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Overexpression of heat shock protein 27 (HSP-27) is associated with bad prognosis in oral squamous cell carcinoma

Związek nadmiernej ekspresji białka szoku termicznego 27 (HSP-27) ze złym rokowaniem w raku płaskonabłonkowym jamy ustnej

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

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Abstract

Background. Heat shock protein 27 (HSP-27) is a member of the small-molecular-weight HSP family, the expression of which is increased when cells are exposed to elevated temperatures or any other kinds of stress; it seems that the cellular protective properties this protein demonstrates might also help cancer cells stay immortal. Family members of HSPs are either expressed continuously or controlled inductively, and are present in different subcellular structures.

Objectives. The aim of this study was to investigate the prognostic value of HSP-27 expression in the histological grades of oral squamous cell carcinoma (OSCC).

Material and methods. In the present study, HSP-27 expression was compared immunohistochemically among 30 cases with OSCC (15 men and 15 women), ranging between 22 and 74 years of age (mean age: 48 years). The cases were divided into 3 groups ($n = 10$) according to the histological grade.

Results. While all grades expressed HSP-27 in the cancerous epithelial cells, the intensity of expression rose gradually from grade 1 to grade 3 tumors (grade 1 < grade 2 < grade 3). The statistical analysis indicated significant differences between the 3 groups ($p = 0.000$).

Conclusions. This study has found that HSP-27 may be used as a marker for the histological grades of OSCC and that its expression may be an indicator of the biological behavior of the tumor.

Key words: squamous cell carcinoma, heat shock proteins, overexpression

Słowa kluczowe: rak płaskonabłonkowy, białka szoku termicznego, nadmierna ekspresja

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Introduction

Heat shock proteins (HSPs) are conserved molecular chaperones; they are ubiquitous and have several functions in cellular homeostasis, including the regulation of gene expression, the replication of DNA, the transduction of signals, differentiation, apoptosis, and cellular survival or immortalization. They also protect cells from various kinds of stress, such as hypoxia, ischemia or rapid increases in temperature.[1]

Mammalian HSPs have been arranged into 6 families depending on their molecular size: HSP100, HSP90, HSP70, HSP60, HSP40, and small HSPs (15–30 kDa), including heat shock protein 27 (HSP-27). Family members of HSPs are either expressed continuously or controlled inductively, and they are present in different subcellular structures.[2]

Heat shock protein 27 belongs to the family of small HSPs, which play essential roles in cells under physiological conditions and prevent cells from damage caused by stress. It is a molecular chaperone helping cells remain stable under various stress conditions, such as heat shock, irradiation, oxidative stress, endoplasmic reticulum (ER) stress, and chemotherapy for cancer patients.[3]

Head and neck cancer is one of the most critical malignancies in the world; it is the 3rd most common cancer in developing countries,[4,5] and squamous cell carcinoma has the highest mortality rate among head and neck cancers (54%). Therefore, a huge number of oncological studies have been done on this neoplasm so far,[4,5] with many advances being made in the field of cancer treatment. However, little improvement has been achieved.[4,5]

Tumor grading is related to how similar the cancer tissue is to the parent tissue, and to the ability of the dysplastic squamous epithelial cells to product keratin. The biological behavior of the tumor relates to its histopathological grading.[6] Additionally, several proteins are called markers and can predict the biological behavior of the tumor. Many studies have been done to assess these markers and their ability to initiate carcinogenesis.[7]

The aim of the present study was to investigate the prognostic value of HSP-27 expression in the histological grades of oral squamous cell carcinoma (OSCC).

Material and methods

Approval to conduct the study was granted by the Ethics Committee at the University of Damascus in Syria (approval ref.: 1806/2018).

The sample population consisted of 10 formalin-fixed, paraffin-embedded blocks of squamous cell carcinoma in each grade (grades 1–3; a total of 15 men and 15 women at the age of 22–74 years and 10 blocks of normal epithelium (biopsies taken from the mucosa that covers the bone before implantation – the para-keratinized mucosa).

Sections were cut from the blocks, and used for both histological and immunohistochemical examination. Four sections were made and loaded onto slides. The sections were deparaffinized, washed in deionized water and subjected to antigen retrieval. A solution of approx. 3% hydrogen peroxide was used to block endogenous peroxidase.

The standard streptavidin–biotin–peroxidase complex method was performed to bind the primary antibodies. The reaction products were visualized by treating them with 3,3′-diaminobenzidine (DAB) (Bio SB, Inc., Santa Barbara, USA) solution diluted according to the manufacturer's instructions. The manufacturer's data: Twenty micrometers of DAB chromogen were added to each 1 mL of poly-detector DAB buffer. For the control samples, the serial sections were treated with all the previous reagents, but without the primary antibody; the samples were confirmed to be unstained.

Heat shock protein 27 was assessed by counting the stained cells in 4 non-overlapping microscopic fields (positive cells showed positivity for the antibody as brown color in the cytoplasm) and by assigning it a score for color intensity (0 – no staining; 1 – mild and pale staining; 2 – moderate staining; and 3 – intense staining).

The Kruskal–Wallis and Mann–Whitney tests were used in the statistical analysis. The χ^2 test was conducted to determine whether there was a statistically significant difference between the groups: the χ^2 number was 16.057 with a p-value of 0.000 (much smaller than 0.05). These results refer to the presence of a significant difference between the groups.

Results

– Normal epithelium (n = 10):

The supra-basal layers of normal epithelium expressed moderately positive staining in almost all 10 samples (Fig. 1).

– OSCC grade 1 (n = 10):

All cancerous cells showed positive expression for HSP-27 in all 10 samples; the staining was mild and pale (Fig. 2).

– OSCC grade 2 (n = 10):

All cancerous cells showed positive expression for HSP-27 and the samples were moderately stained with the HSP-27 antibody (Fig. 3).

– OSCC grade 3 (n = 10):

All cancerous cells showed positive expression for HSP-27, with intense staining in almost all of the samples (Fig. 4).

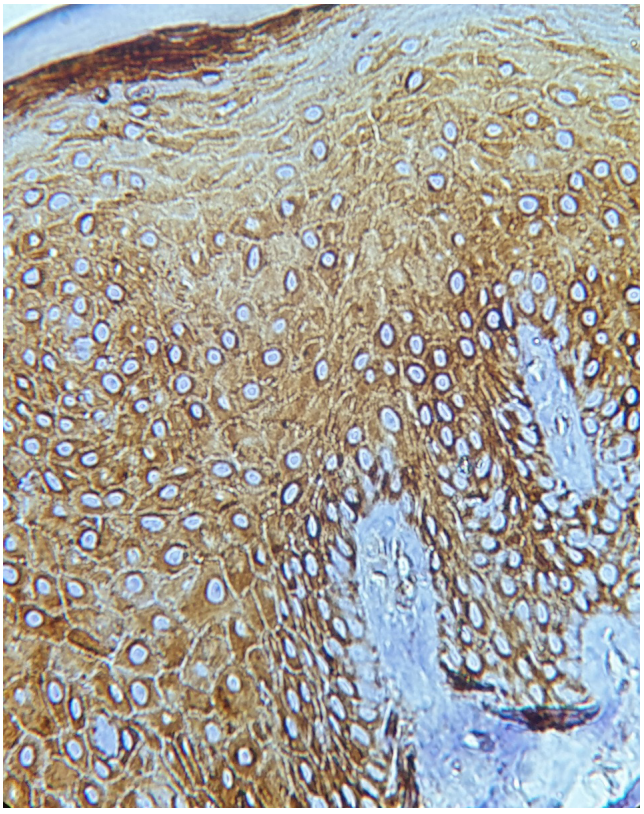

Fig. 1. Moderate positivity for heat shock protein 27 (HSP-27) in the cytoplasm of nearly all epithelial cells in normal mucosa
Magnification ×400.

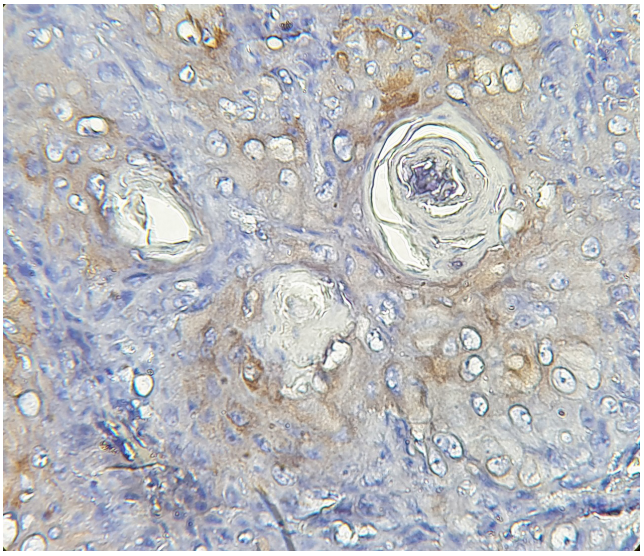

Fig. 2. Mild positivity for heat shock protein 27 (HSP-27) in the cytoplasm of all cancerous cells, grade 1 oral squamous cell carcinoma (OSCC)
Magnification ×400.

Discussion

Head and neck squamous cell carcinoma (HNSCC) is considered the 6th most prevalent cancer in the world. Radiotherapy has been the primary treatment for patients affected with this inoperable disease.[8,9]

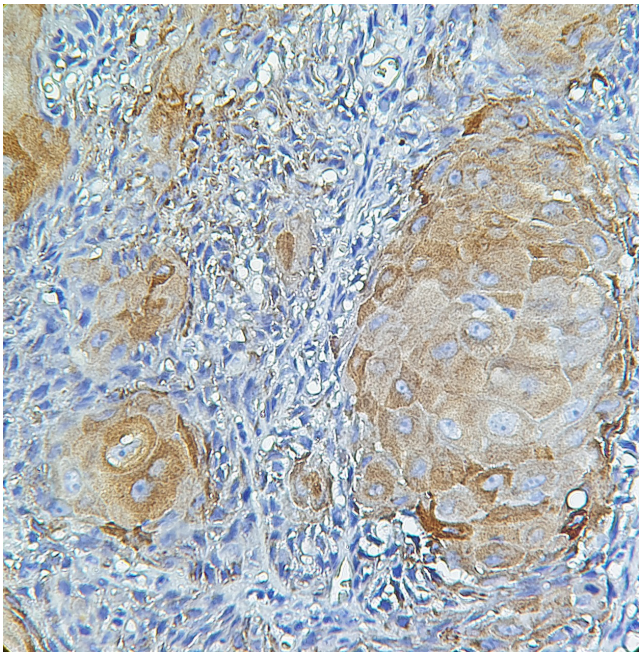

Fig. 3. Moderate positivity for heat shock protein 27 (HSP-27) in the cytoplasm of all cancerous cells, grade 2 oral squamous cell carcinoma (OSCC)
Magnification ×400.

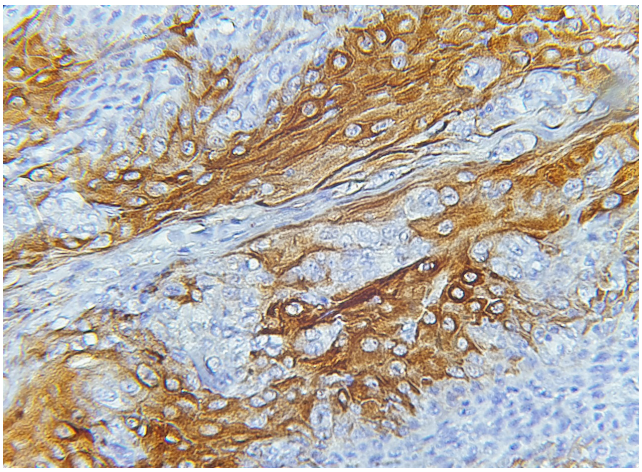

Fig. 4. Intense staining for heat shock protein 27 (HSP-27) in the cytoplasm of nearly all cancerous cells, grade 3 oral squamous cell carcinoma (OSCC)
Magnification ×400.

In spite of these huge improvements, the lowest 5-year survival rate associated with HNSCC has remained the same, due to frequent recurrence after the initial therapy. Therefore, advanced therapeutic methods should be applied to defeat resistance to anticancer therapy. One option suggests suppressing specific physiological proteins with antiapoptotic roles, such as HSP-27. The overexpression of this protein has been detected in many cancers, including breast cancer,[10,11] prostate cancer[12,13] and gastric cancer.[14,15]

Heat shock protein 27 has also been found to be overexpressed in HNSCC cases.[5] In addition, HSP-27 has been associated with the most serious behaviors of cancer cells – metastasis,[16,17] short survival time[10] and poorly differentiated cells.[18] With its antiapoptotic property, HSP-27

causes the resistance of cancer cells to chemoradiotherapy.[19,20] Heat shock protein 27 plays a protective role for tumor cells against oxidative pressure with the unique ability of glucose-6-phospate-dehydrogenase to keep glutathione in its decreased form, and also with the activity of an in vivo chaperone against oxidized proteins.[21] Therefore, decreasing the antioxidant protection of tumor cells through HSP-27 suppression should augment the benefit of the cytotoxic competence of radiotherapy and enhance the clinical outcome.

Apart from that, HSP-27 participates in the regulation of Akt (serine/threonine kinase), which is an important indicator molecule for cell survival.[22]

Heat shock protein 27 plays an essential role in the chemoresistance of the squamous cell carcinoma of the tongue (SCCT) cells via its extracellular and intracellular signaling process. Heat shock protein 27 could serve as a useful biomarker and a precise therapeutic target in the treatment of SCCT.[23]

There has been a particular increase in the amount of HSP-27 in multidrug-resistant SCCT cells. Both HSP-27 knockdown and anti-HSP-27 antibody treatment oppose chemoresistance. Inversely, the overexpression of HSP-27 and recombinant human HSP-27 treatment increase chemoresistance.

Furthermore, chemotherapy has been reported to have a significant effect on the HSP-27 levels by inducing the protein in SCCT cells and their culture medium as well as in the tumor tissues and serum of SCCT patients. For that, the overexpression of HSP-27 can predict the poor outcome of SCCT patients receiving chemotherapy; specifically, extracellular HSP-27 binding with toll-like receptor 5 (TLR5) and the activation of nuclear factor kappa B (NF-κB) signaling keep cancer cells alive. Toll-like receptor 5 knockdown or the level of the restored inhibitor of NF-κB (IκBα) damage extracellular HSP-27-induced NF-κB transactivation and chemoresistance. Additionally, the action of intracellular HSP-27 binding to BAX and BIM prevents their translocation to the mitochondria, and cytochrome C is subsequently released under chemotherapy, which causes the suppression of the mitochondrial apoptotic pathway.[23]

Moreover, some studies have reported the overexpression of HSP-27 in cancer stem cells. One group of researchers showed the augmented expression and phosphorylation of the protein in breast cancer stem cells.[11] They revealed that HSP-27 had to play a role in the epithelial–mesenchymal transition process to help with the maintenance of cancer stem cells.[11] Another study illustrated that lung cancer stem cells had elevated levels of the activated type of HSP-27 due to superoxide and traditional chemotherapy treatment.[24]

The expression of HSP-27 in well-differentiated OSCCs was significantly lower than in moderately differentiated OSCCs (p = 0.000), and in moderately differentiated OSCCs, the expression was lower than in poorly differentiated OSCCs (p = 0.002). The analysis showed a clear correlation between the expression of HSP-27 and the histopathological grade of OSCC (p = 0.000) (Table 1, Fig. 5). We attribute this to the major role of the protein as an anti-apoptosis agent helping cancerous cells remain immortal.

