks.	The test sites showed significant improvements in BOP, API, PPD, and CAL compared to the control group, alongside a notable decrease in CFUs.
Araujo Nobre[29]	30 mixed (58.4 +- y)	15 with use of HA	15 with use of CHX	Management of the implant platform and healing screw at implant uncovering with gel	The clinical parameters evaluated: modified plaque index (mPlI), modified bleeding index (mBI), PPD in mL, suppuration (Sup), clinical implant mobility (mob). Both groups were followed up for 6 months, and the clinical observations were performed on day 10, and at 2, 4, and 6 months post surgery	HA and CHX effectively supported peri-implant health. The HA group had significantly better modified bleeding index at the second check. At 6 months, CHX showed potentially superior outcomes in modified plaque and bleeding indices.

Galli[12]	8 mixed (36 +- 67 y)	4 with use of HA	Not specified	Post implant wound management with gel	The PPDs, gingival recession, and CAL were evaluated before treatment and after 1 year.	After 1 year there were this following result: PPD reduction, gingival recession increase, and CAL gain.
Ballini[7]	19 mixed (43.8 +- y)	19 with use of EHA	Not specified	Post implant wound management with gel	The PPDs, gingival recession, and CAL were evaluated before treatment and after 1 year.	Clinical results showed a mean gain of CAL (gCAL) of 2.6 mm of the treated sites, confirmed by radiographic evaluation.
Koray[11]	34 mixed (23 +- y)	34 with use of HA	34 with use of BnzHCl	Management of Bilateral extraction of the lower octaves with gel HA or BnzHCL spray	Swelling was measured with a tape, and trismus by the maximum inter-incisal opening. Evaluations occurred on the surgery day, and 2- and 7-days post-surgery.	The patients with HA spray experienced statistically significant results for the swelling and trismus values than those with the BnzHCl spray.

Romeo[30]	49 mixed (45.5 +- y)	31 with use of HA	18 with use of placebo	Management of excisional biopsy with HA gel	The lesion area was measured after surgery (T0) and after 7 days (T1). A percentage healing index (PHI) was calculated indicating healing extension in 7 days.	Not specified
Srinivas[31]	Not specified	1 with use of HA	Not specified	Gel on gingival recession	RD, PPD and CAL, was tracked at baseline, and then at 1, 3-, 6-, 12-, and 24-weeks post-surgery.	Despite the lack of statistical significance, the experimental group's root coverage was observed to be more clinically stable than the control group at 24 weeks.
Lee[19]	50 mixed (40 y)	33 with use of HA	17 with placebo	Gel on oral ulcers in Behcet's Disease	Subjective assessment: number of ulcers, healing period and VAS; Objective assessment: number and maximal size of ulcer.	Ulcer inspection revealed a 57.6% reduction in numbers and a 78.8% decrease in area among patients. Post-treatment, significant improvements were seen in swelling and local heat.

Nolan[3]	106 mixed (37 y)	60 with use of HA	56 with use of placebo or reduced level of HA	Gel on oral ulcers	Average ulcer count, ulcer history over 7 days, patients experiencing ulcers in this period, and treatment assessment scores ranging from very good to not recorded.	Both groups noted quick discomfort relief from ulcers, lasting around 30 minutes before reverting towards initial levels. Ulcer counts slightly dropped over 7 days, regardless of treatment. By day 5, the HA group reported significantly fewer ulcers compared to the placebo group. Despite new ulcers appearing in both groups during the study, the HA group saw a notably lower incidence of new ulcers by day 4.
Lopez[21]	1 man (32 y)	1 with use of HA	Not present	Application of HA gel in intracrestal sinus lift	The filling volume obtained was measured with a comparative software programme and using an ellissoid formula. This technique allows the surgery to be performed in a way that is both minimally traumatic and invasive, fully careful of the membrane and represents a viable alternative to those surgical techniques for crestal sinus lift currently in use.	Not specified
Schwartz[14]	26 mixed (45 +- y)	26 with use of HA	Not present	Application of HA gel and bone graft in lateral sinus lift	All 32 sinus lifts succeeded, with Cone Beam scans showing bone height increasing from 2.84 mm pre-treatment to 15.2 mm post-treatment.	This study confirmed the hypothesis that new bone formation is graft dependent alone or in combination with other materials.

Weindl[9]	45 mixed (23 +- 45 y)	25 with use of HA	20 with use of placebo	Treatment of gingival recession with use of HA gel	Recession depths in the first, third, and sixth month were 1.82 ± 0.442, 1.31 ± 0.47 mm, and 0.91 ± 0.29, respectively, which showed a significant reduction.	Within the limitations of the present study, the data obtained by periodic assessment of the clinical parameters indicate the use of amnion membrane and hyaluronic acid, and proper technique may thus be the panacea for root coverage procedure.
Gorski[32]	24 mixed (34 +- y)	24 with use of HA	Not applicable	Use of HA gel in the treatment of multiple gingival recession using the modified coronally advanced tunnel technique (MCAT) combined with subepithelial connective tissue graft (SCTG), with or without cross-linked hyaluronic acid (HA).	No significant improvement in root coverage was observed because of adding HA. After 6 months, mean root coverage (MRC) was 85% for SCTG + HA group and 83% for SCTG group (p = 0.9819). Complete root coverage (CRC) was observed in 91% (test) and 93% (control) of the cases (p = 0.9001).	Both treatments were similarly effective in treating multiple GRs and led to comparable improvements in clinical parameters. However, application of HA improved the appearance of soft tissue texture.

(y:years; PBI: papilla bleeding index; HA; hyaluronic acid; API: Approximal plaque index; DMF-T:Decayed – Missing – Filled – Teeth; GI:gingival index; SFFR: Sulcus-Fluid-Flow-Rate; BOP: bleeding on probing; PAL: Probing Attachment Level; CAL clinical attachment level; PD: probing depth; SRP: Scaling root planning; MPO: myeloperoxidase; GFC: crevicular fluid volume; Chlorhexidine; EHA: esterified low molecular HA; BnzHCL: BenzydamineHCL; RD: recession deep)

Figure 2. Quality assessment

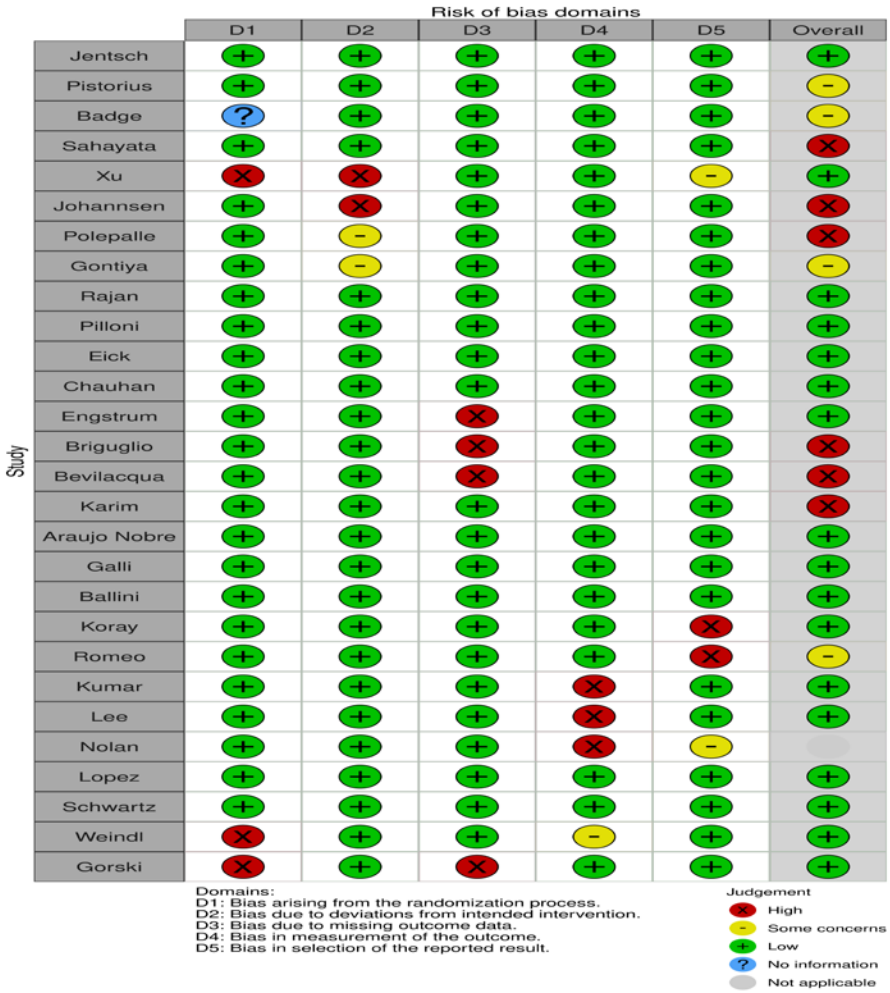

Figure 3. Risk of bias.

Resluts

Navigating through the world of dentistry, the role of Hyaluronic Acid (HA) emerges not just as a treatment modality but as a beacon of innovation, bridging traditional practices with the promise of enhanced healing and patient comfort. The journey into its application spans various facets of dental care, each illuminated by studies that not only underscore its efficacy but also hint at the broader potential of HA in revolutionizing dental treatments (Table 2).