Table 1. Binary comparison of the intensity of heat shock protein 27 (HSP-27) in the histological grades of oral squamous cell carcinoma (OSCC)

Sample 1	Sample 2	*U*-value	*p*-value	Differentiation
OSCC grade 1	OSCC grade 2	4.5	0.000	significant differences
OSCC grade 1	OSCC grade 3	1	0.000	significant differences
OSCC grade 2	OSCC grade 3	15	0.002	significant differences

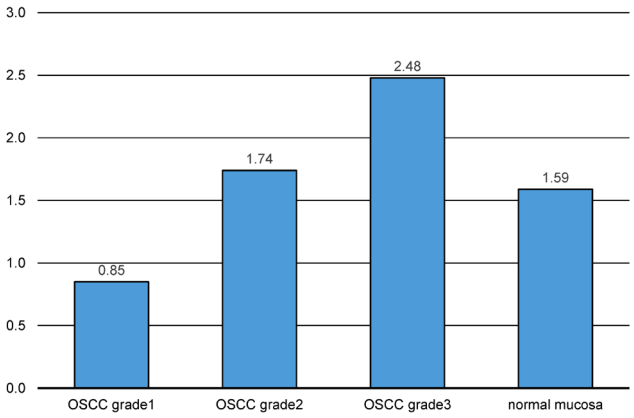

Fig. 5. Intense levels of heat shock protein 27 (HSP-27)

These findings are in agreement with previous studies, e.g., by Lambot et al., who investigated HSP-27 expression in esophagitis, esophagus dysplasia, and the 3 grades of esophagus squamous cell carcinoma in comparison with the normal epithelium of the esophagus.[25] The study concluded that there was a clear relationship between high HSP-27 expression and the atypia of cells.[25] Also, a study by Mese et al., which was conducted on biopsies from both OSCC areas and metastasis areas in different parts of the body, reported results similar to ours, with a stronger expression of the protein for metastasis biopsies.[26] Muzio et al. conducted research with exactly opposite results.[27] The correlation was between low-grade OSCC and the intensity of HSP-27 expression. We relate this to the variation of standards in the 2 studies, as they used biopsies taken from patients who had already gone through multiple types of treatment whereas our samples were taken and studied before any treatment.

Conclusions

This study has found that HSP-27 can be used as a marker for the histological grades of OSCC and that its expression is a possible indicator of the biological behavior of the tumor.

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Histologic grading of the tumor/tissue interface to predict lymph node metastasis in squamous cell carcinoma of the tongue

Histologiczne stopnie złośliwości tkanki nowotworowej a predykcja przerzutowania do węzłów chłonnych w raku płaskonabłonkowym języka

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Abstract

Background. The invasive front is presumed to contain the most aggressive subpopulation of tumor cells that ultimately invade, spread locally and metastasize. Studying the histopathological grading of the tumor/tissue interface at the invasive front may help in developing the treatment plan.

Objectives. The aim of this study was to check the reliability of the tumor/tissue interface in predicting lymph node metastasis in oral squamous cell carcinoma (OSCC) of the tongue by evaluating the following: the histopathological grading of hematoxylin and eosin (H&E)-stained excision biopsy specimens according to the modified version of Broder's classification system; and the invasive tumor front (ITF) with the modified version of Bryne's grading system. The study also aimed at studying the lymph nodes for metastases and comparing these histopathological grading systems and lymph node metastases.

Material and methods. All retrospective and prospective cases from the archives of the Department of Oral Pathology and Microbiology of the A.B. Shetty Memorial Institute of Dental Sciences (ABSMIDS), NITTE University in Mangalore, India, collected during the period from 2012 to 2014 were considered for histopathological grading.

Results. This study found a significant association between the modified version of Bryne's ITF grading system and lymph node metastases whereas the widely used modified version of Broder's classification failed to show any statistical significance. Only the multifactorial malignancy grading of the deep invasive margins of OSCC proved to be of high prognostic value.

Conclusions. The study found that the degree of keratinization, nuclear polymorphism, the pattern of invasion, and the host response showed significant variation at the invasive front of the tumor as compared to superficial parts, which makes Bryne's grading system more reliable than Broder's grading system.

Key words: lymph node metastasis, oral squamous cell carcinoma of the tongue, Broder's grading, Bryne's grading, invasive tumor front

Słowa kluczowe: przerzutowanie do węzłów chłonnych, rak płaskonabłonkowy języka, stopniowanie złośliwości wg Brodera, stopniowanie złośliwości wg Bryne'a, inwazyjny front raka

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Introduction

Among cancers affecting oral sites, oral squamous cell carcinoma (OSCC) of the tongue is known to exist as a biologically distinct entity. Oral squamous cell carcinoma of the tongue is considered severe, as it is associated with high rates of metastasis.[1] It has been estimated that approx. 20% of squamous cell carcinomas (SCCs) that occur in the oral cavity are believed to emerge from the tongue, and that 75% of the tongue SCCs arise from the ventrolateral aspect of the mid and posterior tongue. This could be due to the accumulation of carcinogens. In spite of the fact that patients as well as physicians have easy access to the tongue, the malignancy usually presents late and is also painless, so it is often ignored by patients. Gradually, it presents as an ulcer that is non-healing and demonstrates growth over time.[2] The early identification and treatment of OSCC is most important in reducing the mortality and morbidity related to this devastating disease.[3] During diagnosis, nodal metastasis is said to be more common (37–58%) in the case of the tongue than any other site in the oral cavity. The reason could be the extensive lymphatic drainage of the tongue. Therefore, the reported complaint in these cases may be a neck mass.[2] Lymph node metastases are most likely to be present in head and neck cancers.[3] As a result, in the case of cervical node metastases, there is a chance of a decrease in the survival rate by 50% and an increase in distant metastases.

Histologic grading systems have been devised by many researchers to study the nature of oral carcinoma. Based on its biological behavior, OSCC is differentiated as well-differentiated, moderate or poorly differentiated. The quantitative grading of cancer was primarily developed by Broder in 1920. Broder's classification system for grading a tumor is a classic tool in pathology of documented prognostic value.[4,5]

The invasive front is presumed to contain the most aggressive subpopulation of tumor cells that ultimately invade, spread locally and metastasize. Several events occur at the molecular level, such as the addition or removal of adhesion molecules, the secretion of proteolytic enzymes, and increases in the proliferation of cells and angiogenesis at the tumor/host interface of the invasive front. Hence, histopathological grading at the tumor/tissue interface at the invasive front is necessary and may help in preparing the treatment plan.[6] This study is an attempt to determine the efficacy of the modification of Broder's grading system and the modification of Byrne's invasive tumor front (ITF) grading system in assessing tumor biology, and their role in predicting lymph node metastases in OSCC of the tongue.

Material and methods

Source of data

This study was approved by the Ethics Committee of the A.B. Shetty Memorial Institute of Dental Sciences (ABSMIDS), NITTE (Deemed to be University) in Mangalore, India (ABSM/EC/52/2012). From among the retrospective as well as prospective cases registered from November 2012 to August 2014, 62 cases were selected, of which a total of 30 cases that met the inclusion criteria were included in the study: the cases of OSCC of the tongue diagnosed by excision biopsy and histopathology with radical neck dissection, the archival formalin-fixed and paraffin-embedded representative samples of deep margins with an adequate connective tissue stroma, and cases that were available with sufficient clinical data. The cases of OSCC other than regarding the tongue or without radical neck dissection were excluded. The formalin-fixed excision biopsy specimens of OSCC of the tongue treated with radical neck dissection were collected from the archives of the ABSMIDS Department of Oral Pathology and Microbiology. The cases submitted during the study period were also considered.

Data collection technique

Histological grading was done on routine 3–5-micrometer-thick sections, stained with Harris hematoxylin and eosin (H&E) and examined under light microscopy. The observers were blinded to the lymph node status. The main slide containing the whole thickness with an adequate connective tissue stroma of the tumor was taken for grading in each case. Each tumor was graded according to the modification of Broder's grading system[7] and the modification of Bryne's ITF grading.[8] The lymph nodes of the radical neck-dissected specimens were checked for the absence or presence of metastases both in the gross and histopathologically stained slides. The case histories, including age, sex, the past medical history, the duration of the disease, and habits, were all recorded.

Statistical analysis

The data was tabulated and statistical tests were done using the SPSS for Windows v. 16.0 software (SPSS, Inc., Chicago, USA). Categorical data were presented as percentages. The reliability of the ratings by 3 pathologists using Bryne's modified grading system was measured with Cohen's kappa coefficient. Fisher's exact test was applied to assess the relation between Broder's modified grading system and Bryne's modified grading system with regard to cervical lymph node metastasis. The results were considered statistically significant at a p-value <0.05.

Results

Reviewing a total of 62 cases of OSCC reported from 2012 to 2014, 30 cases of OSCC of the tongue (Fig. 1) treated with radical neck dissection that met the inclusion criteria were diagnosed histopathologically according to the tumor, node and metastasis (TNM) classification, Broder's modified system and Bryne's modified grading.

Of the 30 cases, 17 (56.7%) were males and 13 (43.3%) were females. The mean age was 54.9 years, ranging from 17 to 73 years. The mean age among the males was 55.4 years and among the females – 54.5 years.

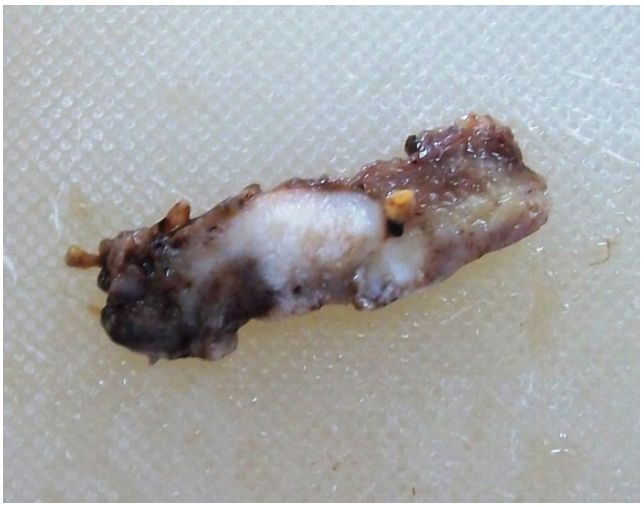

Fig. 1. Gross pathology of a metastatic lymph node

Table 1. Distribution of the study subjects according to the lymph node status

Lymph node status	Frequency *n*	Frequency %
Metastatic	14	46.7
Non-metastatic	16	53.3
Total	30	100.0

Table 2. Relationship between the tumor size and the lymph node status

Tumor size	Metastatic group *n* (%)	Non-metastatic group *n* (%)	Total *n* (%)	*p*-value
T1 (<2 cm)	6 (42.9)	7 (43.8)	13 (43.3)	0.813
T2 (2–4 cm)	3 (21.4)	5 (31.2)	8 (26.7)	
T3 (>4 cm)	5 (35.7)	4 (25.0)	9 (30.0)	
Total (*N* = 30)	14 (46.7)	16 (53.3)	30 (100)	

Fisher's exact test.

Lymph node metastases were observed in 14 (46.7%) of the cases whereas 16 (53.3%) were free of metastases (Table 1). In the metastatic group, 6 (42.9%) of the cases were males and 8 (57.1%) were females, while in the non-metastatic group, 11 (68.8%) were males and 5 (31.2%) were females.

The duration of the disease in all 30 cases ranged from 1 to 36 months, with an average of 5.8 months. The difference in the mean duration of the disease between the metastatic and non-metastatic groups was not significant, indicating a lack of any correlation between disease duration and lymph node metastasis.

Among the males, 12 (70.6%) were habitual users of tobacco (chewing, smoking) and/or alcohol. Neither of these habits was noted among the women.

The tumor diameters ranged from 0.6 cm to 6 cm, with an average of 3.3 cm. With regard to the primary tumor size, of the 14 cases analyzed in the metastatic group, 6 (42.9%) were T1 tumors, 3 (21.4%) were T2 tumors and 5 (35.7%) were T3 tumors, while of the 16 cases in the non-metastatic group, 7 (43.8%) were T1, 5 (31.2%) were T2 and 4 (25.0%) were T3. There was no statistically significant relationship between the tumor size and lymph node metastasis (Table 2).

With regard to Broder's modified grading system, 24 (80%) of the cases were well-differentiated, 5 (16.7%) were moderate and 1 (3.3%) was poorly differentiated (Fig. 2). The relationship between the modified version of Broder's grading system and lymph node metastasis is presented in Table 3. Among the 14 cases in the metastatic group, 10 (71.5%) were well-differentiated, 3 (21.4%) were moderate and 1 (7.1%)

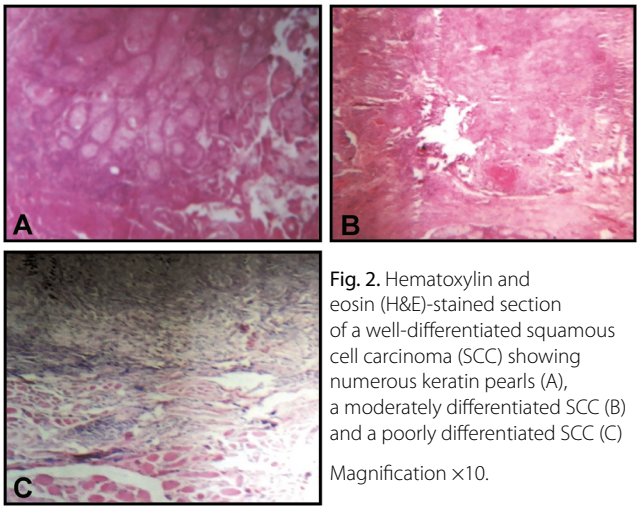

Fig. 2. Hematoxylin and eosin (H&E)-stained section of a well-differentiated squamous cell carcinoma (SCC) showing numerous keratin pearls (A), a moderately differentiated SCC (B) and a poorly differentiated SCC (C)

Magnification ×10.

Table 3. Relationship between Broder's modified grading system and the lymph node status

Broder's modified grading system	Metastatic group *n* (%)	Non-metastatic group *n* (%)	Total *n* (%)	*p*-value
Well-differentiated SCC	10 (71.5)	14 (87.5)	24 (80.0)	0.471
Moderately differentiated SCC	3 (21.4)	2 (12.5)	5 (16.7)	
Poorly differentiated SCC	1 (7.1)	0 (0)	1 (3.3)	
Total (*N* = 30)	14 (46.7)	16 (53.3)	30 (100)	

SCC – squamous cell carcinoma; Fisher's exact test.

was poorly differentiated; among the 16 non-metastatic cases, 14 (87.5%) were well-differentiated and 2 (12.5%) were moderately differentiated. The statistical analysis failed to detect any significant relationship between Broder's modified grading system and lymph node metastasis.

Bryne's modified grading system examines 4 morphological features: the rate of keratinization, polymorphism in the cell nucleus, the pattern of invasion, and the response from the host. These parameters are assessed in the most invasive margins of the tumor. Scores range from 1 to 4. The modified version of Bryne's ITF grading was used by 3 pathologists to score all the cases included in the study and there was a strong agreement (0.81) among the scorers. Of the 30 cases, 14 (46.7%) were classified as grade I, 13 (43.3%) as grade II and 3 (10%) as grade III.

Among the 14 cases in the metastasizing group, 2 (14.3%) were classified as grade I, 9 (64.3%) as grade II and 3 (21.4%) as grade III. Among the 16 non-metastasizing cases, 12 (75%) were classified as grade I and 4 (25%) as grade II (Fig. 3–5, Table 4). Bryne's modified grading system showed a significant association (p = 0.001) with lymph node metastasis (Table 4). It is evident from the comparison of the 2 grading systems that Bryne's ITF grading classification correlates more strongly with lymph node metastasis than Broder's system does (Fig. 6).

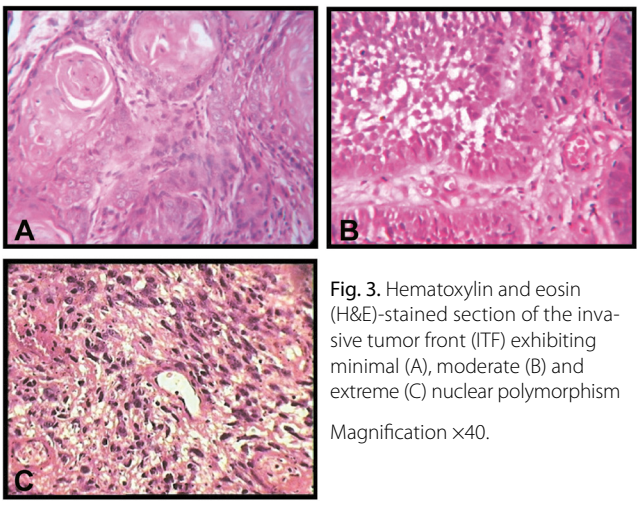

Fig. 3. Hematoxylin and eosin (H&E)-stained section of the invasive tumor front (ITF) exhibiting minimal (A), moderate (B) and extreme (C) nuclear polymorphism

Magnification ×40.

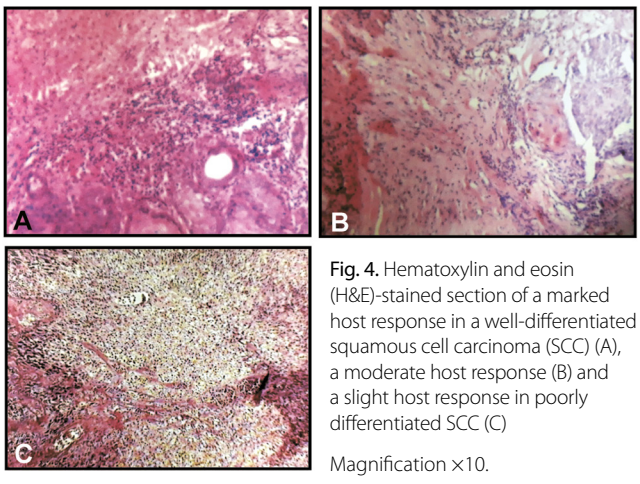

Fig. 4. Hematoxylin and eosin (H&E)-stained section of a marked host response in a well-differentiated squamous cell carcinoma (SCC) (A), a moderate host response (B) and a slight host response in poorly differentiated SCC (C)

Magnification ×10.

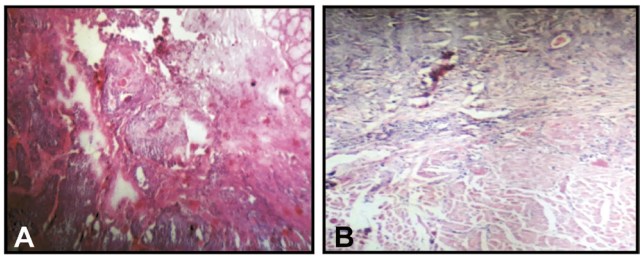

Fig. 5. Hematoxylin and eosin (H&E)-stained section of the invasive tumor front (ITF) exhibiting infiltrating solid cords or bands (A) and small cords of infiltrating cells with muscle invasion (B)

Magnification ×10.

Table 4. Relationship between Bryne's modified grading system and the lymph node status

Bryne's modified grading system	Metastatic group *n* (%)	Non-metastatic group *n* (%)	Total *n* (%)	*p*-value
Grade I	2 (14.3)	12 (75.0)	14 (46.7)	0.001*
Grade II	9 (64.3)	4 (25.0)	13 (43.3)	
Grade III	3 (21.4)	0 (0)	3 (10.0)	
Total (N = 30)	14 (46.7)	16 (53.3)	30 (100)	

* statistically significant; Fisher's exact test.

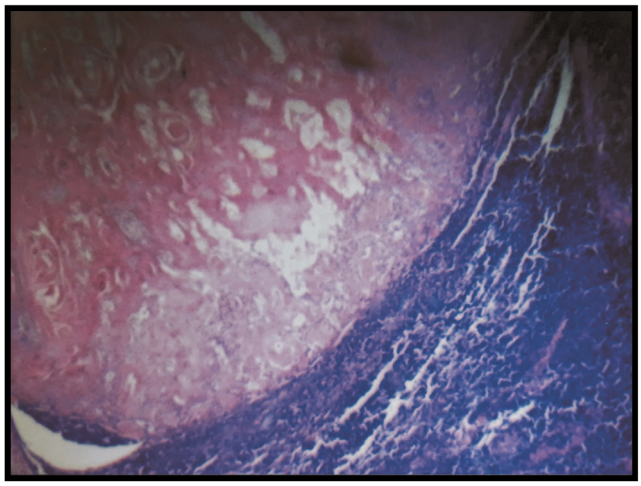

Fig. 6. Hematoxylin and eosin (H&E)-stained section of a lymph node metastasis showing keratin formation

Magnification ×10.

Discussion

Oral cancer is the most common type of cancer in India, with a total cancer mortality of 50–70%. In this study, among the 30 cases of OSCC of the tongue, males comprised 56.7%. Many studies have shown the prevalence of OSCC in males.[5,9,10] A high rate of OSCC among males could be related to a high rate of tobacco use (chewing and smoking) among them. This is relevant in the present study, where habitual tobacco chewing and smoking, and/or alcohol consumption were prevalent among the males (70.6%).

Invasion and growth into surrounding tissues are known to characterize OSCC. Metastases are considered the most challenging feature of cancer progression. They generally signify limited survival rates and ineffective therapy.[11] The most important factor for prognosis in head and neck SCC is cervical lymph node metastasis.[12] With the development of carcinoma in the oral cavity, the cancer may spread to regional lymph nodes through the lymphatic drainage system. This process is further increased by the poorly differentiated behavior of these tumors. This determines the survival rate of patients, as in the case of carcinomas that have spread to regional lymph nodes, there is a 5-year survival rate, which is half of that observed for cancers in the oral cavity that have not metastasized.

Various studies have reported a significant relationship between the degree of histologic differentiation and the occurrence of lymph node metastasis in SCC of the head and neck region.[13–15]

Broder initiated the grading of cancer in 1920 with a quantitative method based on the proportion of differentiated cells to undifferentiated cells. Despite slight modifications in Broder's system of classification of SCC, limitations remain when prognosis and the choice of treatment are considered. It may be due to the heterogeneity of the cell population present in SCC tumors.

Although Broder's system has been used for many years, a lack of association between the system and prognosis has been mentioned in the literature. However, in their study, Odell et al. found an association between Broder's grading system and local recurrence and metastasis.[16] On the other hand, both Dissanayake and Doshi et al. failed to observe any relationship between Broder's grading system and lymph node metastasis.[5,10] A study by Jamadar et al. on 20 cases of OSCC showed no correlation of this grading system with the lymph node status.[17] The present study also failed to observe any association between Broder's modified grading system and lymph node metastasis.

As a result, the need for a new system of grading has been felt. Jakobsson et al. extended Broder's 2-factor grading system to multifactorial parameters, such as the structure of the tumor, the ability to differentiate, nuclear polymorphism, and the number of mitoses.[18] Following this, many other grading systems have been developed and improved over a few decades by many researchers.[13,17]

Bryne et al. took into consideration the fact that in malignancies, there are heterogeneous tumor cells.[19] They observed that cells in the deep invasive margin were less differentiated than those in the superficial part of the tumor.[19] The histologic grading of the superficial areas of the tumor may not give the accurate diagnosis of its aggressive behavior and accurate prognosis for the tumor.

Bryne et al. modified Anneroth's multifactorial grading system.[8] In this modified system, cells in the deep invasive margin of the tumor were graded. The invasion stages and the mitotic count were removed from the system, increasing the reproducibility of the grading system. The mitotic count, which was used as a marker for prognosis, was dependent on factors such as tumor heterogeneity, disagreement among the observers and variations in the high-power field of the microscopes used for the study. The validity of the parameter was also dependent on a very low mitotic count in the deep invasive region of the tumor as compared to more solid tumor areas.

The malignancy grading of the deep invasive margins of OSCCs based on various factors was introduced by Bryne et al., and has proved to be of high prognostic value.[8,21] In the present study, this system correlated significantly with lymph node metastasis.

Studies by Bryne et al. as well as Monevska et al. reported a strong association between the total malignancy grade of several pathologic parameters and prognosis in OSCC.[8,21] A study by Doshi et al. showed a significant association (p = 0.05) between Bryne's grading system and lymph node metastasis, which closely matches the results of the present study.[10] Furthermore, a study by Khwaja et al. identified the ITF grading as the most important predictive factor for cervical lymph node metastasis, and also suggested that the ITF grading could be taken into consideration when selecting the most appropriate treatment approach.[22]

Bryne's grading system has shown to be prognostic, and also to have good inter- and intra-observer reliability.[23] In the present study, inter-observer reliability was r = 0.81, which revealed a strong agreement among the 3 pathologists grading the tumors.

A frequent lack of inter-observer agreement in the process of scoring many parameters is a major problem that limits the clinical usefulness of histologic grading.[23] Biopsies do not represent the whole tumor, but are the only tissue samples available for histologic evaluation, which limits the current study. Therefore, specific criteria need to be set for selecting a representative tumor tissue to conduct histologic grading.

Conclusions

In the present study, the modified version of Bryne's grading system showed a statistically significant correlation with lymph node metastasis, which is compatible with the results of previous studies.[5,10,22,24] Histopathological grading is one of the factors used to make prognosis for OSCCs. The established factors for predicting the biological behavior of these tumors are not very well substantiated. However, pathologists have observed that cells in the most invasive parts of a malignant tumor differ substantially from those in the superficial areas of the tumor. This has led to recognizing the significance of the structural and functional features of the most advanced part of carcinomas – ITF – in determining the biological aggressiveness of the tumor. The study indicates that Bryne's modified grading system at the tumor/tissue interface can be taken as a diagnostic factor and prognosis for lymph node metastasis.

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Copper nanoparticles as nanofillers in an adhesive resin system: An in vitro study

Nanocząsteczki miedzi jako nanowypełniacze w systemie wiążącym – badanie in vitro

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Abstract

Background. The incorporation of an antibacterial agent into an adhesive could improve its clinical performance. Some nanoparticles (NPs), including copper nanoparticles (Cu NPs), display an antibacterial effect. Therefore, Cu NPs could act as a nanofiller when added to an adhesive.

Objectives. The aim of this study was to evaluate the antibacterial activity, cytotoxicity and shear bond strength (SBS) of an experimental dental adhesive with Cu NPs.

Material and methods. Different concentrations (0.0050 wt%, 0.0075 wt% and 0.0100 wt%) of Cu NPs were added to the adhesive. The distribution of Cu NPs in the polymer matrix was observed based on transmission electron microscope (TEM) images. The antimicrobial activity of the adhesive + Cu NPs was evaluated with the agar disk diffusion test against *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*) and *Streptococcus mutans* (*S. mutans*). The cytotoxicity assay was performed by means of the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method with human pulp cells (HPC). Additionally, the SBS tests were carried out ($n = 31$) and the modes of fracture were registered. The vestibular and lingual surfaces of each tooth were randomly assigned to the study groups (group I – control adhesive; group II – adhesive + 0.0100 wt% Cu NPs). The samples were statistically analyzed ($p \leq 0.05$).

Results. The adhesive + 0.0100 wt% Cu NPs showed inhibition zones against the strains under study that were similar to, or slightly smaller than, the halos produced by chlorhexidine (CHX) and specific drugs for each strain (30 µg of cefotaxime against *S. mutans* and *S. aureus*, and 1.25/3.75 µg of sulfamethoxazole/trimethoprim against *E. coli*). The control adhesive was moderately cytotoxic (relative cell viability of 36.7 ±0.8%), being more cytotoxic than Cu NPs themselves (58.3 ±0.1%). A significantly higher SBS was obtained for the adhesive + 0.0100 wt% Cu NPs (6.038 ±2.95 MPa) than for the control group (3.278 ±1.75 MPa). The modes of fracture in group I were almost equally distributed between adhesive and cohesive failures whereas in group II, the failure was mainly cohesive.

Conclusions. The results of this study suggest that incorporating Cu NPs into an adhesive improves its SBS and provides it with antibacterial properties, without increasing its inherent cytotoxicity – 2 desirable characteristics for the dental adhesives of composites.

Key words: copper, nanoparticles, mechanical stress, antibacterial agents, dental bonding

Słowa kluczowe: miedź, nanocząsteczki, naprężenie mechaniczne, czynniki antybakteryjne, wiązanie dentystyczne

Introduction

Considerable scientific advances have been made in the field of adhesive materials used in restorative esthetic dentistry; however, further improvements, e.g., regarding antibacterial properties, are needed to prevent the undesirable formation of secondary caries lesions. As it is well-known, esthetic dentistry is the current tendency. Patients demand long-lasting and invisible restorations. It has been reported that more than a half of the performed dental restorations are replacements for restorations that failed prematurely.[1] A fracture in the restoration or dental structures and secondary caries are the main reasons for the failure of dental restorations.[2] Secondary caries is a frequent concern for dentists in clinical practice, because caries leads to the shortening of the service life of dental restorations, and ultimately results in the need to replace restorative materials.[3]

Ideally, the bond formed at the adhesive–dentin interface should prevent the penetration of noxious substances, such as bacteria, extracellular products or oral fluids.[4] Thus, there is a need to add an antibacterial agent to dental composites for this purpose. Chlorhexidine (CHX) has been studied in this regard. Studies on composites with increasing concentrations of CHX dissolved in resin blends have shown a slight adverse effect on the degree of conversion and a 27–48% decrease in the E-modulus (i.e., a lower polymer stiffness) as compared to controls.[5] In addition, the incorporation of 1% CHX resulted in a reduction in tensile and compressive strengths.[6] The reason for this finding may be the disruption of the monomer curing process or interference in binding the filler and matrix phases by the incorporated agent.[7]

The application of nanotechnology in the field of dental biomaterials is a great step toward the production of materials with better biological properties. It has been demonstrated that some nanoparticles (NPs) possess an antibacterial effect.[8] In brief, the main variables that are involved in antibacterial activity are the particle size, nanostructure shape, dosage, and chemical composition. With regard to the impact of the size on antibacterial activity, NPs must be small enough to penetrate cell membranes and affect intracellular homeostasis. Besides, the interaction between NPs and bacteria depends on the surface area exposed (small particles with a larger available interaction surface area exert a greater bactericidal effect than large-sized particles).[9] More specifically, the antibacterial mechanism depends on the chemical composition of NPs. Particular attention has been paid to the study of metal NPs, such as Au,[10] Ag,[11] Zn,[12] and Cu.[13] However, Cu costs significantly less than Ag or Au, making it attractive from an economic standpoint.[14] The antibacterial mechanisms of Cu NPs have been explained through the production of hydroxyl and superoxides via Fenton reactions, and through binding the disulfide groups of respiratory enzymes in the cellular membrane, leading to the formation of a complex with Cu NPs; both mechanisms result in the disruption of the cell cycle.[15]

The antibacterial properties of Cu NPs have been studied previously.[13,14] One study indicated the potential use of Cu NPs in the field of dental biomaterials; Cu NPs were prepared with a simple chemical method, and their antibacterial activity was tested against *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*) and *Streptococcus mutans* (*S. mutans*).[16] Additionally, it has been reported that using NPs as nanofillers could contribute to higher modulus of elasticity and shear bond strength (SBS) values for dental adhesives.[17]

The aim of the present study was to investigate the antibacterial activity, cytotoxicity and SBS of a novel dental adhesive enriched with Cu NPs as nanofillers.