In the Battle Against Gingivitis

The story of HA begins in the realm of gingivitis, where its capabilities are put to the test. The study by Jentsch et al.[15] revealed how a seemingly simple regimen of topical application of 0.2% HA twice daily can lead to significant improvements in oral health markers such as plaque indices and papillary bleeding index (PBI), heralding almost a new dawn in the non-invasive management of gingivitis. The test group showed a significant improvement in the study area for plaque indices from day 4 ($P = 0.011$) and PBI from day 7 ($P = 0.001$) compared to the placebo group. Crevicular fluid variables improved significantly in the centre of the area of inflammation studied in the test group. This narrative is further enhanced by Pistorius et al. [1], who, through their exploration of an HA-based spray, reveal its powerful effect in containing fissure bleeding. This is a testament to the versatility of HA, demonstrating that whether in gel or spray form, its therapeutic potential remains undiminished. The work of Sahayata [13] et al. adds depth to this story, highlighting how HA, when used in conjunction with conventional oral cleansing and hygiene practices, can significantly outperform placebo treatments. It is as if HA whispers to

the inflamed gum, restoring it to health more effectively than conventional methods alone. Clinically, a significant difference ($p<0.05$) was found for GI and PBI in the test group compared to the other groups, but the reduction in PI was not significant. In the negative control and placebo groups, the difference between the clinical parameters was not significant.

Chronic Periodontitis: A New Frontier

The narrative then shifts to the difficult terrain of chronic periodontitis, where the role of HA expands from supporting actor to protagonist. The local application of HA gel emerges not only as a treatment, but as a beacon of hope, reducing the indications of proliferation and sedating the inflammatory assault, thus charting a new course in periodontal healing. Jentsch [15] demonstrated that subgingival application of a 0.2% hyaluronic acid gel (GENGIGEL®) with SRP in patients with chronic periodontitis improved GI and bleeding index (BI) compared to control sites, as confirmed by a gingival biopsy, which showed a significant reduction of the inflammatory infiltrate.

The saga deepens with the collaborative efforts of Johannsen et al. and Polepalle et al. [16], who, through their meticulous research, unveil the symbiotic potential of HA and Scaling and Root Planing (SRP). Their findings praise HA's ability to significantly reduce bleeding, improve clinical attachment levels and even alter the microbial landscape, painting a picture of a future where HA could be a cornerstone of periodontal therapy [16]. Subgingival administration of 1 mL 0.2 mL 0.8% HA gel once a week for 6 weeks improved sulcus fluid flow rate (SFFR).

Surgical Frontiers and Implant Surgery

The versatility of HA transcends the non-surgical realm, boldly entering the surgical arenas. Here, the work of Araújo Nobre [17] et al. highlights the role of HA in improving the healing milieu of the peri-implant complex, offering a glimpse into its potential to improve implant success rates. Statistically significant differences were found in favour of the HA group in the modified bleeding index at the second observation ($P = 0.003$). The difference was more pronounced in axial implants placed in the fifth sextant ($P = 0.05$). The correlation coefficient between plaque and bleeding index revealed a potentially better outcome for CHX at 6 months.

Bagde [18] et al.'s exploration of HA in the treatment of deep periodontal defects not only highlights its efficacy in reducing pocket depth, but also subtly hints at its role in regenerative dentistry. Meanwhile, research by Ballini [7]et al. suggests the promise of HA in bone regeneration, providing a beacon of hope for those facing the daunting prospect of bone loss. Recession depths in the first, third, and sixth month were 1.82 ± 0.442, 1.31 ± 0.47 mm, and 0.91 ± 0.29, respectively, which showed a significant reduction from the baseline. Recession widths in the first, second, and third weeks were 3.04 ± 0.442 mm, 1.31 ± 0.47 mm, and 1.49 ± 0.59 mm, respectively. There was a statistically significant reduction ($P > 0.005$).[18]

The Healing Touch on Oral Ulcers

In the field of oral ulcers, HA emerges as a gentle healer. Research by Nolan [3]and Lee [19] et al. on its efficacy in the treatment of recurrent aphthous ulcers and Bechet's disease not only emphasizes its therapeutic potential, but also offers comfort to sufferers, promising a future in which pain and discomfort will be only a distant memory26,27. A subjective reduction in the number of ulcers was observed in 72.7% of patients. A reduction in the ulcer healing period was observed in 72.7% of patients; 75.8% reported an improvement in the SEA of pain.

Through this detailed narrative, hyaluronic acid emerges not only as a molecule, but as the harbinger of a new era in dentistry[1,2]. Each study, each discovery adds a layer to our understanding, painting a picture of a future in which HA stands as a pillar of dental care, bridging the gap between traditional methods and the promise of regenerative and minimally invasive treatments [16,20,21]. It is a story of transformation, hope and the relentless pursuit of improvement in dental care, heralding a future where patient comfort and healing are paramount[6,7].

Discussion

Hyaluronan, a versatile glycosaminoglycan embedded in the very tissue of the extracellular matrix of vertebrate tissues, is notable not only for its critical role in wound healing, without leaving scars, but also for its profound implications for oral

health and dentistry [33,34]. Delving deeper into the literature reveals intriguing insights that place hyaluronan at the heart of periodontal tissue healing, suggesting its promising utility in the management of periodontal disease [15,30,34]. HA has proven to be a valuable clinical tool in various fields of medicine, such as ophthalmology, osteology and dermatology, due to its unique biochemical and biophysical properties. Its application in dentistry has recently received increased attention, with HA-based products demonstrating efficacy in the management of gingivitis through both anti-inflammatory and anti-edematous effects. Studies have shown that HA gels, particularly when used in conjunction with mechanical treatments such as scaling, significantly reduce gingival inflammation [26,28]. However, the overall effectiveness of HA in periodontal therapy varies, attributed to different product formulations, application methods and study biases, making it difficult to recommend a specific approach [8,29,35]. Research on the use of HA in the treatment of chronic periodontitis has shown improvements in gingival health when combined with scaling and root planning, although the impact on deeper periodontal parameters is less pronounced[36]. Other studies have explored the role of HA in surgical periodontal therapy and bone regeneration, with positive results in bone growth when used with autologous bone or as a bone cyst filler. The application of HA in the management of temporomandibular joint (TMJ) disorders and oral ulcers, including those of Behçet's disease, has also been reported, highlighting its potential to reduce pain and improve healing[19]. Despite these advances, the exact mechanisms by which HA influences cell behavior and tissue regeneration remain unclear, highlighting the need for further research. After gingivectomy surgery, wounds heal through a process known as secondary intention, which can lead to discomfort and slower recovery than wounds that heal by primary intention. To accelerate the healing process and alleviate discomfort, photo biomodulation (PBM) has emerged as a promising adjunctive treatment, attracting the interest of numerous researchers. Studies have consistently shown that PBM therapy is an effective supportive method that can improve recovery after gingivectomy. In addition, the literature cites several other topical agents that have been shown to contribute to improved wound healing after gingivectomy, including HA gel, herbal gels, non-thermal atmospheric pressure plasma applications, and vitrocure® gel[12]. Furthermore, in agreement with our results, Turgut Çankaya[36] et al. evaluated the effect of HA application after laser-assisted frenectomy. The authors concluded that HA is a viable option to reduce the wound surface within 14 days and act as a wound dressing after frenulectomy. The soft tissue healing potential of HA in our study can be explained based on a histological study conducted by Araujo Nobre [29]et al., who concluded that HA gel (0.2%) has anti-inflammatory properties and induces a increased formation of epithelial tissue and increased vascular supply of connective tissue, histologically. This includes understanding the effects of HA molecular weight and concentration on cells, evaluating the potential toxicity resulting from HA modification techniques, and conducting comprehensive clinical studies to consolidate their effectiveness in dentistry and other medical applications [32]. The future of HA in the clinical setting appears promising, with expected advances in line with the goals of translational and evidence-based medicine, paving the way for personalized therapeutic approaches. The essence of the benefit of hyaluronic acid extends well beyond the superficial layers of the marginal gingiva, reaching the depths of the periodontal tissues [37,38]. It takes advantage of its well-documented wound healing mechanisms to promote remission of symptoms, acting as a relief for those suffering from periodontal disease. This ability to alleviate discomfort and accelerate healing is particularly beneficial in the context of gingivitis and chronic periodontitis, offering a glimpse into a future where treatments align perfectly with the body's natural healing process[18,31,39,40]. Furthermore, the potential of hyaluronan shines through following surgical procedures, such as implants and sinus lifts, where its topical application can significantly accelerate the healing process[41,42]. This not only results in faster recovery times, but also significantly alleviates the discomfort patients experience after surgery, making the healing process smoother and more bearable. In the fight against oral ulcers, Hyaluronan emerges as a formidable ally. Its therapeutic ability underlines its value in a comprehensive dental care strategy, offering hope and healing to those struggling with these painful lesions[36]. The discussion of hyaluronan also brings to light the superior efficacy of topical treatments in delivering pharmacological agents directly to the teeth

and oral mucosa. This localized approach ensures the delivery of high concentrations of therapeutic agents where they are most needed, in stark contrast to systemic routes that may dilute their efficacy[41]. The forward path invites more granular research, especially laboratory investigations and large-scale randomized clinical trials. These future studies are key to unlocking the full potential of hyaluronan as a carrier for periodontal tissue cells, potentially revolutionizing tissue regeneration techniques for both mineralized and non-mineralized periodontal tissues. Still, the questions linger regarding the optimal modes of administration, whether through spray, gel, or nebulization-and more effective post-operative treatment programs tailored to each dental condition. These investigations pave the way for a deeper exploration of the role of hyaluronan in dentistry, suggesting a future in which its application is as nuanced as it is transformative[25,32,42,43]. As we peer into the horizon, hyaluronan's promise to improve dental care and patients' healing pathways is undeniable. His journey from the extracellular matrix component to the cornerstone of dental therapy is a testament to the power of harnessing nature's healing mechanisms, offering a brighter and painless future for patients around the world[15,44,45].

Conclusion

Hyaluronic Acid (HA) is currently widely used in various medical fields, demonstrating considerable potential in dentistry — particularly for the management of inflammatory conditions. A detailed analysis of 28 clinical studies has shed light on the positive effects of HA in tissue repair and wound healing. The findings imply that the application of HA topic-ally could play a significant role not only during the recovery phase post dental surgeries but also in dealing with gingivitis and periodontitis: conditions affecting some patients. It could lead to substantial improvement with quality life among those affected by these dental ailments, given that HA possesses therapeutic properties. While based on these promising findings, it is considered prudent to embark on more investigations through laboratory research, as well as larger randomized controlled trials at a wider scale. This is important to help establish the full effectiveness of HA and further widen its use in dental practices.

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FAKTORI RIZIKA ZA POJAVU OSTONEKROZE VILICA POVEZANE SA UPOTREBOM MEDIKAMENATA

RISK FACTORS FOR THE OCCURRENCE OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW

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Sažetak

Uvod: *Osteonekroza vilica povezana sa upotrebom lekova (medikamenata) ili poznata kao „Medicine related osteonecrosis of jaw“ MRONJ - predstavlja novi patološki entitet, koji se pojavio kao neželjeno dejstvo lekova koji se koriste kod različitih oboljenja a narušavaju normalnu homeostazu koštanog tkiva. Ova vrsta osteonekroze nastaje kod primene antiresorptivnih lekova prvenstveno iz grupe bisfosfonata, ali i drugih lekova koji imaju različiti mehanizam delovanja na koštano tkivo, ali sa posledičnim razvojem osteonekroze.*
Cilj *rada bio je ukazati na faktore koji utiču na razvoj MRONJ-a.*
Rezultati: *Sistemski faktori pored upotebe lekova su brojni, a pre svega endokrini i hormonalni poremećaji kao i imunodefiijencija organizma. Faktori rizika za razvoj MRONJ su vađenje zuba u najvećem broju slučajeva, zatim intervencije koje uključuju zahvatanje koštanog tkiva vilica, implantološke procedure, kiretaža parodontalnog džepa, periapikalne operacije, itd. Preventiva MRONJ-a sprovodi se multidisciplinarnim pristupom koji podrazumeva saradnju reumatologa, onkologa i stomatologa. Usaglašeni multidisciplinarni premedikacijski tertman smanjuje incidencu pojave MRONJ-a za 77,3%. U zavisnosti od stadijuma razvoja MRONJ, postoje konzervativne i hirurške metode lečenja, koje se moraju izvoditi blagovremeno, jer neprepoznavanje i napredovanje lezije dovodi do značajnih posledica po zdravlje i život pacijenta.*
Zaključak: *Osteonekroza vilica povezana sa upotrebom lekova može biti asimptomatska, neodređena lezija koja se veome teško dijagnostikuje, ali se bez blagovreene dijagnostike i terapije može razviti i preći u teži oblik, komplikovan za lečenje, sa patološkom frakturom vilice, mukokutanim fistulama i velikim ožiljcima i unakaženjem Preventiva i multidisciplinarni pretretman i tretman su od ključnog značaja za redukciju pojave i napredovanja ove lezije.*

Ključne reči: *osteonekroza,lekovi, prevencija, terapija*

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Abstract

Introduction *Medication-related osteonecrosis of the jaw (MRONJ) represents a new pathological entity that appears as a side effect of medications used in various diseases disrupting the normal homeostasis of bone tissue. This type of osteonecrosis occurs as consequence of antiresorptive drugs, primarily from the bisphosphonate group, but also other drugs that have a different mechanism of action on bone tissue.*
Aim was *to point out the factors leading to the development of MRONJ.*
Rezults: *There are many systemic factors, primarily endocrine and hormonal disorders, as well as the body's immunodeficiency. Risk factors for the development of MRONJ are interventions that involve the bone tissue of the jaws, primarily tooth extraction, implant procedures, curettage of the periodontal pocket, periapical operations, etc. Prevention from MRONJ is carried out with a multidisciplinary approach that involves the cooperation of rheumatologists, oncologists and dentists. Coordinately applied multidisciplinary premedication treatment reduces the incidence of MRONJ by 77.3%. Depending on the stage of development of MRONJ, there are conservative and surgical methods of treatment, which must be performed in a timely manner, because the progression of the lesion leads to significant consequences for the patient's health and life.*
Conclusion: *Osteonecrosis of the jaw associated with the use of medicaments can be an asymptomatic, indeterminate lesion that is very difficult to diagnose, but without proper diagnosis and therapy it can develop and turn into a more severe form, complicated for treatment, with a pathological fracture of the jaw, mucocutaneous fistulas and large scars and mutilation. Prevention and multidisciplinary pretreatment and treatment are of key importance for reducing the occurrence and progression of this lesion.*

Key words: *osteonecrosis,medications, prevention, therapy*

Introduction

Medication-related osteonecrosis of the jaw presents the new pathological entity that appeared in the medical public less than two decades ago. MRONJ is actually a side effect of some medicaments used for treating different illnesses, endangering normal homeostasis of the bone tissue. MRONJ happens during or after using antiresorptive therapy such as bisphosphonates, non-bisphosphonates, antiangiogenic, oncological or immunomodulating therapy. The typical clinical presentation is a necrotic bone that is partially exposed necrotic jawbone in the mouth cavity. The prevalence of MRONJ is different, according to the literature, it amounts to 2.3–3.4%[1,2] depending on the type and the length of the therapy[3,4]. Most of the MRONJ cases are related to tooth extraction[5]. There is data about the deaths caused by complications of MRONJ[6].

1. Main causes for the occurrence of MRONJ

1.1 Bisphosphonates (BP) are medicaments used in pathological conditions of the body's bones, such as osteoporosis, osteomalacia, osteogenesis imperfecta, multiple myeloma, and bone metastases of the breast, prostate and other cancers. Bisphosphonates are divided into two groups: nitrogen-containing BP, which include zoledronate and alendronate and non-nitrogen-containing BP, which include etidronate and clodronate. The presence of two amino groups is a significant factor differentiating their affinity for bone hydroxyapatite[7], where BP fulfil their main role. There are three potential mechanisms of BP acting that give them unique effects. The first one is the inhibition of calcium carbonate precipitation while molecules of bisphosphonates incorporate into hydroxyapatite matrix. BP make a hard connection with osteoclasts, and after osteoclast apoptosis, BP stay in the extracellular matrix where they incorporate into surrounding bone, and show cumulative effects[8]. This way of acting enables BP to be in the bone for more than 11 years[9]. Microstructure of bone tissue changes preventing pathological fracture of the bones. The second manner is the inhibition of osteoclast differentiation and osteoclast apoptosis, resulting in decreased bone resorption. The third manner is reduction of bone metabolic activity. Osteoblast bone repairing activity depends on increasing osteoclasts bone resorption activity in normal homeostasis process. This results in fewer cellular elements left into bone tissue, poorer blood and bone remodeling process.

The first time the side effects of BP became known was in 2003 after some reports about osteonecrosis in oncological patients[10,11]. The first known medications that caused osteonecrosis of the jaw were BP, so this condition was named bisphosphonate related osteonecrosis of the jaw (BRONJ). Still, after getting knowledge that other medications are also able to cause similar symptoms, the name was changed into medication-related osteonecrosis of the jaw (MRONJ[12]). The main reason for occurrence of this lesion in the jaw rather than in some other bones is that jaws have much faster “turn over” than the other tubular bones, especially pronounced in the lower jaw[13]. The physiological process of tissue damage and tissue repair is constantly present in the bones by virtuing normal homeostasis. Bisphosphonates disturb normal homeostasis process and physiological remodelation of jaws. BP also reduce proli-feration and transport of oral keratinocytes, and intoxicate oral mucosa[14] causing fragility to trauma and lack of resistance to small damage. This enables ingress of infections and the creation of fistulas. BP also reduce circulation and normal blood flow through the bones, independently of osteoblastic osteoclastic activity[15]. The lower jaw has a stronger cortex, fewer nutritional channels and reduced circulation, i.e. blood supply, especially in the elderly, so this may be why the presence of MRONJ is higher in the mandible (73%) than in the maxilla (22.5%)[7].

1.2. The non-bisphosphonate antiresorptive drug—denosumab (Prolia) is an antiresorptive agent that exists as a humanized RANK monoclonal antibody that inhibits the RANK ligand, which is necessary for the maturation of osteoclasts from precursor cells in the bone marrow, as well as for the stimulation of osteoclasts to resorb bone. It has been in circulation since 2009. Unlike bisphosphonates, denosumab has a half-life of 30 days, does not have a cumulative effect[5,16] and has a more transient effect on the inhibition of bone resorption. The effect on bone remodeling generally diminishes within 6 months of stopping therapy. Surprisingly, the studies show a high incidence of MRONJ with the use of denosumab[17].

1.3. Antiangiogenic drugs are used in the suppression of malignant tumors, and their official use began in 2004[18]. Antiangiogenic drugs are divided into vascular endothelial growth factor inhibitors VEGF: bevacizumab (Avastin), aflibercept (Eylea); tyrosine kinase inhibitors sunitinib (Sutent), sorafenib (Nexavar), cabozantinib (Cabometyx); and anti-mTor drugs—everolimus. This kind of

medications reduce angiogenesis in malignant but also in normal tissue[10]. VEGF plays a very important role in the regulation of osteoclast differentiation and function[13,14] while the decrease in angiogenesis affects the ability of the bone to regenerate, remodelate and heal, and increases the possibilities of super-infections. A combination of antiresorptive and antiangiogenic drugs increases the risk of developing MRONJ by about 16%[19].