Material and methods

The type of adhesive system used for the experiments was a two-step, single-component, etch-and-rinse, light-cure dental adhesive (Adper™ Single Bond Plus Adhesive; 3M ESPE, St. Paul, USA). This adhesive is hydrophilic, and its solvent contains ethyl alcohol (25–35%) and water (<5%). As mentioned above, Cu NPs were synthesized. A solution consisting of deionized water and cupric sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) at a concentration of 1×10^{-2} M was prepared, and the pH of the solution was adjusted with sodium hydroxide (NaOH). Later, the metal salt solution was bubbled with nitrogen (N_2) for 30 min. Sodium borohydride ($NaBH_4$) was added at a stoichiometric concentration as a reducing agent. After that, the preparation was stirred for 120 min to finish the reaction. Subsequently, the precipitate was washed 3 times with distilled water and filtered. Then, the product was washed with acetone to displace water and isopropyl alcohol was added to avoid oxidation.[16] The Cu NPs (average particle size = 3.97 nm; range: 2–10 nm) were suspended in the same dilutant for all the experiments described below. For the experimental group, the Cu NPs were added to the dental adhesive and mixed using a vortex agitator in order to completely and uniformly distribute them.

Distribution of nanoparticles in the adhesive

The ultrastructure and qualitative analyses were carried out using the transmission electron microscope (TEM) JEM-2100 (JEOL Ltd., Tokyo, Japan). Micrographs were created to observe the distribution and size of the Cu NPs dispersed in the polymerized adhesive.

Antibacterial test

Antibacterial activity was determined using the agar disk diffusion method, following the recommendations of the National Committee for Clinical Laboratory Standards.[18] Copper nanoparticles were added to the dental adhesive at 3 different concentrations: 0.0050 wt%; 0.0075 wt%; and 0.0100 wt%. The turbidity of the culture was adjusted with sterile saline to achieve a value equivalent to a 0.5 McFarland standard. Mueller–Hinton agar plates were prepared and inoculated with 200 µL of suspension containing the standardized quantity of bacteria. Each disk was prepared with 20 µL of CHX or the adhesive with 3 different concentrations of Cu NPs. The disks were firmly placed one by one on the inoculated agar plates.

The antibacterial test was done against 3 strains: *S. aureus*; *E. coli;* and *S. mutans.* The antibacterial activity of the adhesive was determined using 2 groups for each strain: a non-polymerized adhesive; and an adhesive polymerized for 20 s with a light-emitting diode (LED) (Ortholux® XT; 3M Unitek Corp., Monrovia, USA). Two positive controls were used: 0.2% CHX and specific drugs for each strain (30 µg of cefotaxime against *S. mutans* and *S. aureus*, and 1.25/3.75 µg of sulfamethoxazole/trimethoprim against *E. coli*). The control adhesive without Cu NPs was tested against the same bacteria under study.

Inhibition zones were measured on a standardized photograph using a millimeter scale for calibration. The measurements were taken using the ImageJ 1.47e software (National Institutes of Health, USA) and the average result was rounded to the nearest millimeter. Each experiment was done in triplicate.

Cytotoxicity assay

The protocol for this study was approved by the Bioethics Committee at the National School of Higher Studies León Unit, National Autonomous University of Mexico in Mexico City, Mexico, with the assigned number CE_16/004_SN. A 21-year-old patient, who had previously given informed consent, donated the tissues obtained from a third molar surgery. Human pulp cells (HPC) were isolated from the pulp tissue of the teeth. The cultures were used for the subsequent assays according to the methodology previously reported for our research group.[19] The tests were performed using approx. 2×10^5 cells/mL per well. The adhesives contained Cu NPs at the same concentrations as those used in the antibacterial tests described above. Serial dilutions were made. The test was performed with indirect contact and cell viability was determined by means of the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method. Cytotoxicity was rated according to ISO standard 10993-5. Reproducible data was obtained in triplicate in 3 independent trials.

Shear bond strength

Thirty-one freshly extracted and healthy human third molars (without caries and restoration-free) were cleaned with a rotary brush and stored in a 0.2% solution of thymol at 4°C until further use. Each molar was carefully placed into an acrylic mold until the vestibular and lingual surfaces were parallel to the mold base, which is the appropriate position for performing the SBS test. The enamel of the vestibular and lingual surfaces was cut with a carbide disk under irrigation. Then, the surfaces were pumiced with a fluoride-free paste and rubber prophylactic cups, washed with water, and then air-dried. The surfaces of the teeth were randomly assigned to the control and experimental groups. Thus, it was possible to make a paired comparison between the groups. In both groups, the dentin was conditioned with phosphoric acid at a concentration of 37%, rinsed with water for 30 s and dried with contaminant-free air. In group I (control group), a thin coat of the dental adhesive was applied. In group II (experimental group), the adhesive with 0.0100 wt% of Cu NPs was used to test SBS, as it was the experimental adhesive which showed the strongest antibacterial effect out of all the concentrations of the Cu NPs tested. Pre-formed resin blocks 5 mm × 5 mm × 1 mm (Filtek® Z250 XT, 3M ESPE), light-cured using Ortholux XT for 20 s, were placed on the vestibular and lingual surfaces of each tooth. The samples were incubated in distilled water at 37°C for 24 h. For the test, a universal testing machine (Autograph AGS X; Shimadzu Corp., Tokyo, Japan) with a crosshead speed of 0.5 mm/min was used. An occluso-gingival load was applied to the resin blocks using a chisel-edge plunger, producing a shear load at the resin–tooth interface; the maximum load was recorded in megapascals (MPa).

Failure modes

To perform the qualitative analysis of the type of debonding between the adhesive and the dentin, the failure modes were classified as adhesive, cohesive, or mixed. For each sample, the failure modes were recorded according to the following criteria:

– adhesive failure occurs when the fracture mainly appears at the tooth–composite interface, i.e., the dentin surface remains exposed in over 75% of the bonded area;

– cohesive failure occurs when the fracture mainly appears within the composite, i.e., when over 75% of the bonded area exhibits the fractured composite;
– mixed failure occurs when 25–75% of the bonded area shows both adhesive and cohesive failure.[20]

In addition, the fracture surfaces were examined. The micrographs of different zones on the sample surface were obtained using the scanning electron microscope (SEM) JSM-6510LV (JEOL Ltd.) at 20 keV. Magnification varied between ×100 and ×200.

Statistical analysis

The data is expressed as mean (M) ± standard deviation (SD). The Shapiro–Wilk test (for the normality of data) was performed for the outcomes to determine the subsequent test (parametric or non-parametric). For the antibacterial and cytotoxicity results, multiple comparisons were performed with the Mann–Whitney U tests. For SBS, Student's t test was used to determine the difference of means. For the mode of failure, the χ^2 test was applied. The IBM SPSS Statistics for Windows software, v. 22.0 (IBM Corp., Armonk, USA) was used for the statistical analysis. Differences were statistically significant at $p \leq 0.05$.

Results

Distribution of nanoparticles in the adhesive

Figure 1 shows the distribution of Cu NPs in the adhesive. The shape of Cu NPs was almost spherical, allowing for a greater surface-area-to-volume ratio, which makes NPs more reactive, and consequently, their antibacterial effect is exhibited.[16,21] Adding the polymer does not cause any changes in size or morphology. The distribution of Cu NPs in the adhesive was homogeneous and showed no agglomeration.

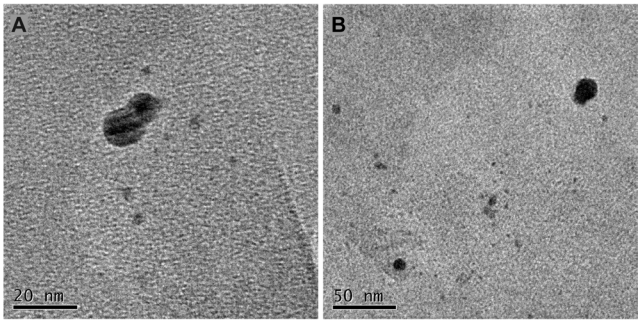

Fig. 1. Distribution of copper nanoparticles (Cu NPs) in the adhesive
Representative images at 2 magnifications – scale bar: 20 nm (A); and scale bar: 50 nm (B).

Antibacterial test

Figure 2 and Table 1 show the observed antibacterial effects. The experimental adhesive containing 0.0100 wt% of Cu NPs demonstrated the highest antibacterial activity and the obtained results are comparable with the antibacterial effect of CHX. The adhesives containing 0.0075 wt% and 0.0050 wt% of Cu NPs showed slight inhibition zones.

Cytotoxicity assay

Figure 3 and Table 2 show the results of the cytotoxicity assay. This test indicated that the adhesive is more cytotoxic than Cu NPs themselves. The control adhesive (without Cu NPs) is moderately cytotoxic, according to ISO standard 10993-5. There were no significant differences between the cell viability of the adhesives with Cu NPs as compared to the adhesive without Cu NPs. This indicates that Cu NPs do not increase the inherent cytotoxicity of the adhesive.

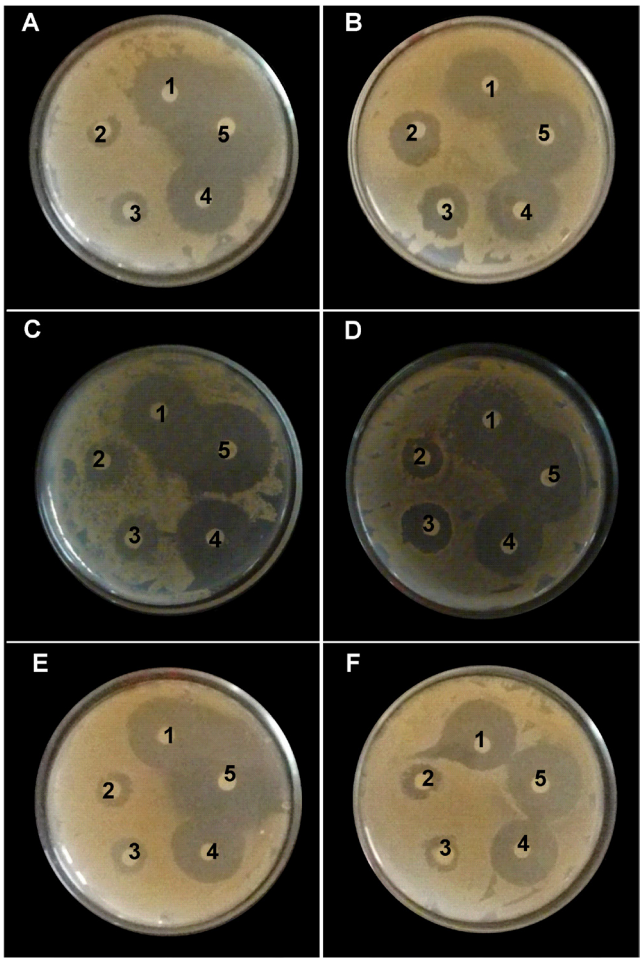

Fig. 2. Results of the antibacterial test using the agar disk diffusion method
A, C and E – agar plates showing disks with the non-polymerized adhesive; B, D and F – agar plates showing disks with the polymerized adhesive; 1 – 0.2% CHX; 2 – adhesive + 0.0050 wt% Cu NPs; 3 – adhesive + 0.0075 wt% Cu NPs; 4 – adhesive + 0.0100 wt% Cu NPs; 5 – specific drugs for each strain; CHX – chlorhexidine; Cu NPs – copper nanoparticles.

Table 1. Inhibition zones produced by different concentrations of the copper nanoparticles (Cu NPs) added to the adhesive and by the controls

Adhesive	Inhibition zones [mm]					
	non-polymerized	polymerized	non-polymerized	polymerized	non-polymerized	polymerized
	*S. aureus**		*E. coli***		*S. mutans**	
Adh + 0.0 wt% Cu NPs	0 ±0^{Aa}	0 ±0^{Aa}	0 ±0^{Aa}	0 ±0^{Aa}	0 ±0^{Aa}	0 ±0^{Aa}
Adh + 0.0050 wt% Cu NPs	0 ±0^{Aa}	12 ±1.0^{Bb}	11 ±1.5^{Bb}	9 ±1.9^{Bb}	10 ±1.1^{Bb}	10 ±1.4^{Bb}
Adh + 0.0075 wt% Cu NPs	10 ±1.5^{Ba}	12 ±1.8^{Ba}	13 ±1.1^{Ba}	14 ±2.0^{Ba}	12 ±1.4^{Ba}	13 ±1.6^{Ba}
Adh + 0.0100 wt% Cu NPs	24 ±1.7^{Ca}	21 ±1.9^{Cb}	24 ±1.3^{Ca}	20 ±0.9^{Cb}	27 ±1.4^{Ca}	25 ±1.5^{Ca}
CHX (0.2%)	24 ±1.5^{Ca}	24 ±1.2^{Ca}	25 ±0.9^{Ca}	24 ±0.5^{Da}	24 ±0.3^{Da}	24 ±1.6^{Ca}
Specific drug	27 ±1.9^{Ca}	25 ±1.9^{Ca}	27 ±1.4^{Ca}	28 ±1.7^{Ea}	29 ±1.8^{Ca}	27 ±1.4^{Ca}

Data presented as mean (*M*) ± standard deviation (*SD*).
Adh – adhesive; *S. aureus* – *Staphylococcus aureus*; *E. coli* – *Escherichia coli*; *S. mutans* – *Streptococcus mutans*; * specific drug –cefotaxime (30 µg); ** specific drugs – sulfamethoxazole/trimethoprim (1.25/3.75 µg). The same letters show that there are no statistically significant differences. Upper-case letters indicate differences between different concentrations of Cu NPs, while lower-case letters denote differences between the strains (Mann–Whitney *U* test; $p \leq 0.05$).