2. Criteria for defining MRONJ

MRONJ is becoming increasingly prevalent overtime due to the cumulative effects of the drugs. Prevalence of MRONJ rises rapidly after two or more years from medication. The following criteria must be met so that a lesion can be declared as MRONJ[3]:

- Patient uses medication belonging to a group of medications that can cause MRONJ
- Presence of intraoral or extraoral fistula which lasts longer than 8 weeks
- Patient did not undergo radiation therapy of the head and neck, and there is no metastatic cancer in area of lesion

3. Predisposing factors for the occurrence of MRONJ

The main factor causing MRONJ is the damage of jawbones associated with some kind of local or systemic factors. A bone can be damaged by extraction of the tooth or many other minor dental interventions such as implantations, curettage of periodontal pockets, drainage of abscesses etc.

Table 1: Predisposing factors for MRONJ

Predisposing factors	Patient-dependent factors	Intervention depending factors
Local	Poor oral hygiene Periodontitis Periapical pathology Non-vital teeth Periodontal abscesses and other infections of the orofacial region Periimplantitis Bony exostoses and toruses Bad habits, biting hard objects	Tooth extraction Poorly adapted prostheses Presence of implants Implantation procedures Curettage of periodontal pockets Oral-surgical and maxillofacial interventions Poor dental fillings
Systemic	Age over 65 years Smoking Hyperthyroidism Diabetes mellitus Autoimmune diseases Anemia Chronic renal insufficiency Hypocalcemia Hypovitaminosis	Simultaneous use of antiresorptive therapy with: Antiangiogenic Oncology therapy: radiation chemotherapy Immunosuppressive therapy Hormonal therapy

Some cases of MRONJ can happen even when none of obvious dental factors are present.

4. Stages of MRONJ

Stage 0 is generally without clear symptoms that would raise suspicion of MRONJ.

The jaw bone is not exposed at this stage, and there are no specific clinical symptoms. Sometimes, odontalgia without clear dental causes, unspecified neuralgiform pain in the jaws or the maxillary sinus, and rarely in the temporomandibular joint could be present. Radiological diagnostics show resorption or sclerosis of the alveolar bone, thickening of the laminae dura, expansion of the periodontal ligament, or discrete thinning of the bone trabeculas that can be observed even in completely healthy patients.

Stage 1. There is minimal or minor exposition of the necrotic bone or a fistula. The bone can be probed through the fistula. Most patients at this stage have no symptoms, and there are no signs of inflammation or infection. A tooth can be luxated without the presence of periodontal disease, periapical fistula also can be present but without pulp necrosis. Radiological diagnosis may resemble the first stage. An alveolus that does not heal is often present. The most often common findings are osteolysis or osteosclerosis of bone. Characteristic radiography shows that all radiological changes are observed within the alveolar ridge of the jaw bone.

Stage 2. There is an intraoral fistula that makes necrotic bone exposed and clearly visible in the oral cavity. Large exposition of

the necrotic bone is accompanied by pain and infection. Oral functions such as swallowing or speech cause discomfort or pain to the patient. Symptoms of inflammation and infection of the surrounding soft tissue region are always present often accompanied by suppuration. Radiological diagnostics can resemble the first or second stage. Sometimes there is diffuse sclerosis of the bone marrow, with or without cortical erosion, thickening of the alveolar ridge, thickening of the mandibular canal, sequestration, periosteal reaction and cloudy appearance of the maxillary sinus. All radiological changes are observed within the alveolar ridge of the jawbones.

Stage 3. This stage is followed by great local morbidity, exposed and necrotic bone, intraoral or extraoral fistulas, with infection, suppuration, and bone necrosis extending beyond the alveolar ridge region. Huge sequesters extend to the base of the mandible, or the maxillary sinus or zygomatic process of the maxilla. Extraoral fistula, oroantral or oronasal communication is mostly present. Spontaneously, smaller fragments breaking off of the necrotic bone may occur. Radiological findings indicate osteolysis extending to the base of the mandible, sinuses, and nose, with pathological fractures, and osteosclerosis of adjacent bones (zygomatic bone and hard palate).

Clinical signs and symptoms that may arouse suspicion of MRONJ are: abscess, exposed bone, intraoral or extraoral fistula, purulent discharge from the nose, oral mucosa, halitosis, jaw pain of unknown origin, deformity or fracture of the mandible, alveolus that does not heal after extraction, paresthesia, i.e. numbness of the lower lip, intraoral soft tissue swelling, spontaneous appearance of bone fragments, appearance of mobility of teeth and implants, and odontalgia without a clear cause. Differential diagnosis should exclude other conditions. Similar symptoms such as alveolitis, sinusitis, periodontitis, periapical processes, atypical neuralgia, fibroses lesions, sarcoma, osteomyelitis, temporomandibular joint disorders may appear[16].

5. Multidisciplinary approach to MRONJ

Beforehand considering the treatment of patients with medicaments that can cause MRONJ, a consultation with a rheumatologist, oncologist, and dentist should be done. Multidisciplinary pretreatment should be coordinated and provided timely, reducing the incidence of MRONJ by 77.3%[17]. Pretreatment significantly contributes to the improvement of oral health and raising the awareness of patients about the importance of maintaining hygiene and regular checkups at the dentists.

Table 2. Specialists and specific interventions involved in the prevention of MRONJ

Specialist	Intervention
ONCOLOGIST	Diagnosing the presence of malignancy Biochemical lab. (Ca, P, etc.) Counseling on timely dental treatment Assessment of the urgency of including therapy due to the presence of a malignant disease Considering monotherapy or combining dual or more therapies that may lead to MRONJ **REFER THE PATIENT TO THE DOCTOR OF DENTAL MEDICINE** **WARN THE PATIENT ABOUT THE POSSIBILITY OF MRONJ DEVELOPMENT**
RHEUMATOLOGIST	Diagnosing the presence and the stage of osteoporosis Assessment of bone tissue condition Densitometry of bone tissue Biochemical lab. (Ca, P) Hormonal status Diagnosing the presence of comorbidities, autoimmune or systemic diseases **REFER THE PATIENT TO THE DOCTOR OF DENTAL MEDICINE** **WARN THE PATIENT ABOUT THE POSSIBILITY OF MRONJ DEVELOPMENT**
DENTIST	Premedication and regular appointments with the dentist Mouth rinsing with 0.12% chlorhexidine twice a day Removal of soft and hard deposits Teeth with a good prognosis should be taken care of with conservative treatment Teeth with a poor prognosis should be extracted with minimal trauma Adjustment of prostheses without pressure on the bone tissue Advising the patient not to use prostheses during treatment with antiresorptive drugs Treatment of initial periodontal disease Treatment of initial peri-implantitis Appoint regular checkups every 3–6 months **WARN THE PATIENT ABOUT THE POSSIBILITY OF MRONJ DEVELOPMENT**

6. *Minor oral surgical interventions with risk of MRONJ*

6.1. Tooth extraction

Acute or chronic infection is the main predisposing factor related to the appearance of MRONJ in risk patients. The tooth that cannot be restored conservatively poses a threat to infection and extraction should be performed correctly and in a timely manner.

Patients treated with low doses of oral BP for a period of less than two years, due to osteoporosis and without other comorbidities, can undergo routine tooth extraction with primary wound closure[1,18.] Patients at high risk, treated with high doses of antiresorptive drugs, or intravenous therapy due to oncological diseases, or those who have combined antiresorptive and antiangiogenic therapy, pose other comorbidities, should be treated using specific surgical protocols that include raising the mucoperiosteal flap, tooth extraction, careful treatment of bone edges, bone polishing and complete closure of the flap without tension[1,19]. It is not wrong to consider every tooth extraction as a high risk intervention, whereby the wound should be completely sutured.

Perioperative application of antibiotic therapy, drugs from the group of penicillins or beta-lactam penicillins, usually with the addition of metronidazole is mandatory. Antibiotics therapy should start at least one day from a minimum of 1 day preoperatively to 7–10 days after the intervention[20]. There is no uniform opinion about drug holiday. There are some opposite opinions due to the effectiveness of drug holiday related to bisphosphonate therapy, due to the multi-year cumulative effects. Denosumab therapy can be excluded 1–2 months before the intervention, in consultation with ordinarius treating osteoporosis or malignancy, and continued 4–6 weeks after the surgical intervention, i.e. until the wound is completely healed[5].

6.2. Dental implants and the risk of MRONJ

Implant procedures are generally contraindicated in patients treated with high doses of BP. Patients treated with low doses of BP may be candidates for implantation, but it is necessary to inform the patient about the potential even higher risk of MRONJ lesions. It is proposed to have written consent, because of the increased risk of MRONJ1 and decreased implantation success. Before any type of intervention that includes damage to the bone, bisphosphonate treatment duration should be taken into account, because the risk increases overtime[3,5,12].

7.Assessment of the degree of risk for the occurrence of MRONJ

Experience of the doctors and data suggest that some of the predisposing factors, which can be found by detailed anamnesis and clinical examination, could help reduce the development of MRONJ. Evaluation of the patients is shown in Table 3.

Table 3. Evaluation of patient's condition for MRONJ development

General anamnesis	Data on the use of: Bisphosphonates Other antiresorptive agents Drugs with antiangiogenic activity Drugs for reduced circulation Antidiabetics Radiopharmaceutical preparations (radium-223) Estrogen inhibitors (raloxifene) Immunomodulators (methotrexate and corticosteroids)
Dental anamnesis	Data on: Occurrence of any change in sensitivity Condition of teeth, soft tissues and periodontium Occurrence of lesions (time, cause) Presence of pain Presence of post dental intervention (postextraction) non-healing wound
Clinical examination	Vitality test Probing Percussive sensitivity Poor dental fillings Initial periodontitis Initial peri-implantitis Inflammation and infection of soft tissues
Radiological examination	Orthopantomography Three-dimensional orthopantomography Come Beam Dental Scanner Computed tomography Magnetic resonance
Biopsy	Only in case of suspected metastatic changes in the jawbones

8. ***Therapy of MRONJ***[3,5,12,21]

The first rule is not to begin with the treatment of MRONJ without appropriate radiography. If some radiological methods, for example, retroalveolar or orthopanthomographic records make some indecisivnesses, do the second, technologically more advanced.

The treatment of MRONJ can be conservative or surgical, depending on the stage of developing lesions and other symptoms. There are some opposite opinions in view of surgery considering changes in the structure and functions of jawbones. Surgical treatment implies sequestrectomy that extends to the limit of healthy bones, but considering that the whole bone structure is similar, surgery should be done very sparingly and carefully. This is the reason why most protocols advocate primarily curative—conservative therapy.

Conservative therapy is desirable in any stage of MRONJ. Especially in case where the surgical treatment can be complicated with the presence of comorbidities. The curative preventive methods enable remission or complete healing, depending on the stage of lesions, and other local and systemic factors.

In the zero stage of MRONJ preventive hygienic dietary measures (vitamin A, D, C) and maintenance of oral hygiene with soft brushes, usage of oral antiseptic solutions (0.12% chlorhexidine twice a day) are recommended. This way of acting enables removing of biofilm from teeth and mucosa, reducing the number of microorganisms.

In the first stage of MRONJ, suggested treatment is strict oral hygiene, rinsing mouth with oral suspensions of chlorhexidine 0.12%, twice per day. Biofilm from the necrotic exposed bone can be removed by a cotton swab dipped in chorchexidine. If the pain is present, some analgesics should be prescribed.

In the second stage of MRONJ, treatment is the combination of preventive hygienic dietary measures and surgery. Application of antibiotics, primarily penicillin with clavulonic acid in combination with metronidazole is mandatory. The duration of antibiotic therapy lasts from 7 to 14 days. In case of penicillin allergy, it can be changed with erythromycin, clindamycin or ciprofloxacin. If the bone sequester is formed, operative removal could be postponed by curettage and polishing of the surface layer of the bone. That means a gentle sequestrectomy only of the exposed bone in patients who are not favorable candidates for surgical therapy (oncology patients, patients with major comorbidities). If this treatment provides no improvement, surgical treatment should be performed. The exposed necrotic bone is a continuous source of irritation and infection, so sequestrectomy is the solution. In case of surgical removal of the sequester, antibiotic therapy lasts 21–28 days[10,12].

In the third stage of MRONJ, standard non-surgical treatment must be combined with surgical treatment, including removal of necrotic sequestrated and surrounding damaged bone, until the surrounding jawbone does bleed. Marginal mandibulectomy or maxillectomy is suggested considering the size of the necrotic lesion and bone sequester. In more severe cases, segmental or en bloc resection followed by osteoplasty of the defect is indicated. Bone removal should always be done from macroscopically visible altered bone tissue to vital vascularized bone tissue, allowing the healing. Antibiotic and analgesic therapy are mandatory, but show less effectiveness over time[3,5,10,12,21].

Surgical therapy is not reserved exclusively for the third stage but can be carried out in the first and second stages as well if there is no improvement in symptoms or disease progression occurs.

Conclusion

Medication-related osteonecrosis of the jaw negatively affects quality of life and leads to significant morbidity. Changes in the jawbones, more common in the mandibula than maxilla, can vary from asymptomatic, through discrete undefined pain, to very severe lesions. Pathological fracture of the jawbones, infection, cutaneous fistulas and large scars and disfigurement can develop in case of non-timely diagnosis and prevention Neglecting prevention, late diagnosis and delaying treatment of MRONJ can lead the patient to mutilation, dysfunction and poor life quality.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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ULOGA I ZNAČAJ GLJIVICE *CANDIDA ALBICANS* U NASTANKU I RAZVOJU KARIJESA RANOG DETINJSTVA

THE ROLE AND SIGNIFICANCE OF THE FUNGUS *CANDIDA ALBICANS* IN THE FORMATION AND PROGRESSION OF EARLY CHILDHOOD CARIES

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Sažetak

Uvod: Karijes ranog detinstva je *prema definiciji Američke akademije za dečiju stomatologiju iz 2021. svaki karijesni zub, zub koji nedostaje (zbog karijesa) ili plombirana površina na bilo kom mlečnom zubu kod dece do šest godina. To je multifaktorska bolest, koja podrazumeva sinhronizovanu aktivnost kariogenih mikroorganizama, osetljivost domaćina i fermentabilnih ugljenih hidrata. Streptococcus mutans je glavni kariogeni mikroorganizam. Nedavna otkrića pokazuju da se Candida albicans, oportunistička gljivica, često otkriva u većem broju kod dece sa karijesom ranog detinjstva. Istraživanja ukazuju da postoji sinergistički efekat C. albicans i S. mutans, što povećava patogenost, a samim tim i težinu kliničke slike.*
Cilj studije *je da pokaže uticaj gljivice C. albicans na nastanak, tok i prognozu karijesa ranog detinjstva..*
Materijal i metode*: Pretraživanjem PubMed baza podataka, uz korišćenje ključnih reči Candida albicans, Streptococcus mutans i karijes ranog detinjstvu, analizirano je 17 studija koje su uključene u ovaj rad.*
Rezultati: *Studije pokazuju da interakcija između C. albicans i S. mutans utiče na etiologiju, tok i prognozu karijesa ranog detinjstva.*
Zaključak*: Neophodna su dodatna longitudinalna istraživanja kako bi se ispitao uticaj sinergističkog dejstva ova dva mikroorganizma na pojavu karijesa ranog detinjstva.*

Ključne reči*: candida albicans, streptococcus mutans, karijes ranog detinjstva.*

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Abstract

Introduction*: Early childhood caries is defined by the 2021 American Academy of Pediatric Dentistry as any decayed tooth, missing tooth (due to decay), or filled surface on any baby tooth in children under six years of age. It is a multifactorial disease, which involves synchronized activity of cariogenic microorganisms, sensitivity of the host and fermentable carbohydrates. Streptococcus mutans is the main cariogenic microorganism. Recent findings show that Candida albicans, an opportunistic fungus, is often detected in higher numbers in children with early childhood caries. Research indicates that there is a synergistic effect of C. albicans and S. mutans, which increases the pathogenicity and thus the severity of the clinical picture.*
The aim *of the study is to show the influence of the fungus C. albicans on the onset, course and prognosis of early childhood caries.*
Material and methods: *By searching PubMed databases, using the keywords Candida albicans, Streptococcus mutans and early childhood caries, 17 studies included in this paper were analyzed.*
Results*: Studies show that the interaction between C. albicans and S. mutans affects the etiology, course and prognosis of early childhood caries.*
Conclusion*: llongitudinal studies are necessary in order to examine the influence of the synergistic effect of these two microorganisms on the occurrence of caries in early childhood. Key words: candida albicans, streptococcus mutans, early childhood caries.*

Key words: *candida albicans, streptococcus mutans, early childhood caries*

Introduction

Early childhood caries (ECC) is an infectious, destructive disease of hard dental tissues, which occurs in babies and young children in the first few years of life and is characterized by rapid carious destruction of milk teeth. According to Voss, it is the most common chronic childhood disease with almost one billion and eight hundred million new cases per year worldwide[1]. Any sign of caries in children under six years of age is considered ECC. Early childhood caries affects children's quality of life. Pain and swelling lead to greater absenteeism from school, treatment costs and the possibility of hospitalization increase, sleep disorders occur, and growth, height and weight parameters can slow down[2,3].

The prevalence of ECC is significantly high in many parts of the world, although it varies by geographic area, socioeconomic status, and access to dental care. Statistics show that ECC is a common phenomenon in poor countries as well as in developing countries. The fact that in a period of twenty years (1998-2018), 72 studies which only dealt with the prevalence of ECC in preschool children were published, shows that ECC preoccupies researchers. The average prevalence of ECC in one-year-olds was 17%, in two-year-olds 36%, and in three, four and five-year-olds it was 43%–63%[4].

The results of the research on the average prevalence are worrying, because the percentage of children with ECC increases with the increase in the age of children of preschool age. According to the research of some authors, ECC is cited as the most common oral disease that especially affects children[5]. The etiology of ECC is multifactorial and includes a combination of biological factors and behavioral habits. It is known that the main etiological factors for ECC are microorganisms, fermentable carbohydrates, host factors and time. The human oral microbiome includes more than 700 different microorganisms, including bacteria, fungi, viruses, protozoa and mycoplasmas as stated by Marshi and Zaura[6].

Microorganisms interact with each other and form a biofilm of different content. *S. mutans* is the main microorganism in the development of caries. It is naturally present in the oral cavity immediately after dentition. In order to survive, it forms a biofilm, i.e. organized microbial community[6].

Biofilm formation begins when saliva components are selectively adsorbed on the enamel, forming the acquired dental pellicle. The pellicle provides an attachment site for oral microorganisms, including *S. mutans*, which allows colonization of it. In such conditions, this bacterium begins to multiply and produce exopolysaccharides, forming a community that contains channels for a better distribution of oxygen, nutrients and signaling molecules. Further, sucrose-dependent biofilm metabolism relies on an extracellular, self-secreted glucosyltransferase (GtFB, GtFC, GtFB)[7].

Although many facts are known about the prevention and treatment of ECC, the prevalence of this disease is still high, which leads researchers to look for another potential etiological factor such as the fungus *C. albicans* which is linked to the occurrence and progression of ECC.

A feature of the fungus *C. albicans* which makes it a significant opportunistic pathogen, is its ability to adapt and multiply in different environments, such as acidic environments[8]. In this context, the fungus *C. albicans* can coexist with other oral microorganisms in a biofilm or carious lesion as a natural consequence of an acidic microenvironment.