Table 2. Results of the cytotoxicity assay (cell viability [%]) for the adhesives enriched with copper nanoparticles (Cu NPs) using the MTT method

Serial dilutions [%]	Adh + 0.0 wt% Cu NPs	Adh + 0.0050 wt% Cu NPs	Adh + 0.0075 wt% Cu NPs	Adh + 0.0100 wt% Cu NPs	Cu NPs
0 (control)	■100.0 ±4.9^{Aa}	■100.0 ±0.3^{Aa}	■100.0 ±1.8^{Aa}	■100.0 ±0.3^{Aa}	■100.0 ±0.1^{Aa}
0.78125	■86.2 ±3.2^{Ab}	■87.2 ±1.3^{Ab}	■77.0 ±2.7^{Bb}	▲70.6 ±1.0^{Cb}	■99.7 ±0.3^{Da}
1.5625	▲59.5 ±4.0^{Ac}	◆47.9 ±5.1^{Bc}	◆47.8 ±4.6^{Bc}	◆43.3 ±1.9^{Bc}	■100.7 ±0.1^{Ca}
3.125	◆38.6 ±6.6^{Ad}	◆35.2 ±2.0^{Ac}	◆33.4 ±0.8^{Ad}	◆36.8 ±2.0^{Ad}	■96.7 ±0.1^{Bb}
6.25	◆34.6 ±1.5^{Ae}	◆37.0 ±1.0^{Ac}	◆34.3 ±0.6^{Ad}	◆37.7 ±1.1^{Ad}	■83.5 ±0.2^{Bc}
12.5	◆35.1 ±1.6^{Ae}	◆39.8 ±2.2^{Ad}	◆34.6 ±0.6^{Ad}	◆41.2 ±3.6^{Ad}	■82.5 ±0.2^{Bd}
25	◆36.5 ±4.0^{Ae}	◆39.4 ±1.0^{Ad}	◆38.5 ±2.4^{Ad}	◆37.1 ±1.5^{Ad}	▲63.5 ±0.1^{Be}
50	◆36.7 ±0.8^{Ae}	◆39.8 ±0.6^{Bd}	◆37.3 ±0.1^{Ad}	◆41.0 ±1.5^{Bd}	▲58.3 ±0.1^{Cf}

Data presented as mean (*M*) ± standard deviation (*SD*).
Cytotoxicity was rated according to ISO standard 10993-5 as: ■ non-cytotoxic; ▲ slightly cytotoxic; ◆ moderately cytotoxic; and ● severely cytotoxic. The same letters show that there are no statistically significant differences. Upper-case letters indicate differences within a group (wt% Cu NPs) in the same dilution, while lower-case letters denote differences between the dilutions (Mann–Whitney *U* test; $p \leq 0.05$).

Statistically significant differences ($p \leq 0.05$) were observed between Cu NPs and the control adhesive as well as the adhesive enriched with Cu NPs at different concentrations.

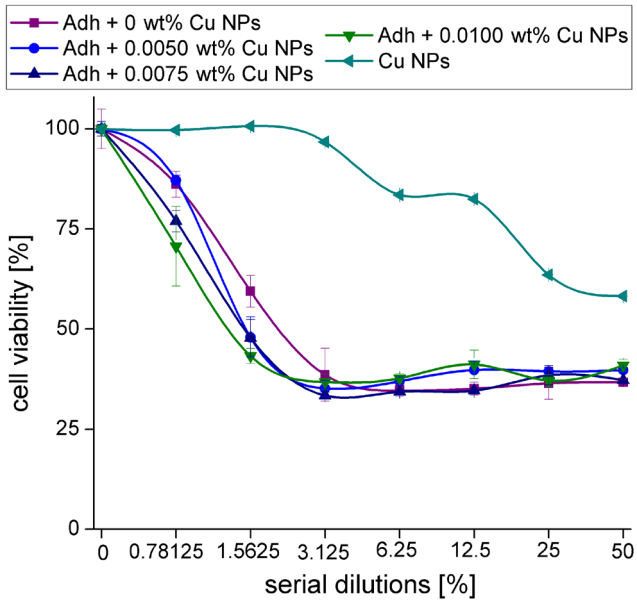

Fig. 3. Relative cell viability results of the cytotoxicity assay

Shear bond strength

Table 3 shows the SBS values and descriptive statistics. The mean SBS of group II was significantly higher than that of group I (6.038 ±2.95 MPa and 3.278 ±1.75 MPa, respectively; $p = 0.0001$). Thus, the Cu NPs incorporated into the adhesive significantly increased its SBS.

Table 3. Comparison of the shear bond strength (SBS) of the adhesive between the control (I) and experimental (II) groups

Group	*n*	SBS [MPa]	Maximum [MPa]	Minimum [MPa]	*p*-value
Group I	31	3.278 ±1.75	20.47300	3.89819	0.0001
Group II	31	6.038 ±2.95	40.59340	6.78409	

Data presented as mean (*M*) ± standard deviation (*SD*).
df (degrees of freedom) = 30; Student's *t* test.

Failure modes

Table 4 shows the values which indicate the amount of the adhesive remaining after the SBS test. In this study, there was a significant difference in the debonding pattern between the groups. The modes of fracture were classified as adhesive, cohesive and mixed failure (Fig. 4).

The modes of fracture in group I were almost equally distributed between adhesive and cohesive failures whereas in group II, the failure was mainly cohesive ($p \leq 0.0001$).

Table 4. Frequency and distribution of the adhesive failure for the control adhesive and for the adhesive enriched with copper nanoparticles (Cu NPs)

Type of adhesive failure*	Control adhesive	Adhesive with Cu NPs
Adhesive failure	11	3
Cohesive failure	12	19
Mixed failure	8	9
Total *n*	31	31

* $\chi^2 = 27.66$; df = 4 (χ^2 test; $p \leq 0.0001$).

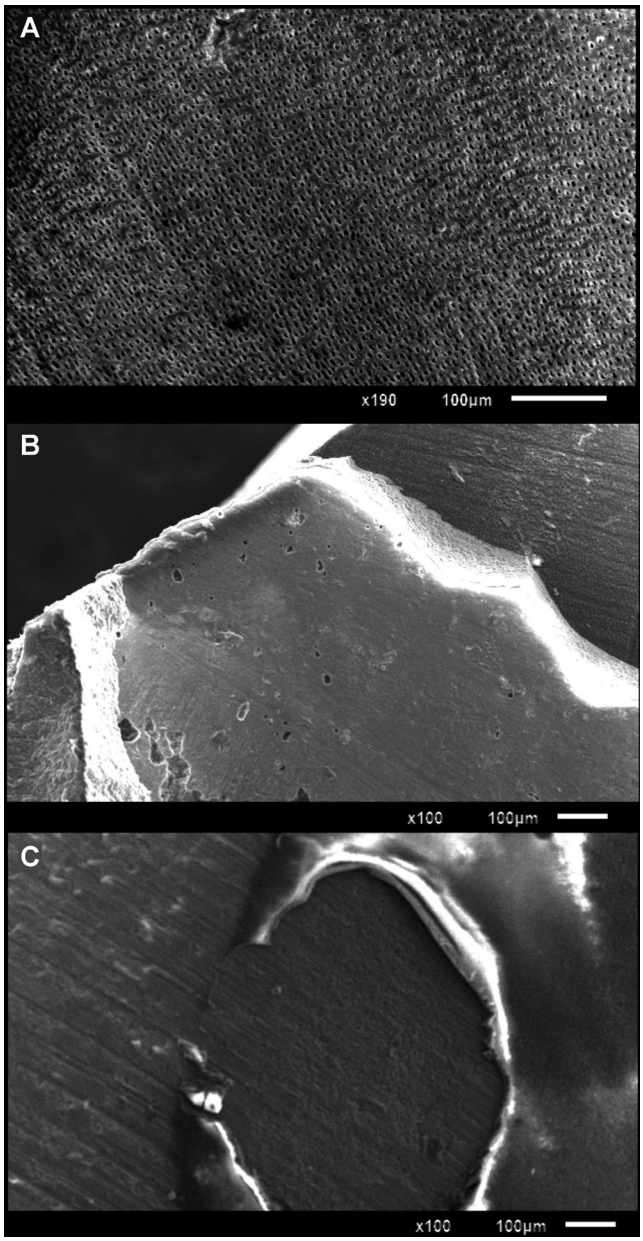

Fig. 4. Representative failure modes from scanning electron microscope (SEM) images

A – adhesive; B – cohesive; C – mixed.

Discussion

In the present study, the experimental adhesive enriched with Cu NPs exhibited an antibacterial effect against the Gram-positive and Gram-negative strains under study. The antibacterial activity of NPs is related to their concentration, size, shape, and surface chemistry as well as environmental factors. Not only it is well-known that the antibacterial activity of NPs is dose-dependent, as a larger concentration of NPs releases more ions, but their maximum efficacy also depends on the other factors. It has been suggested that the ability of NPs to bind with bacteria is determined by their surface size as well as their potential to infiltrate the bacterial wall, causing irreversible cell damage.[14] Smaller NPs possess a larger surface area, making it possible to interact more effectively with bacteria and resulting in more pronounced bactericidal activity. Similarly, it has been confirmed, experimentally, that a lower particle size results in a stronger antimicrobial effect.[22] Such data points to the importance of controlling the size of NPs during synthesis for their successful use.[23,24] Furthermore, the shape of NPs can help to interact with the bacterial wall, triggering direct contact injury.[25] Also, NPs induce oxidative stress to prokaryotic cell walls by producing reactive oxygen species.[15] However, further studies are required in order to determine all the mechanisms involved in the bactericidal effect of NPs. Even with an adhesive with antibacterial activity, a proper adhesion of the composite is necessary for extending the life of the restoration, preventing microfiltration, and therefore preventing the formation of secondary caries in a long term.

The dentin is a tissue that contains water and commonly has a film of odontoblast tubular fluid on the cut surface. In contrast, the resin composite is a hydrophobic material, and therefore is relatively incompatible with the dentin.[26] The dentin surfaces are connected to the pulp through dentinal tubules. One of the concerns about the use of NPs is their potential toxicity. Nevertheless, the dental adhesive penetrates only a few micrometers (about 10 µm) into the dentin, which could prevent damage to the pulp tissue.[27] Since NPs are embedded in the adhesive, they are probably unable to migrate into the pulp tissue. In fact, it would be advisable to use the same precautions to protect the pulp when it is in close proximity to any direct restoration. The cytotoxicity results showed that the control adhesive was moderately cytotoxic (relative cell viability: 36.7 ±0.8%); the adhesive with 0.100 wt% of Cu NPs was also moderately cytotoxic, but cell viability was higher (41.0 ±1.5%), showing a significant difference between these adhesives ($p \leq 0.05$). In the future, the toxic effect in an animal model could be tested to determine the fate of NPs and corroborate our assumption.

The studied adhesive has the following chemical composition: bisphenol A-glycidyl methacrylate (Bis-GMA); 2-hydroxyethyl methacrylate (HEMA); dimethacrylates; polyalkenoic acid; copolymer; initiator; 34% water;

and ethanol. The vehicle used for Cu NPs was isopropanol. Thus, the chosen adhesive system contained HEMA – for its hydrophilicity – and ethanol, which exhibits an affinity for isopropanol. When the dentin is attacked by phosphoric acid, it reacts with the inorganic part of the dentin tissue. The type 1 collagen fibers, which mainly constitute the organic portion of the dentin, become exposed. By placing the adhesive in the tooth cavity, the HEMA molecules in the adhesive interact with glycine amino acid sites, forming an electrostatic-type hydrogen bond between the oxygen of the carboxyl group of glycine and the hydrogen of the hydroxyl group of HEMA.[28] Nanoparticles, due to their total charge, are very unlikely to affect the binding sites for hydrogen bonds.

On the other hand, if the polymerization shrinkage is reduced, there is a greater possibility of forming hydrogen bonds between the collagen fibers and the adhesive. Such shrinkage is due to the arrangement of polymer chains and the evaporation of the solvent during polymerization. The remaining space could be occupied by fillers such as NPs, thus preventing the shrinkage of the polymeric adhesive. This effect is reflected in the increased resistance to debonding.[29] However, further studies should be performed in order to confirm the role of Cu NPs in the polymerization process of this adhesive.

In a previous study on an orthodontic adhesive, it was observed that varying the weight percentage of nanofillers in the adhesive favorably influenced the debonding characteristics. When the amount of nanofillers exceeds a certain weight fraction of the adhesive, the strength of the polymer is reduced.[30] Also, it has been reported that the addition of NPs improves the coefficient of thermal expansion of the polymer, making it more dimensionally stable.[31] In the present study, SBS increased noticeably with the addition of 0.0100 wt% of Cu NPs into the experimental adhesive as compared to the controls.

The main mechanism for the adhesion of the resin composites is the micromechanical retention. Some authors have claimed that the interactions between the adhesive and the dentin molecules play an important role in adhesion,[23,24] but the chemical bond between the hydroxyl or carboxyl groups of the monomer and the hydroxyapatite hydroxyl groups are electrostatic interactions, at best, such as van der Waals forces or hydrogen bonds.[32]

According to the failure modes, the amount of the adhesive remaining in the dentin was higher in the experimental group than in the control group, indicating that adhesion between the dentin and the adhesive increased with the addition of Cu NPs. It is important to note that a SBS value cannot be considered a material property.[33] Therefore, the absolute test values cannot be compared with the data gathered in other studies. Only relative study outcomes, in the sense of "one is better than the other", are a valid basis for further interpretation of the results.[34]

Finally, obtaining the desired properties of nanocomposites requires the homogeneous dispersion of the filler within the polymer matrix. The propensity of NPs to form agglomerates can seriously impact their properties; it depends on the synthesis method and the stability of the particles. In this work, the TEM images show an adequate dispersion of Cu NPs within the adhesive. However, further studies are needed to determine the toxicity in vivo of these NPs in dental restorative applications.

Conclusions

The results of this study suggest that incorporating Cu NPs into an adhesive improves its SBS and provides it with an antibacterial effect, without increasing its inherent cytotoxicity – 2 desirable characteristics for the dental adhesives of composites.

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Surface microhardness of a self-adhesive composite in comparison with conventional composite resins

Mikrotwardość powierzchni samoadhezyjnego materiału kompozytowego w porównaniu z klasycznymi żywicami kompozytowymi

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Background. The surface microhardness of dental composites greatly affects the durability of restorations.

Objectives. The aim of this study was to compare the surface microhardness of a self-adhesive composite with that of other conventional composites. The effect aging has on surface microhardness was also evaluated.

Material and methods. In this in vitro experimental study, the composite resins were poured into molds measuring 3 mm × 3 mm × 6 mm and cured for 40 s. The samples were then immersed in distilled water at 37°C for 24 h. After polishing, the surface microhardness of the samples was measured using the Vickers hardness tester. For this purpose, a 100-gram load was applied to 3 points on the surface of each composite sample for 20 s, and the mean value of surface microhardness was used as the Vickers hardness number. The samples were then subjected to 30,000 thermal cycles at 5–55°C in order to age them; after that, their surface microhardness was measured again. The one-way analysis of variance (ANOVA) was used for the statistical analysis.

Results. The maximum hardness value before and after aging belonged to Filtek® Z250, followed by Premise™ Flow and Vertise™ Flow, with significant differences between them ($p < 0.001$). After aging, the surface microhardness of all composites decreased significantly ($p < 0.001$). The effect of aging on surface microhardness was the same in all groups ($p > 0.05$).