C. albicans is most often associated with mucosal infection (candidiasis), while research in recent years has shown that it may also play a role in the etiology and progression of ECC. Numerous studies deal with the etiology, epidemiology, prevention and interaction between the fungus *C. albicans* and the bacterium *S. mutans* in the development of this disease[9,10].

The fact that immunity in younger children is in the process of formation, and the *C. albicans* species has the potential to increase in concentration during a state of low immunity, may partially explain the rapid progression of ECC in this age group. On the other hand, due to impaired immunity, patients with ECC are often malnourished, which makes them susceptible to *C. albicans* infection. Numerous studies have analyzed the role of *C. albicans* spp. in the biofilm of teeth and gums, as well as its interaction with cariogenic bacteria such as *S. mutans*. These studies also indicated an association between Candida and ECC[11,12]. The study aimed to show the influence of the fungus *C. albicans*, and its interaction with the bacterium *S. mutans* on the occurrence, course and prognosis of ECC.

Relationship of S. mutans and C. albicans spp. in the Development of Early Childhood Caries

The structure of the cell wall of *C. albicans* is cited as a possible link between bacteria and fungi. The main components of the cell wall are mannins, glucans and chitin.

Mannins are found on the outer layer of the cell wall of *C. albicans*. It is possible that these biomolecules are involved in the binding of glucosyltransferase exoenzymes to the fungal cell surface[13].

The joint presence of *C. albicans* and *S. mutans* in the biofilm produces a higher amount of protein, oxidation and resistance to antibacterial stress, acid resistance, larger microcolonies and a much more complex 3D structure[9].

A possible mechanism of synergistic action is based on the exoenzyme glucosyltransferase B (GtfB) from the microorganism *S. mutans*, which is a key producer of exopolysaccharides. The GtfB exoenzyme binds to the surface of the fungus *C. albicans* in an active form and produces exopolysaccharides that ensure better binding of *S. mutans*, which ultimately leads to the formation of a biofilm containing a large amount of exopolysaccharides of *S. mutans* and *C. albicans* species[9,14].

In the thus formed biofilm with a rich content of exopolysaccharides, a vicious circle is created that limits diffusion and creates good conditions for the growth of *S. mutans* and *C. albicans*9, which also implies an increase in the acidity of the biofilm and ultimately demineralization of teeth[15].

The binding strength of the GtfB enzyme to the surface of *C. albicans* is astonishing, it is 2.5 times greater and 20 times more stable than the adhesion of the enzyme to *S. mutans*.

The strong and highly stable binding of GtfB to *C. albicans* could explain, at least in part, why this exoenzyme efficiently forms a link between *C. albicans* and *S. mutans*[16].

The question arises whether saliva affects the synergistic reaction between S. mutans and *C. albicans*, specifically regarding its effect on the increase in biofilm virulence. It was investigated whether 100% purified saliva (without antimicrobial peptides) could affect the mature biofilm. The results indicate that saliva has no effect in the initial phase of biofilm formation, while it can affect the mature biofilm[17].

There is no interaction between Candida C. albicans and Streptococcus S. mutans in a healthy oral environment, nor is *C. albicans* colonization observed on the tooth surface. In ECC, one of the main factors contributing to the serious destruction of dental tissues is the prolonged consumption of drinks and food rich in sucrose, which allows increased physical adhesion between *S. mutans* and *C. albicans* and colonization of the teeth.

Previous studies suggest the possible influence of *C. albicans* in the development and progression of ECC.

Conclusion

Research results of the last ten years show that the etiology, progression and severity of the clinical picture of caries in early childhood are significantly correlated with the combined colonization of *C. albicans* and *S. mutans* spp. Certainly, additional longitudinal studies are necessary to explain the impact of bacterial–fungal interactions on ECC, which could lead to new perspectives in anticariogenic procedures and therapies.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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PISMO UREDNIKU
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NOVI TERAPIJSKI PROTOKLI U LEČENJU PACIJENATA SA BRUKSIZMOM

NEW THERAPEUTIC PROTOCOLS IN THE TREATMENT OF PATIENTS WITH BRUXISM

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Sažetak

Pitanja bruksizma i poremećaja temporo-mandibularnog zgloba (TMZ), često su zanemarena. Bruksizam, može dovesti do značajnih stomatoloških i zdravstvenih problema. Protokoli tradicionalne terapije koje je predložilo nekoliko autora u Vašem časopisu uključujući tvrde i meke elastične udlage (noćne štitnike) pre i posle protetske rehabilitacije ne predstavljaju najefikasniji savremeni tretman. Tretman botulinskim toksinom dovodi do inhibicije mišićne kontrakcije i smanjujenja bola i nelagodnosti. Bihevioralna terapija može igrati ključnu ulogu u identifikaciji okidača i upravljanju stresom, koji su često u etiologiji bruksizma.

Ključne reči: *bruksizam, temporomandibularne disfunkcije, botulinski toksin*

Abstract

Issues of bruxism and temporomandibular joint disorders (TMJ) are often neglected. Bruxism can lead to significant dental and health problems. Traditional therapy protocols proposed by several authors in your journal including hard and soft elastic splints (night guards) before and after prosthetic rehabilitation do not represent the most effective modern treatment. Botulinum toxin treatment inhibits muscle contraction and reduces pain and discomfort. Behavioral therapy can play a key role in identifying triggers and managing stress, which are often at the etiology of bruxism.

Key words: *bruxism, temporomandibular joint disorders, Botulinum toxin*

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Dear Editor,

Temporomandibular disorders (TMD) after dental pain are the most common cause of orofacial pain. It may affect approximately 70–80% of the adult population between the age of 20 and 45, which makes it a public health concern. It is important to bring attention to the often-overlooked issues of temporomandibular disorders and bruxism, which are increasingly prevalent, yet frequently misunderstood[1].

Parafunctional behaviors are common activities that can apply very high masticatory forces in teeth, implants, and dental prostheses. These forces can lead to fracture or loosening of screws and abutments, chipping of the veneering material, or fracture of the prosthetic reconstruction[2].

Bruxism as parafunction with involuntary grinding or clenching of teeth, can also lead to other significant dental and health problems, including worn teeth, headaches, and jaw pain[3]. Despite continuous efforts to understand the nature and mechanisms, an exact pathophysiology remains unclear. Many factors were associated with bruxism including anatomical abnormalities, tooth interference in dental occlusion, psychological factors, sleep disorders, genetics, and medication side effects. Recent studies suggest that parafunctional behaviors develop due to central regulatory mechanisms[4].

Many individuals may not even be aware they suffer from this condition, as it often occurs during sleep or periods of stress. Moreover, TMJ disorders, which can arise from bruxism and other parafunctional habits, can cause pain, discomfort and dysfunction in the jaw joint, impacting daily activities such as eating and speaking. The implications of this disorder are far-reaching, not just for dental health but for overall well-being and quality of life[5].

Due to its multifactorial etiology and severity of the symptoms, the suggested traditional therapy protocols by several authors including hard and soft elastic splints (night guards) before and after prosthetic rehabilitation do not present the most effective treatment[6]. Splints help to protect the teeth from damage and can alleviate pressure on the jaw muscles. They create a barrier between the upper and lower teeth, reducing the effects of grinding. They can provide some relief, but may not always be sufficient for severe cases because splints do not address the muscle activity contributing to teeth grinding[7].

This is where neuromodulators like Botulinum toxin come into play. Botulinum toxin is a bacterial-derived extract that acts at neural synapses by inhibiting the uptake of acetylcholine by neurons, thus causing inhibition of muscle contraction, and diminishing pain and discomfort. The toxin is injected into masticatory muscles (masseter and temporalis) to treat trismus, bruxism, masticatory muscle myalgia, temporomandibular joint disorders or muscle hypertrophy.

In addition to its effectiveness, Botox therapy for bruxism is minimally invasive and can be administered in a dental or medical office, often with little to no recovery time.

As awareness of this treatment grows, dental professionals and patients alike need to consider it as a viable option for managing bruxism, especially for those who have not found relief through other traditional methods[8].

Of course, for our severe and chronic patients, it is crucial to adopt an approach that incorporates behavioral therapy, medications, lifestyle changes, and physical therapy. Behavioral therapy can play a pivotal role in identifying triggers and managing stress, which are often at the root of bruxism. Additionally, pharmacotherapy may be necessary for some individuals to alleviate muscle tension and anxiety associated with bruxism. Lifestyle

modifications such as reducing caffeine and alcohol consumption, and implementing good sleep hygiene practices, can significantly mitigate symptoms[9].

Over the past years, treating TMD and bruxism have evolved to a dynamic field of macromolecules, natural products, and novel functional materials. Nature derivatives with anti-inflammatory and analgesic effects like Lectins, extracts from plants and algae, sulfated polysaccharides, terpene, resveratrol, cocoa were classified as "generally safe" products from the FDA[10].

I urge dental professionals to incorporate screenings for bruxism and TMJ disorders into routine dental visits. Additionally, more community education initiatives should be developed to inform individuals about the signs, symptoms, and potential treatment options available. Addressing these issues can improve the quality of life for many affected individuals.

Thank you for your attention to this important topic.

Sincerely,

Prof. dr Aneta Mijoska

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UPUTSTVA AUTORIMA

Acta Stomatologica Naissi je naučni časopis Klinike za dentalnu medicinu, Medicinskog fakulteta Univerziteta u Nišu, koji publikuje radove iz svih oblasti stomatologije i srodnih medicinskih grana.