Conclusions. The surface microhardness of composites was significantly different before and after aging. All composites experienced a reduction in their surface microhardness after aging.

Key words: aging, self-adhesive composite, surface microhardness

Słowa kluczowe: starzenie się, samoadhezyjny materiał kompozytowy, mikrotwardość powierzchni

Introduction

Dental composites have grown in popularity due to their optimal esthetics, favorable physical and mechanical properties, easy application, and ability to bond to the tooth structures.[1]

Optimal durability is the main prerequisite for successful composite restorations; it depends on the inherent properties of the material as well as on its surrounding environment. In recent decades, great strides have been made in restoring the function and morphology of the lost tooth structure with the use of composite resins.[2] The preparation of the enamel and the dentin surface is time-consuming and constitutes one of the challenges encountered in restoring the teeth with composites. Thus, researchers have always been in search of methods that would reduce the clinical steps in order to minimize the risk of contamination and the subsequent failure of composite restorations. Such failure may include marginal discoloration, secondary caries and the debonding of the restoration from the tooth structure.[3] Recently, a new type of flowable composites – self-adhesive composites – have been introduced onto the market. The manufacturers claim that self-adhesive composites eliminate the need for a separate bonding step, and thereby reduce the clinical working time and enhance the process of tooth restoration.[4] Vertise™ Flow by Kerr is one of self-adhesive composite resins. The manufacturer claims that it is ideal for small class I and class II restorations, fissure sealant therapy and porcelain repair.[5]

The prognosis and clinical service of restorations depend on the physical, mechanical and biological properties of the material used. Surface microhardness is an important physical property, assessed in order to determine the durability of restorations. The surface microhardness of restorative materials may be diminished due to the continuous contact with saliva and the application of masticatory forces and stresses.[6] Surface microhardness depends on the cohesive strength of the material and on the presence of wear caused to or by the opposing teeth. Hardness refers to the resistance of the material against indentation and is an important criterion with regard to the shape and durability of restorations over time. The higher the filler content and the degree of polymerization of composite resins, the higher their surface hardness is. The smooth, hard surfaces of restorations create esthetic appearance as well as decrease the accumulation of plaque. Worn, abraded surfaces cause plaque to accumulate and increase the risk of caries development around the margins of restorations. Optimal hardness is required to maintain the form and stability of composite restorations against flexural stresses from complex chewing forces in the oral environment.[7]

A clinical setting is often simulated by artificial aging in order to assess the effect of saliva and masticatory forces in vitro, since clinical tests are costly and time-consuming. The mechanical characteristics of dental composite materials, like Vickers hardness, could be influenced by artificial aging. Thermocycling and water storage are among the well-known and accepted techniques for aging.[8] Thermocycling is often done to age dental composite resins. In this technique, samples are subjected to frequent thermal alterations. High temperatures decrease the physical and chemical properties of composite resins. Thermal alterations can reduce the number of unreacted double bonds on the surface of or within the composite resin.[9]

The water absorption of the resin matrix and the hydrolysis of the filler–matrix interface can cause the composite restoration to deteriorate. Leachates from the composite restoration in the oral cavity might disturb the mechanical and physical properties of the polymers. A decrease in the integrity of the resin composite may contribute to its longevity being compromised.

Thus, considering the significance of the surface hardness of composites, the introduction of self-adhesive composites and the gap in information regarding the effect aging has on the surface microhardness of self-adhesive composites, this study was designed to assess the effect of aging on the surface microhardness of a self-adhesive composite in comparison with conventional composites.

Material and methods

This in vitro experimental study evaluated a methacrylate-based microhybrid composite (A2 shade of Filtek® Z250; 3M ESPE, St. Paul, USA), a nanofill composite (A2 shade of Premise™ Flow; Kerr, Bolzano, Italy), and a self-adhesive composite resin (A2 shade of Vertise Flow; Kerr) (n = 14). Table 1 presents the characteristics of the materials used in this study.

The composite resins were poured into plexiglass molds measuring 3 mm × 3 mm × 6 mm. The mold was placed on a glass slab measuring 3 mm × 3 mm × 6 mm and the composite was applied to the mold. Another glass slab was placed over it and a 5-kilogram weight was used to apply pressure from the top for 3 min. This was done to ensure uniform thickness of the samples and to eliminate any voids. The samples were then light-cured from each side for 20 s using an LED light-curing unit (Guilin Woodpecker Medical Instrument Co., Ltd., Guilin, China) with a light intensity of 1,000 mW/cm^2. Light intensity was checked after every 5 samples by using a radiometer (Optilux® 100; Demetron/Kerr, Danbury, USA). After curing, the samples were immersed in distilled water at 37°C for 24 h. The upper surfaces of the samples were polished using 1,000- and 2,000-grit silicon carbide abrasive papers in order to obtain smooth surfaces with no contamination. Polishing was done under gentle water irrigation for 20 s.

Table 1. Characteristics of the materials used in the study

Material	Composition	Manufacturer
Filtek Z250	filler: 0.01–3.5 µm Zr/Si (60% by volume) resin: – Bis-GMA – Bis-EMA – UDMA	3M ESPE, St. Paul, USA
Premise Flow	filler: – 0.4 µm barium glass (75.5% by weight) – 30–50 µm pre-polymerized fillers – 0.02 µm silica nanoparticles resin: – Bis-GMA – Bis-EMA – TEGDMA – light-cure initiators and stabilizers	Kerr, Bolzano, Italy
Vertise Flow	filler: – pre-polymerized fillers containing 0.7 µm Ba – 1 µm barium glass – 10–40 nm nanosized colloidal silica – 40 nm nanosized YbF3 resin: – Bis-GMA – Bis-EMA – BISPAD, – GDMA adhesive monomer, incorporating Kerr OptiBond™ adhesion technology	Kerr, Bolzano, Italy

Bis-GMA – bisphenol A-glycidyl methacrylate; Bis-EMA – ethoxylated bisphenol A-glycidyl methacrylate; UDMA – urethane dimethacrylate; TEGDMA – triethylene glycol dimethacrylate; BISPAD – (1S,2S)-1-phenyl-2-amino-1,3-propanediol bis-silylate; GPDM – glycero-phosphate dimethacrylate.

Vickers hardness test

The Vickers hardness test (in micron scale) was performed on the composite samples using a Vickers hardness tester (MH3 model; Koopa Pazhoohesh, Tehran, Iran). For this purpose, a 200-gram load was applied to 3 points on the surface of the sample for 15 s; the mean value of surface microhardness was calculated and used as the hardness number of the sample.

Aging

The samples were thermocycled to simulate aging – 30,000 cycles at 5–55°C with a dwell time of 20 s and a transfer time of 10 s. Then, they were again subjected to the hardness test.

Statistical analysis

The two-way repeated measurement analysis of variance (ANOVA) with a significance level of 0.05 was performed to compare the microhardness of different composite samples before and after aging by considering their microhardness at different time points as the repeated factor, and aging and the type of composite as between-subject factors. The data was analyzed with PASW Statistics for Windows v. 18 (SPSS, Inc., Chicago, USA).

Scanning electron microscopy

Two additional samples were fabricated in each group for scanning electron microscopy (SEM) assessment. The samples were dried and coated with gold. The surfaces of the samples were inspected under an electron microscope (TESCAN VEGA, Brno, Czech Republic) at ×3,000 magnification and a voltage of 20 kV before and after aging.

Results

Table 2 shows the means (*M*) and standard deviations (*SD*) of the Vickers hardness number for the 3 types of composites before and after aging. Before aging, the highest hardness number belonged to Filtek Z250 (100.09 ±3.32 N/mm^2), followed by Premise Flow (49.10 ±2.26 N/mm^2) and Vertise Flow (43.19 ±1.53 N/mm^2). The differences between the groups in this regard were significant ($p < 0.001$).

The surface microhardness of all composites significantly decreased after aging ($p < 0.001$). The effect of aging on microhardness was the same in all groups and no significant differences were noted between the different composites in the degree to which their surface microhardness was diminished after aging ($p = 0.058$).

After aging, the highest microhardness value was noted in the Filtek Z250 group (85.47 ±5.01 N/mm^2), followed by Premise Flow (38.13 ±1.58 N/mm^2) and Vertise Flow (31.87 ±1.44 N/mm^2). The differences between the groups in this regard were significant ($p < 0.001$).

Figures 1–6 show SEM images for the different types of composite used in this study before and after aging. Also, the mean values with *SD*s of the microhardness of the 3 composites are presented in Fig. 7.

Table 2. Surface microhardness [N/mm^2] of the composites before and after aging ($n = 14$)

Composite	Time point	Minimum value	Maximum value	*M*	*SD*	*p*-value
Filtek Z250	before aging	95.77	106.00	100.09	3.32	0.001^a
	after aging	77.97	95.03	85.47	5.01	0.001^d
Premise Flow	before aging	44.87	54.73	49.10	2.26	0.001^b
	after aging	34.83	40.07	38.13	1.58	0.001^e
Vertise Flow	before aging	40.50	45.23	43.19	1.53	0.001^c
	after aging	29.43	34.40	31.87	1.44	0.001^f

M – mean; *SD* – standard deviation. Different superscript letters show significant differences.

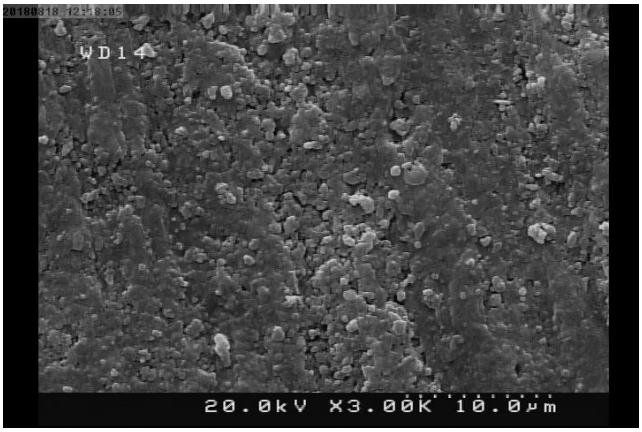

Fig. 1. Filtek Z250 before aging

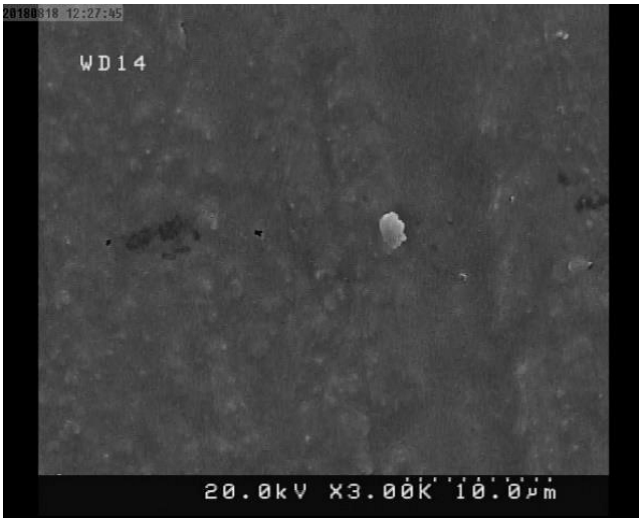

Fig. 2. Filtek Z250 after aging

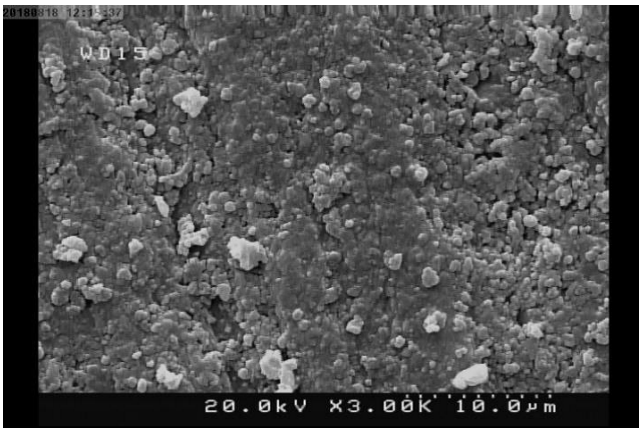

Fig. 3. Premise Flow before aging

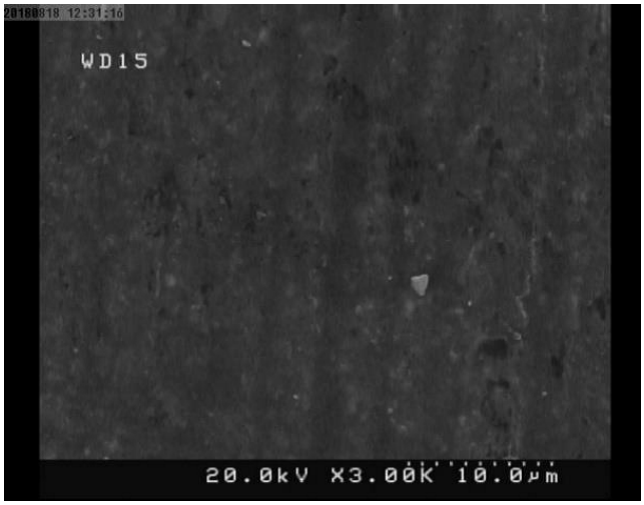

Fig. 4. Premise Flow after aging

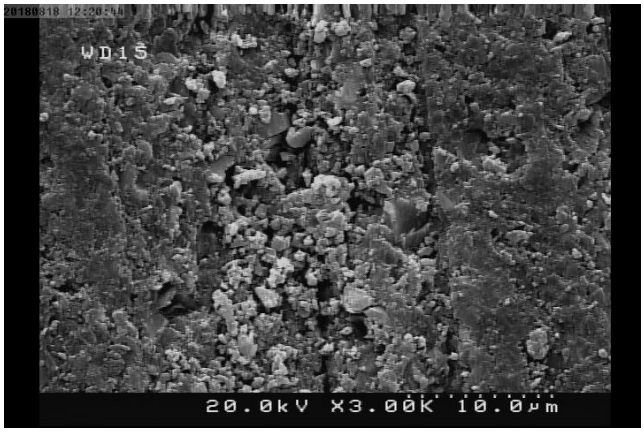

Fig. 5. Vertise Flow before aging

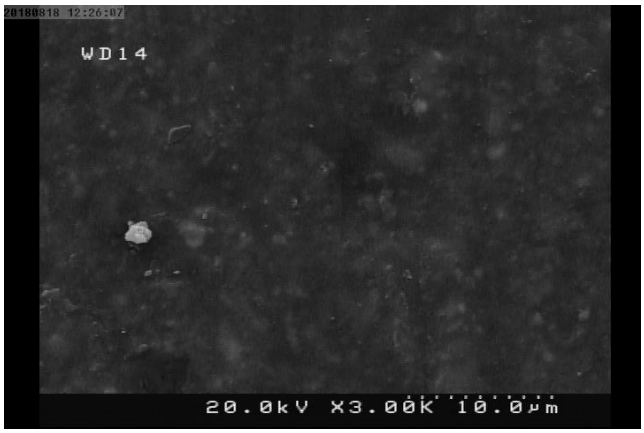

Fig. 6. Vertise Flow after aging

Discussion

There are several laboratory tests which assess the mechanical stability of materials, including the tests of flexural strength, tensile strength, compressive strength, fracture toughness, surface microhardness, and the modulus of elasticity.[10]

The present in vitro study assessed the surface microhardness of a self-adhesive flowable composite, a microhybrid composite and a nanofill composite before and after aging. The knowledge of the mechanical properties of composite resins is imperative in order to understand and predict their clinical behavior and longevity.[11] This study revealed significant differences in the surface

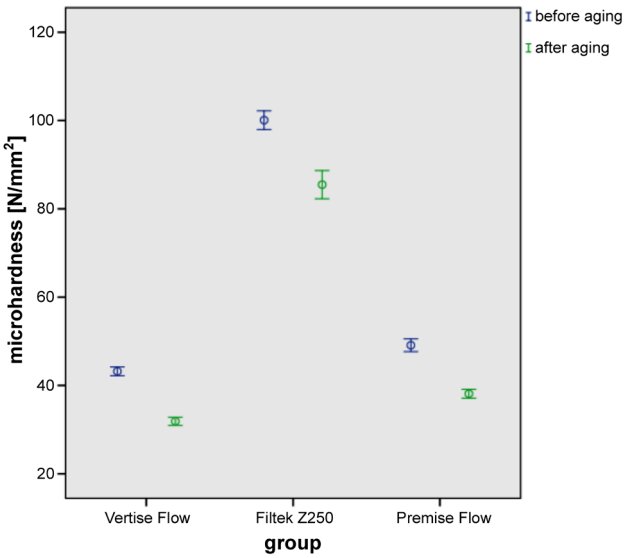

Fig. 7. Mean (*M*) and standard deviation (*SD*) values of microhardness for the 3 composites before and after aging

microhardness of the composites before and after aging. The surface microhardness of all composites was significantly different among them before and after aging. Before aging, Filtek Z250 showed the highest microhardness, followed by Premise Flow and Vertise Flow. The composites were in the same order of microhardness after aging.