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ETIKA

Kada se radi o eksperimentima na humanom materijalu ili pacijentima, ukazati da li je primenjeni postupak u skladu sa etičkim standardima odgovornog komiteta za ljudske eksperimente ili sa Deklaracijom iz Helsinkija (1964, amandmani iz 1975 i 1983) Svetske medicinske asocijacije.

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APSTRAKT I KLJUČNE REČI

Originalni radovi moraju da sadrže strukturni apstrakt od 250 reči, podeljenih na sledeća 4 paragrafa:

Uvod: opisuje problem o kome se radi u radu

Materijali i metode: opisuje kako je istraživanje sprovedeno

Rezultati: opisuje primarno rezultate

Zaključak(ci): saopštenje autora o zaključcima proisteklim iz rezultata, i implicira njihovu kliničku primenljivost.

Strukturni apstrakti nisu potrebni kod uvodnika i pisma. Ispod apstrakta stoje ključne reci i to tri do pet. Ključne reči mogu biti uzete samo iz Medical Subjects Headings (MeSH).

Apstrakt treba da bude preveden i na engleski jezik (US style), sa naslovom, imenima autora, institucija i ključnim recima.

Za pisanje radova u formi prikaza slučaja, treba uraditi strukturirani apstrakt, na sledeći način:

Osnova problema: (opisati problem ili pojavu u nekoliko rečenica),

Metode rada: (opisati kako je obrađen i dijagnostikovan pacijent i koja bolest ili poremećaj je u pitanju),

Rezultati: (opisati rezultate rada i krajnji ishod),

Zaključak: (1-3 rečenice koja može da služi i kao opis celog postupka koji je rađen i napisan u radu).

TABELE I FIGURE

Svaka tabela sa jasnim naslovom na srpskom i engleskom treba da bude otkucana sa duplim proredom na odvojenom papiru. Obeležiti brojevima tabele jednu za drugom kako nailaze posle prvog navođenja u tekstu (obeležavaju se arapskim brojevima). Dati svakoj kolumni kratko ili skraćeno zaglavlje. Staviti objašnjenja u legendama svih nestandardnih skraćenica korišćenih u tabeli. Za jedinice i merenja vidi odeljak niže. Ne koristiti unutrašnje horizontalne i vertikalne linije. Staviti sve tabele na kraju vaseg fajla. Uvek odvojiti posebne kolumne upotrebom tabulatora, a ne upotrebom razmaknice, tabele moraju biti u tekst formatu.

Linijski prikazani dijagrami i ilustracije (fotografije, fotomikrografije itd.), trebaju biti osmišljene kao figure. Oni takođe treba da budu smešteni na odvojenom listu papira i numerisani jedan za drugim arapskim brojevima u saglasnosti sa prvim koji je citiran u tekstu. Figure treba da budu profesionalno nacrtane i fotografisane. Svaka figura treba da bude etiketirana pozadi ukazujući broj figure, prezime i prvo slovo imena autora, i vrh figure. Fotografije treba da se daju u dva primerka. Kolor fotografije ce se štampati samo u dogovoru sa urednikom ili ako autor sam snosi troškove. Fotomikrografije moraju imati obeleženu unutrasnju razmeru, i simbole, i strelice ili slova treba da su u kontrastu sa pozadinom. Na fotografijama pacijenata mora se sakriti identitet, osim ako se pacijenti u pismenoj formi slože sa objavljivanjem njihovih fotografija sa identitetom. Ukoliko ste pozajmili ili već publikovali negde fotografije priložite i pismenu dozvolu za reprodukovanje. Naslovi i detaljna objašnjenja fotografija treba da budu data u legendama. Ako su korišćeni simboli, strelice, brojevi ili slova za identifikaciju delova slike objasniti svaku jasno u legendi.

ZAHVALNOSTI

Priznanja i zahvalnosti prethode literaturi specificirajući generalnu podršku kao i odeljenje i ime šefa odeljenja, priznanja tehničkoj pomoći i konačno finansijskoj i materijalnoj pomoći. Navesti naziv i broj projekta, odnosno naziv programa u okviru koga je nastao članak i naziv institucije koja je finansirala projekat, u posebnoj napomeni pri dnu prve strane članka.

LITERATURA

Autori su odgovorni za tačnost literaturnih podataka. Reference treba da budu na posebnom listu i delu odmah iza teksta. Samo reference bitne za studiju mogu biti citirane. Kada je citiranje literature neophodno primeniti Vankuver stil. Na posebnom listu se navode citati referenci koji su označeni rednim brojevima po redosledu u kome se pojavljuju u tekstu i svaki citat odgovara brojevima koji sadrži navedenu referencu. Primeri tačnih oblika referenci :

RADOVI U ČASOPISIMA

1. Standardni članak u časopisu (lista svih autora, ali ako je broj veći od šest citirati tri i dodati et al): Glass DA, Mellonig JT, Towle HJ. Histologic evaluation of bone inductive proteins complexed with coralline hydroxyapatite in an extraskeletal site of the rat. J Periodontol 1989; 60:121-125.

2. Organizacija kao autor: Federation Dentaire Internationale. Technical Report No. 28. Guidelines for antibiotic prophylaxis of infective endocarditis for dental patients with cardiovascular disease. Int Dent J 1987;37:235.

3. Nije dat autor: Coffee drinking and cancer of the pancreas (editorial).BMJ 1981;283:628.

4. Volumen sa suplementom: Magni R, Rossoni G, Berti R, BN52021 protect guinea pig from heart anaohylaxis. Pharmacol Res Commun 1988; 20 Suppl 5:75-8.

Knjige ili druge monografije

5. Lični autor (i): Tullman JJ, Redding SW. Systemic Disease in Dental Treatment. St.Louis: The CV Mosby Company;1983:1-5.

6. Poglavlje u knjizi: Rees TD. Dental management of the medically compromised patient. In: McDonald RE, Hurt WC,Gilmore HW, Middleton RA, eds.Current Therapy in Dentistry, vol.7. St. Louis: The CV Mosby Company; 1980:3-7.

7. Disertacije i teze: Teerakapong A. Langerhans Cells in human periodontally healthy and diseased gingiva. (Thesis). Houston, TX: University of Texas; 1987.92 p.

Ostali publikovani materijal

8. Novinski članak: Shaffer RA.Advances in chemistry are starting to unlock mysteries of the brain. The Washington Post 1989 Ang 7; Sect. A:2 (col. 5).

Reference-elektronski citati

9. On line časopisi bez podataka o volumenu i strani. Berlin JA , Antman EM. Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials (serial online). June 4;doc 134. Accessed July 20, 2000.

10. Online časopisi sa podacima o volumenu i strani. Fowler EB, Breault LG. Ridge augmentation with a folded acellular dermal matrix allograft: A case Report. J Contemp Dent Pract (serial online). 2001;2(3):31-40. Available from: Procter&Gamble Company, Cincinnat, OH. Accessed December 15, 2001.

11. World Wide Web.Centers for Disease Control and Prevention. Preventing emerging infectious diseases: Addressing the problem of antimicrobial resistance. Available at: http://www.cdc.gov/ncidod/emergplan/antiresist/. Accessed November 5, 2001.

JEDINICE MERE

Sva merenja treba da budu izražena u terminima Internacionalnog Sistema Jedinica (Si).

SKRAĆENICE I SIMBOLI

Ako se koriste nestandardne skraćenice potrebno je prilikom prvog korišćenja celog izraza u tekstu dati njegov puni naziv, a zatim u daljem tekstu koristiti skraćenicu. Nazivi simptoma, znakova i bolesti, kao i anatomski i histološki detalji ne mogu se skraćivati.

OFFPRINTS

Korespondirajući autori svih tipova radova izuzev pisama, novosti i pregleda knjiga primiće 1 broj časopisa oslobođena plaćanja.

SIMBOLI ZA OZNAČAVANJE (FUSNOTE)

Mogu se koristiti samo za identifikaciju zapošljenja autora, za objašnjenje simbola u tabelama i ilustracijama itd. Koristite sledeće fusnote: *,&, #,**, itd.

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Poslati 3 kopije rada i elektronsku verziju (CD-ROM, E-mail). Kopije rada i sav sadržaj treba spakovati u tvrdu kovertu kako bi se sprecilo oštećenje za vreme poštanskog saobraćaja. Radovi moraju biti potkrepljeni sa zatvorenim pismom potpisanim od svih autora. Ono mora da sadrži: a) izjavu da je rad pročitan i odobren od svih autora; b) informaciju o prethodnoj ili dupliciranoj publikaciji ili davanju rada na drugom mestu ili nekog njenog dela ranije; c) izjavu o finansijskim ili drugim vezama koje mogu dovesti do sukoba interesa; d) ime, adresu i broj telefona autora za korespondenciju koji je odgovoran za komunikaciju i korespondenciju; e) izjavu da su klinička i eksperimentalna istraživanja sprovedena u skladu sa institucijskim etičkim komitetom ili sa Helsinskom deklaracijom. Sem ovoga, pismo treba da sadrži i obaveštenje o vrsti rada i da li autori plaćaju ekstra cenu za kolor reprodukcije.

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Sekretari: Asist. Simona Stojanović, Mr. sci dr Miloš Tijanić

Klinika za Stomatologiju

Bul. Zorana Đinđića 52

18000 Niš, Srbija

E-mail: tarana.simona@gmail.com, tijanicm@yahoo.com

Predavanje materijala direktno uredniku ili bilo kom članu uređivačkog odbora otežaće i odužiće proces recenzije i prijema rada za štampanje.

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Skladištenje informacije: CD-ROM u Windows XP ili veći format. Software: radovi na disku treba da budu u Word-u za Windows. Etiketa: Napišite prvo ime autora na nalepnici CD-a, zajedno sa imenom i verzijom korišćenog word procesora. Oznaciti sve CD sadržajem figura, dijagrama itd, sa imenom prvog autora, imenom fajla, formatom i sabijenim šemama ako su korišćeni. Fajlovi: priložiti tekst i tabele svakog rada kao pojedinacni fajl, ali stavite sve figure, grafikone itd., u odvojenim fajlovima. Dozvoljeni grafički formati su EPS i TIF. Veličina figura treba da bude 8,5 cm ili 18,0 cm u rezoluciji od minimalno 300 dpi. Molimo Vas da pošaljete originalne fotografije, ne šaljite foto-kopije. Format: unosite svoj tekst besprekidno, samo umetnuti hard return na kraju paragrafa ili poglavlja, podnaslova, lista itd. Ne upotrebljavajte softwareski plan stranica. Molimo Vas da koristite Times New Roman 12 font za Word za Windows. Neku reč ili frazu u tekstu koju želite da izdvojite označite kroz rad u italic pismu. Boldirajte ono što se koristi uzastopno u tekstu za određene matematicke simbole, na primer, vektori. Molimo da proverite disk na virus i verifikujte da on sadrži ispravan fajl.

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Autori mogu predati svoje revidirane radove uključujući tabele i figure na CD-u sa PC ili Mac fajlom. Vratiti revidirane radove sa celokupnim materijalom na istu adresu sekretarijat.

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Acta Stomatologica Naissi is a scientific journal of the University of Niš, Faculty of Medicine and Clinic of Dental Medicine, which publishes articles relevant to the science and practice of Dentistry in general and related areas.

Please read carefully the following instructions to authors prior to manuscript preparation and submission. Papers which are not prepared according to the propositions and instructions will be returned to authors for corrections before forwarding them to reviewers. In case of unacceptable articles only illustrations will be returned.

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Acta Stomatologica Naissi publishes editorials, original scientific or clinical articles, review articles, preliminary reports, case reports, technical innovations, letters to the editor, articles from up-to-date literature, book reviews, reports and presentations from national and international congresses and symposiums which have not been previously submitted for publication elsewhere. All submitted articles will be reviewed by at least 2 reviewers, and when appropriate, by a statistical reviewer. Authors will be notified of acceptance, rejection, or need for revision within 6 weeks of submission. Articles are not paid for.

LANGUAGE

All submitted articles should be written in bilingual (Serbian and English) language. Abstracts should be written in Serbian and precise and grammatically correct English language, preferably US English. Avoid using Latin terms; however if necessary, put them in parentheses.

ETHICS

When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration (1964, amended in 1975 and 1983) ofthe World Medical Association.

GENERAL INSTRUCTIONS

PREPARATION

Articles should be written on A4 white bond paper size (21x29.5cm) on one side of the paper only, and double-spaced (including illustration legends and references) providing 25 mm ample margins all around. Only one copy of the manuscript should contain the surname and the author's first name initial in the upper right corner. Manuscripts should be organized as follows: Title Page, Abstract and Key words, Introduction, Patients/Materials and Methods, Results, Discussion, Conclusions, Acknowledgments, References, Figure Legends, Tables, Figures. Title page is numbered as page 1, and all other pages should be numbered conse-quently.

TITLE PAGE

The title page should contain: a) the full title of the article (in upper case); b) first name, middle initial, and last name of each author without the academic degree; c) name of department and institutional affiliation for each author; d) running title of no more than 10 characters. At the bottom of the page, please indicate the name, academic degree and address (including E-mail, telephone and fax number) of the author responsible for correspondence.

It is recommendable to use the words appropriate for indexing and searching. If there are not such words in the title, then subtitle should be added.

If the article in the previous version has been orally exposed (under the same or similar title), such information should be separately noted at the bottom of the first page ofthe article.

Abstract and Key words

All original abstracts should be submitted with a structured abstract, consisting of no more than 250 words, and the following 4 paragraphs:

Background: Describes the problem being addressed.

Material and Methods: Describes how the study was performed.

Results: Describes the primary results.

Conclusion: Reports what authors have concluded from these results, and notes their clinical implications.

Key words: A maximum of 5 key words drawn from MeSH documentation. Abstract should be translated into English (US style), with the title, name(s) of author(s), institutional affiliation and key words.

To write papers in the form of a case report, a structured abstract should be done, as follows:

Basis of the problem: (describe the problem or occurrence in a few sentences),

Methods of work: (describe how the patient was treated and diagnosed and which disease or disorder is in question),

Results: (describe the results of the work and the final outcome),

Conclusion: (1-3 sentences that can also serve as a description of the whole procedure that was done and written in the paper).

To write papers in the form of a case report, a structured abstract should be done, as follows:

Basis of the problem: (describe the problem or occurrence in a few sentences),

Methods of work: (describe how the patient was treated and diagnosed and which disease or disorder is in question),

Results: (describe the results of the work and the final outcome),

Conclusion: (1-3 sentences that can also serve as a description of the whole procedure that was done and written in the paper).

TABLES AND FIGURES

Each table with a brief title (on Serbian and English) should be typed double-spaced on a separate sheet of paper. Number tables consecutively (with Arabic numbers) in the order of their first citation in the text. Give each column a short or abbreviated heading. Place explanations in legends of all nonstandard abbreviations which are used in table. For units and measurements see paragraph below. Do not use internal horizontal and vertical rules. Place all tables at the end of your file. Always separate the individual columns using tabulators, not using space bar, i.e. tables must be in text format. Line drawings diagrams and halftone illustrations (photographs, photomicrographs, etc.) should be designated as figures. They should be listed on separate sheet and numbered consecutively with Arabic numerals according to the order in which they have been first cited in the text. Figures should be professionally drawn (not simply typewritten) and photographed. Each figure should be labeled on its back indicated the number of the figure, last name and the first letter of the author, and the topside of the figure. Photographs should be supplied in two copies. Color photographs are published only in case if author himself bears expenses. Photomicrographs must have internal scale markers, and symbols, arrows or letters should contrast with the background. Photographs of patients must conceal their identity unless patients approve the publishing of the photograph in written form. If you borrow or use already published photographs please submit a written permission for reproduction. Permission is not required for the documents in the public domain. Figures will not be returned unless requested. Captions and detailed explanations of the figures should be given in the legends. If symbols, arrows, numbers, or letters are used to identify parts of the figure identity and explain each one clearly in the legend.

ACKNOWLEDGEMENTS

Acknowledgements are positioned before the reference list specifying general support by department chairman, acknowledgements of technical as well as financial and material support. Acknowledgement includes the title and number of the project, i.e. the title of the programme within which the article was composed and the title of the institution funding the project; it should be written as a separate notification at the bottom ofthe first page of the article.

REFERENCES

Authors are responsible for accuracy of literature data. References should be listed in a separate section immediately following the text. Only references important for the study should be cited. It is necessary to apply Vancouver style. Citations are numbered consecutively in the order in which they appear in the text and each citation corresponds to a numbered reference containing publication information about the source cited in the reference list at the end of the publication. Examples of references are given bellow:

Journals:

1. Standard journal reference. (Note: list all authors if six or less; when seven or more, list only first three and add et al): Glass DA, Mellonig JT, Towle HJ. Histologic evaluation of bone inductive proteins complexed with coralline hydroxyapatite in an extraskeletal site of the rat. J Periodontol 1989;60:121-125.

2. Corporate author: Federation Dentaire Internationale. Technical Report No.28. Guidelines for antibiotic prophylaxis of infective endocarditis for dental patients with cardiovascular disease. Int Dent J 1987;37:235.

3. No author given: Coffee drinking and cancer of the pancreas (editorial). BMJ 1981;283:628.

4. Volume with supplement: Magni R, Rossoni G, Berti R, BN52021 protect guinea pig from heart anaphylaxis. Pharmacol Res Commun 1988; 20 Suppl 5:75-8.

Books or other monographs:

5. Personal author(s): Tullman JJ, Redding SW. Systemic Disease in Dental Treatment. St. Louis: The CV Mosby Company; 1983:1-5.

6. Chapter in a book: Rees TD. Dental management of the medically compromised patient. In: McDonald RE, Hurt WC, Gilmore HW, Middleton RA, eds. Current Therapy in Dentistry, vol. 7. St. Louis: The CV Mosby Company; 1980:3-7.

7. Dissertations and thesis: Teerakapong A. Langerhans Cells in human periodontally healthy and diseased gingiva. (Thesis). Houston, TX: University of Texas; 1987.92 p.

Other published material:

8. Newspaper article: Shaffer RA.Advances in chemistry are starting to unlock mysteries ofthe brain. The Washington Post 1989Ang 7; Sect.A:2 (col. 5).

References - electronic quotations:

9. Online journals without volume and page information. Berlin JA, Antman EM. Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials (serial online). June 4; doc 134. Accessed July 20, 2000.

10. Online journals with volume and page information. Fowler EB, Breault LG. Ridge augmentation with a folded acellular dermal matrix allograft: A case Report. J Contemp Dent Pract (serial online). 2001;2(3):31-40. Available from: Procter&Gamble Company, Cincinnat, OH. Accessed December 15, 2001.

11. World Wide Web.Centers for Disease Control and Prevention. Preventing emerging infectious diseases: Addressing the problem of antimicrobial resistance. Available at: http://www.cdc.gov/ncidod/emergplan/antiresist/. Accessed November 5, 2001.

UNITS OF MEASUREMENTS

All measurements should be reported in terms of the International System of Units (SI)

ABBREVIATIONS AND SYMBOLS

Avoid abbreviations in the text but whenever possible use standard abbreviations. However, if nonstandard abbreviations are used, the full term of which and abbreviation stands for should precede its first use in text. Names of symptoms, signs and diseases, as well as anatomic and histologic characteristics cannot be abbreviated.

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