The results suggest that surface microhardness highly depends on the type of material and is affected by the quality of the fillers (the percentage of fillers by weight and volume as well as their size, shape and distribution) and of the matrix. Also, it has been reported that the degree of conversion of composites is positively correlated with their surface microhardness.[12]

In this study, Filtek Z250 had the highest volume percentage of the fillers (60%), followed by Premise Flow (60%) and Vertise Flow (44%). According to Scougall-Vilchis et al., surface microhardness depends on the size and volume and weight percentage of the fillers as well as on the chemical composition of the composite resin.[13] As the volume percentage of the fillers increases, the flexural strength, modulus of elasticity and surface microhardness of the composite also increase.[13] However, this statement does not apply to all materials, because Premise Flow showed lower microhardness values than Filtek Z250, although they share an almost equal weight and volume percentage of the fillers.

The type of fillers may be one explanation of the higher microhardness of Filtek Z250, since its fillers mainly include crystalline silica and zirconia, which are harder than the amorphous glasses in the composition of the other 2 composites.[14] Craig suggested that composites with harder filler particles demonstrate a higher surface microhardness as well.[acc.15] Moreover, the composites with pre-polymerized fillers showed significantly lesser microhardness in our study. Blackham et al. reported that composite resins containing pre-polymerized fillers behaved more poorly in the hardness and strength tests than conventional hybrid composites such as Filtek Z250.[16] Pre-polymerized fillers are added to composite resins primarily to minimize their dimensional changes during polymerization and to decrease the amount of unpolymerized resin. However, the addition of pre-polymerized resin may lead to poorer mechanical properties.[17] Moreover, differences in the distribution and size of the fillers can cause differences in the hardness of the composites containing this type of filler.[18]

The composition of the organic matrix is another factor that affects the surface microhardness of composite resins. The organic matrix of Filtek Z250 includes bisphenol A-glycidyl methacrylate (Bis-GMA), ethoxylated bisphenol A-glycidyl methacrylate (Bis-EMA) and urethane dimethacrylate (UDMA). The organic matrix of Vertise Flow, however, contains Bis-GMA, Bis-EMA, (1S,2S)-1-phenyl-2-amino-1,3-propanediol bis-silylate (BISPAD), and glycero-phosphate dimethacrylate (GPDM). Different monomers have different properties. They may vary in their degree of hydrophilicity, degree of conversion or cross-linking during polymerization.[19] Filtek Z250 does not contain the TEGDMA monomer in its composition. It is a low-molecular-weight monomer whereas UDMA and Bis-EMA have higher molecular weights. All of these monomers are added as thinners, along with Bis-GMA. Moreover, Filtek Z250 contains UDMA, which is much more reactive than other monomers.[20] Urethane dimethacrylate has a very flexible structure with weak hydrogen bonds, probably due to the presence of a urethane group in its structure. This explains the higher degree of conversion of this monomer, and the degree of conversion directly affects hardness.[21]

Filtek Z250 may contain higher amounts of photoinitiators than other composite resins, which may be another explanation for its higher Vickers hardness number. Manufacturers do not often disclose the amount of photoinitiators in the composition of composite resins. However, according to David et al., 3 types of photoinitiators – camphorquinone (CQ), tertiary amine, and iodonium salt – are present in the composition of the 3M ESPE composite resins.[22] Iodonium salt may play an important role in increasing the polymerization rate of composite resins.[22]

In the present study, the hardness of all composites significantly worsened after 30,000 thermal cycles, which corresponds to 3 years of clinical service.[23] There is no consensus regarding the effect of thermocycling on the mechanical properties of composite resins, such as surface microhardness. De Moraes et al. found that the modulus of elasticity and hardness of composite resins decreased after 6 months of water storage.[24] Conversely, Yap et al. reported no change in the modulus of elasticity or hardness of the composite resins stored in water for 30 days.[25] Hahnel et al. evaluated the mechanical properties (microhardness and flexural strength) of 5 different

composites after artificial aging (storage in distilled water or artificial saliva, or 2 × 3,000 thermal cycles) and stated that the solution used for the aging process and the frequency of cycles had no significant effect on the hardness or flexural strength of composite resins.[26] Göhring et al. reported that water storage with/without thermocycling decreased the flexural strength of the Bellaglass®, Sinfony® and Targis® composites, irrespective of their filler content or resin matrix composition.[27]

The destructive effects of water storage on the mechanical properties of composite resins occur for 2 reasons. First, water sorption increases the volume of the matrix and degrades its organic components due to the hydrolysis of silane bonds. The other reason is the solubility and release of some composite components into water, especially inactivated monomers.[28] Fan et al. evaluated the mechanical properties of 4 types of composite resins following immersion in 3 different media.[29] They showed that the hardness of composites with the Bis-GMA base, such as Filtek Z250, decreased after storage in distilled water, which is attributed to the potential of their resin matrix to soften in water.[29] Crutis et al. suggested that a reduction in the hardness of nanocomposites in water may be related to the degradation of the resin matrix interface following greater water sorption due to the increased surface/volume ratio of nanofillers.[30]

A reduction in the hardness of the Vertise Flow self-adhesive composite following water aging may be related to the quality of its resin matrix, which has a high potential for water sorption. Vertise Flow contains glycero-phosphate dimethacrylate (GPDM) as its active monomer. This monomer contains an active acidic phosphate group and 2 active methacrylate groups. It has been reported that acidic resin monomers have greater water sorption than neutral resin monomers.[31] Wei et al. concluded that Vertise Flow had greater hygroscopic expansion than UDMA with a polymer base, which is due to the presence of hydrophilic acid phosphate and spacer groups in GPDM.[32]

The filler type may also play a role in the water sorption of composite resins. It has been confirmed that composites containing barium and zinc glass fillers have a higher potential for hydrolytic degradation than those with silica and zirconia fillers. This may be due to the fact that some ions in the composition of these fillers are electropositive and have a greater tendency to react with water, which leads to the leaching of the fillers into water. Subsequently, the hydrogen ions of water penetrate into the spaces filled with barium and zinc and the increased accumulation of hydrogen ions leads to the failure of siloxane bonds and the silica network.[33]

A reduction in the hardness of the composites in this study might depend on the degree of conversion, which is an important factor that affects the hardness and modulus of elasticity of composite resins. The hardness of the resin matrix improves with an increased cross-linking between the polymer chains. In insufficiently polymerized resins, water molecules bond to unreacted monomers, causing a reduction in hardness. Thus, increasing the degree of conversion decreases the effect of water molecules on the mechanical properties of composite resins.[34] The SEM micrographs from this study revealed changes in the composite surface, the separation of the filler particles, and the impaired smoothness as well as the erosion of the resin surface after aging in all 3 composite types, which explains a reduction in surface microhardness. These observations further confirmed the results of the Vickers hardness test.

Although surface microhardness is an influential mechanical property in the clinical service of composite restorations, some other physico-mechanical properties, such as flexural strength, wear resistance, the degree of conversion, and color stability, should also be taken into account when selecting a composite resin for tooth restoration, especially in high-stress-bearing areas.[35]

Conclusions

There were statistically significant differences in the surface microhardness of the composites before and after aging. All composites experienced a reduction in their surface microhardness after aging.

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Comparison of OneShape, 2Shape and One Curve endodontic instruments for debris and irrigant extrusion

Porównanie efektywności usuwania resztek i płynów płuczących z kanałów korzeniowych za pomocą pilników OneShape, 2Shape i One Curve

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Abstract

Background. Better understanding is needed about the debris-and-irrigant-extrusion potential of the instruments used for root canal preparation procedures, manufactured of different heat-treated alloys.

Objectives. The aim of the study was to evaluate the single-file nickel-titanium (NiTi) rotary system OneShape® and compare it with 2 different heat-treated instrumentation systems produced by the same manufacturer – a single-file C-wire system (One Curve®) and a multi-file T-wire system (2Shape®) – in terms of debris and irrigant extrusion.

Material and methods. The mesiobuccal root canals of 51 extracted mandibular molar teeth were selected for the study. The roots were applied to the test apparatus prepared with the Myers and Montgomery method. The roots were divided into 3 groups according to the instrumentation system: OneShape; One Curve; and 2Shape. The root canals were prepared according to the manufacturer's instructions. The analysis of variance (ANOVA) and the post hoc Tukey tests were used to evaluate the significance of the amount of the extruded debris and irrigant ($p < 0.05$).

Results. The One Curve group produced less debris extrusion than the 2Shape group ($p < 0.05$). There were no significant differences between the 2Shape and OneShape ($p = 0.136$), or the One Curve and OneShape groups ($p = 0.159$). The weight of the extruded irrigant was significantly lower for the One Curve group as compared to other systems ($p < 0.05$). The mean weight of the extruded irrigant did not differ significantly for the 2Shape and OneShape groups ($p = 0.976$).

Conclusions. The C-wire One Curve system was associated with less apical irrigant extrusion in comparison with the OneShape and 2Shape systems. The amount of debris extrusion produced by the One Curve system was similar to that produced by the OneShape system and lower than in the case of the 2Shape system.

Key words: endodontics, Nitinol, root canal preparation

Słowa kluczowe: endodoncja, Nitinol, przygotowanie kanału korzeniowego

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Introduction

During root canal preparation procedures, dentine chips, pulpal tissue remnants, irrigation solutions, and microorganisms are often extruded into the periapical region.[1] This extruded material may cause post-operative pain and flare-ups, and impede apical healing.[2,3] The amount of the extruded material depends on the size and kinematics of the files and/or the preparation and irrigation techniques applied.[4]

Several improvements in alloys and instrumentation kinematics have revolutionized root canal instrumentation technology in recent years.[5] However, all instruments and instrumentation techniques have been found to be linked with some amount of material extrusion to the periapical area.[6,7] Rotary instruments have proven to be associated with a minimized amount of debris extrusion as compared to hand files.[4] Owing to the development of single-file systems, the multi-step rotary instrumentation system has been simplified to a single step. OneShape® (Micro-Mega SA, Besançon, France) is a single-file nickel-titanium (NiTi) system (tip size 25/.06 taper) that has 3 different cross-sectional designs along the cutting part of the file.[8] Another single-file system manufactured by Micro-Mega is the One Curve® system (25/.06). This instrument is produced from heat-treated NiTi called C-wire, a shape-memory alloy that facilitates root canal preparation with its pre-bending ability.[9] The One Curve system provides better centering and cutting abilities due to its variable cross-sectional file design[10] whereas the 2Shape system (Micro-Mega SA) is manufactured with T-wire technology, which provides better cyclic fatigue resistance.[11] This system contains 2 files – TS1 (25/.04) and TS2 (25/.06). The instruments have an asymmetrical cross-sectional design, comprising a triple helix with 2 main cutting edges and 1 secondary cutting edge for successful debris removal and improved cutting ability.[12]

The OneShape, One Curve and 2Shape systems work in a continuous rotary motion. Previous studies showed that the push-pull instrumentation techniques tended to produce more apical debris extrusion than rotary systems.[7,13] To date, several studies have examined various rotary systems,[8,14] or compared the OneShape[15–18] and 2Shape files[19] with other file systems with regard to debris extrusion. However, there are no studies in the available literature evaluating the effects of the systems produced with heat-treating technology on debris and irrigant extrusion. Therefore, the purpose of this study was to compare the OneShape, One Curve and 2Shape systems in terms of debris and irrigant extrusion. The null hypothesis was that there would be no difference among the amount of the extruded debris and irrigant produced with these systems.

Material and methods

Ethical approval was obtained from the Ethics Committee of Ankara Yıldırım Beyazıt University in Turkey (No. 2019-237). We examined 51 extruded mandibular molar teeth radiographically and visually to confirm the absence of decay, resorption, calcification, open apices, fractures, or cracks. The curvature angle of the mesiobuccal root canals was calculated with Schneider's method, through the digital radiographic images taken from the buccolingual and mesiodistal directions.[20] Root canals having a curvature of up to 5° were selected for the study. The mesiobuccal roots of the teeth were divided from their crowns at the cementoenamel junction with a high-speed diamond saw under water cooling to set the root length at 16 mm. A size 10 K-file was moved into the root canal until it could be seen at the apical foramen; the working length was determined to be 1 mm shorter than the root length, i.e., 15 mm. After the working length was achieved with a size 15 K-file, the root canals were randomly allocated into 3 groups: OneShape; One Curve; or 2Shape.

Test apparatus

The Myers and Montgomery method was used for the test apparatus.[21] The rubber plugs of glass vials were drilled and the teeth were fixed to those holes with cyanoacrylate. Previously weighed 2-milliliter Eppendorf tubes were inserted into the glass vials. The roots fixed to the plugs were placed in the Eppendorf tubes to save apically extruded material, and two 21-gauge needles were stuck into the rubber plugs to equalize the outside and inside pressure. The Eppendorf tubes were weighed 3 times before being placed in the vials, and the mean weight was determined as the pre-weight. The Eppendorf tubes were weighed on a 10^{-4}-gram precision balance.

Experimental groups

The OneShape group (n = 17): The root canals were prepared with the OneShape file (25/.06) in a continuous rotary motion at a speed of 400 rpm and a torque of 4 N/cm; the root canals were irrigated with 2 mL of distilled water after the preparation procedure.

The One Curve group (n = 17): The root canals were prepared with the One Curve file (25/.06) in a continuous rotary motion at a speed of 300 rpm and a torque of 2.5 N/cm; the root canals were irrigated with 2 mL of distilled water after the preparation procedure.

The 2Shape Group (n = 17): The root canals were prepared with the TS1 (25/.04) and TS2 (25/.06) files in a continuous rotary motion at a speed of 300 rpm and a torque of 2.5 N/cm; a total of 2 mL distilled water – 1 mL at the instrument change and 1 mL after the preparation procedure – was used for the irrigation procedure.

All the instruments were used with an electric torque-controlled motor (EndoTouch® TC2; SybronEndo, Glendora, USA) in a progressive brushing movement in 3 waves (up-and-down movements) until the apical foramen was reached, according to the manufacturer's instructions. Each file was used to prepare 1 root canal. After the apical foramen was reached, a size 15 K-file was inserted 1 mm beyond the apical foramen to maintain apical patency before distilled water irrigation. A total of 2 mL of distilled water was used for each root canal. A 27-gauge open-ended irrigation needle was inserted to a maximum depth of 1 mm shorter than the working length and was used with an in-and-out motion for the irrigation procedure.

Evaluation of debris and irrigant extrusion

After root canal preparation, each Eppendorf tube was removed and immediately weighed 3 times. The mean of these values was taken as final weight-1. All the tubes were incubated at 68°C for 5 days to evaporate the extruded irrigant. The tubes were again weighed 3 times and the mean of these measurements was registered as final weight-2. Final weight-2 was subtracted from final weight-1 and recorded as the weight of the extruded irrigant. The pre-weight of the tube was subtracted from final weight-2 and recorded as the weight of the extruded debris.

Statistical analysis

The statistical analysis was performed using the IBM SPSS Statistics for Windows software v. 21.0 (IBM Corp., Armonk, USA). Statistical significance was defined at $p < 0.05$. The data was examined for the normality of distribution using the Shapiro–Wilk test. The data revealed a normal distribution for the groups. The analysis of variance (ANOVA) and the post hoc Tukey tests were used to evaluate the significance of the amount of the extruded debris and irrigant.

Results

Table 1 presents the mean (*M*) and standard deviation (*SD*) values of debris and irrigant weights for each group. The results showed that there were significant differences between the groups in terms of the extruded debris ($p = 0.002$) and irrigant weights ($p = 0.007$). The One Curve group produced less debris extrusion as compared to the 2Shape group ($p = 0.001$), but there was no significant difference between the 2Shape and OneShape ($p = 0.136$), or the One Curve and OneShape groups ($p = 0.159$). As far as irrigant extrusion is concerned, the One Curve group produced a lower irrigant extrusion weight as compared to the 2Shape ($p = 0.022$) or OneShape groups ($p = 0.013$). The mean weight of the extruded irrigant did not differ significantly for the 2Shape and OneShape groups ($p = 0.976$).

Discussion

This study compared the apically extruded debris and irrigant produced with the OneShape, One Curve and 2Shape instrumentation systems. All the instrumentation systems were operated in a continuous rotation motion. The OneShape and One Curve systems are single-file systems whereas the 2Shape system is a multi-file system. The amount of the extruded debris produced with One Curve was lower than the amount produced with 2Shape, but similar to the amount produced with OneShape. The weight of the extruded irrrigant was lower for the One Curve group as compared to other systems. Thus, the null hypothesis of the study was rejected.

All the file systems used in the study created some amount of debris and irrigant. The systems were operated with rotational movements, which tend to move tissue remnants toward the root canal orifice.[22] All the systems used in the study provided similar final apical sizes and tapers in the root canals. Variability in the amount of the extruded material produced by the 3 systems could be related to differences in the file design and alloy materials. The OneShape system is produced from NiTi whereas the other 2 systems are manufactured from different heat-treated NiTi alloys. The cutting part of the OneShape file has 3 different cross-sectional designs.[23] In the apical part, 3 cutting edges are present whereas the middle part has either 2 or 3 cutting edges. In the coronal third, there are 2 S-shaped cutting edges. The One Curve system files are produced with C-wire technology, which provides shape memory. Its alloy is obtained through electropolishing and heat-treatment procedures.

Table 1. Weights of the extruded debris and irrigant for each group

Group	Debris [g]			Irrigant [g]		
	M ±*SD*	*F*-value	*p*-value	*M* ±*SD*	*F*-value	*p*-value
OneShape	0.00058 ±0.00020^{a,b}	7.300	0.002*	1.19014 ±0.40538^{a}	5.502	0.007*
One Curve	0.00044 ±0.00013^{a}			0.84802 ±0.26694^{b}		
2Shape	0.00072 ±0.00028^{b}			1.16596 ±0.31980^{a}		

M – mean; *SD* – standard deviation; * statistical significance (ANOVA; normally distributed data). Different lower-case letters indicate significant differences between the groups in either debris or irrigant weights ($p < 0.05$).

The 4-millimeter apical part of the One Curve file has a triple-helix cross-sectional design and the rest of the file is designed with an S-shaped cross-section with 2 blades.[24] The 2Shape system consists of 2 files manufactured with T-wire technology. A triple-helix cross-sectional design beyond the shaft of the 2Shape file allows better adaptation to the root canal walls.[25]

The triple-helix cross-sectional design of the 2Shape file underlies the entire cutting part of the file, while only the apical part of the One Curve file has this design. This difference may bring the 2Shape system into a tighter contact with the root canals, thus improving the shaping ability.[25] However, a tight contact may also block the produced debris from being removed through the root canal opening. More instrument usage was associated with more debris production.[26] The 2Shape system is the only multi-file system we tested and its mean debris extrusion value was the highest among the groups. The amount of debris extrusion for the OneShape and One Curve groups was similar. The configuration of the One Curve system was developed as a modified form of the OneShape system.[24] Their design similarity may affect the removal of debris in a similar direction.

A total of 2 mL distilled water was used for the irrigation procedure in all 3 groups. In the OneShape and One Curve groups, irrigation was performed at the end of the preparation procedure, since these 2 systems are single-file systems. The 2Shape system consists of 2 files, so the irrigation procedure was applied in 2 stages, with 1 mL of distilled water for each stage. The One Curve system produced a lower amount of irrigant extrusion as compared to the OneShape and 2Shape systems.

Sodium hypochlorite (NaOCl) is a widely accepted irrigation solution due to its excellent antimicrobial activity. However, in this study, distilled water was used as the irrigation solution, although it is not generally preferred as the main irrigant. Sodium hypochlorite has been reported to increase the weight of the extruded debris by producing particulate precipitates, thus compromising the reliability of measurements.[27]

A commonly applied experimental model, which was described by Myers and Montgomery, was used for saving the debris and irrigant collection.[21] This system does not simulate clinical conditions, since it does not mimic periradicular tissues. Other recommended models, such as floral foam or agarose gel models, are reported to provide resistance around the apical foremen and to mimic periapical back pressure.[28,29] Moreover, these systems give the total value of debris and irrigant weights, and the wide surface area of floral foam lets the irrigant evaporate immediately and may lead to incorrect results. The Myers and Montgomery method, on the other hand, offers the opportunity to individually evaluate debris and irrigant weights.

The OneShape system is produced from the NiTi alloy, which provides the file with superelasticity, shape memory and ease in canal preparation.[30] Various kinds of thermomechanical treatment of NiTi developed the structure and transformation performance of file systems.[31,32] The OneShape, One Curve and 2Shape systems are produced by the same manufacturer with different designs and heat-treated alloys. The One Curve system, produced with C-wire technology, was introduced most recently, and this system provided lower debris and irrigant extrusion than the other ones.

Conclusions

The One Curve system exhibited lower amounts of debris and irrigant in comparison with the 2Shape system. The debris extrusion produced by the OneShape and 2Shape systems was similar.

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Effect of artificial saliva on the mechanical properties of a polymer material reinforced with fiber, used in esthetic tooth restorations

Wpływ sztucznej śliny na właściwości mechaniczne materiału polimerowego wzmocnionego włóknem, stosowanego w estetycznych rekonstrukcjach zębów

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Abstract

Background. The oral environment can negatively affect the physical properties of fiber-reinforced composite (FRC) materials, which can lead to the deterioration of mechanical stability and reduce the span of their clinical usefulness.

Objectives. The aim of this study was to determine the influence of artificial saliva on the selected mechanical properties of FRC.

Material and methods. The core of the polymer material selected for the study was a bundle of ultra-high-molecular-weight polyethylene (UHMWPE) fibers. Fourteen samples were stored in an incubator at 37°C, in 20 mL of artificial saliva solution, and weighed on days 1 and 28. At the same time, mechanical tests were performed, including the measurements of Young's modulus, tensile stress, maximum tensile force, and tensile deformation.

Results. The analysis of basic statistics together with the results of the Shapiro–Wilk test and the distribution of Spearman's *rho* coefficient showed a strong negative relationship between the pair of variables – tensile deformation and the sorption of synthetic saliva. The results related to Young's modulus of elasticity and tensile stress were not statistically significant.

Conclusions. Water penetration into the space between the fibers does not adversely affect the mechanical properties of the material tested. In the static tensile test, high and desired mechanical strength was observed, which may justify the effective use of this type of material in clinical practice and may be a good alternative to prosthetic restorations, whose retention is obtained only through a mechanical connection with the abutment tooth.

Key words: absorption, artificial saliva, mechanical stresses, composite materials

Słowa kluczowe: absorpcja, sztuczna ślina, naprężenia mechaniczne, materiały kompozytowe

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Introduction

High strength and low weight make fiber-reinforced composite (FRC) materials an effective alternative to other prosthetic solutions. A fiber-reinforced composite is a material made of fibers (the reinforcing phase) and a resin polymer matrix (the organic phase). The polymer matrix constitutes a structural basis for the reinforcing fibers, protects them against occlusal trauma and transfers external tension to them. Moreover, the polymer resin combines with the luting cement and gives the material a desired shape. Introducing fibers of a high elastic modulus into a soft matrix improves the strength and stiffness of the material, ensuring excellent mechanical properties of the composite in selective directions. Long-term loading thereof has become possible in situations in which so far the application of conventional fixed dentures has only been recommended.[1]

Ultra-high-molecular-weight polyethylene (UHMWPE) fibers, which reinforce the material, are characterized by an extremely high strength-to-weight ratio and great abrasion resistance.[2] The lack of active chemical groups in UHMWPE (ester, amide or hydroxyl ones) results in its resistance to the activity of water, most chemical substances, UV radiation, and microorganisms. Under loading, this polymer undergoes elongation, constant in time as long as the applied force works. Ultra-high-molecular-weight polyethylene fibers are non-polar, characterized by low surface energy values; nevertheless, their inertness makes the adhesion of UHMWPE to the polymer matrix hard to achieve.[3,4] In order to improve the strength of the bond between the fibers and the organic matrix, the surfaces of the fibers are modified.[5] All ways of activating UHMWPE lead to surface oxidation by increasing the number of the polar functional groups. The oxidation reaction changes energy and surface affinity; what undergoes change as well is the strength of the bond with some hydrophilic polymer systems, in contrast to unmodified fibers, and wettability in relation to non-activated polymers, which may lead to the progressive damage of the material, consisting in a loss of the cohesion of the fibers and the organic matrix, resulting from the changeable straining forces affecting them.[6]

The organic matrix of FRC may undergo hydrolysis and absorb water to various degrees, depending on its chemical composition. The water molecules diffusing into the spaces between the polymer chains may cause changes in the material dimensions. Such loosening of the spatial polymer network often translates into changes in the composite parameters, including its mechanical strength. The FRC organic matrix absorbs water by diffusion. Water molecules penetrate into the free spaces created between the chains of the polymer macromolecules, which results in loosening the polymer network. Changes in the volume and dimensions of the organic matrix are usually slight and can be reversible. However, the exploitation of the material in the humid and changeable oral environment may cause irreversible changes in the physical and chemical parameters of the composite material.[4,7]

The process of the modification of the fiber surfaces in an environment of increased humidity may contribute to the deterioration of physical parameters, such as tensile strength and the longitudinal modulus of elasticity. Such changes in the properties of FRC materials may seriously weaken stability in the changeable and difficult oral environment. Moreover, they may lead to the shortening of the clinical life span and limit the possibility of applying the materials in medical and dental practice.

Therefore, it seems justified to conduct research on water sorption and to determine its influence on changes in the selected strength characteristics of a polymer FRC material used in dentistry to build prosthetic restorations.

Material and methods

A ready-to-use FRC product (ARKONA LFS, Nasutów, Poland), Lot 2018-08-01, was used for the study. The core of the FRC is a bundle of polyethylene fibers of ultra-high molecular weight, 60 mm in length, made up of approx. 1,000 single filaments, each 5–10 μm in diameter, whose surfaces were physically activated, and then impregnated with a mixture of methacrylate resins of low viscosity and low molecular weight. The polyethylene filaments, constituting about 30% of the volume of the product, are embedded in a microhybrid composite of increased mechanical resistance. The layers of the composite above and under the bundle of UHMWPE filaments are about 0.3-millimeter thick. The chemical composition of the composite material used in the study is shown in Table 1. The modification of the UHMWPE bundle by means of the resin impregnation preceded by the physical activation of the surfaces of the filaments was aimed at ensuring adhesion between the fibers and the composite material, resulting in the improvement of the mechanical parameters and the performance of the FRC produced in this way.

Prior to the tests, all samples were conditioned in 20 mL of artificial saliva, which had been obtained by dissolving chemical compounds in 1 dm^3 of distilled water in the following quantities: NaCl (0.4 g), KCl (0.4 g), NaOH (0.05 g), $CaCl_2 \cdot 2H_20$ (0.22 g), NaH_2PO_4 (0.12 g), and urea (1 g), at a temperature of 37°C, for 24 h.

Table 1. Chemical composition of the composite material used in the study

Type of the material	Organic matrix	Filler	Manufacturer
Microhybrid composite	dimethacrylates: Bis-GMA, UDMA, TEGDMA	Ba-Al-F-silicate glass, pyrogenic silica powder	ARKONA LFS, Nasutów, Poland

Bis-GMA – bisphenol A-glycidyl methacrylate; UDMA – urethane dimethacrylate; TEGDMA – triethylene glycol dimethacrylate.

Mechanical studies

The mechanical properties of the material were determined during the static tensile test with the use of the Instron 5969 machine (Instron, Norwood, USA). In the study, 14 samples of the tested material were used; 2 extreme results were rejected. The sample, which was 2.33 ±0.12 mm wide and 0.856 ±0.064 mm thick, and whose measuring length was 50 mm, was elongated along its longitudinal axis at a constant clamp movement speed of 1 mm/min. The test was continued until a 20% decrease in the material strength was accomplished. The tests were performed on the 1st and the 28th day of the experiment. The following parameters were measured:

– the longitudinal modulus of elasticity (Young's modulus) – a property that measures the elasticity of a material when stretched, expressing the relationship between relative linear deformation and the strain which occurs for elastic deformations, individual for a given material; the value thereof was calculated from the following equation:

$$E_t = \frac{\sigma_2 - \sigma_1}{\varepsilon_2 - \varepsilon_1} \quad [\text{MPa}] \tag{1}$$

where:
E_t – modulus of elasticity under strain [MPa],
σ_1 – strain measured at the deformation value ε_1 = 0.0005 (0.05%) [MPa],
σ_2 – strain measured at the deformation value ε_2 = 0.0020 (0.20%) [MPa];

– tensile stress, which is the tensile force affecting the initial cross-section surface unit, applied to the measuring length; its value was calculated from the following equation:

$$\sigma = \frac{F}{A} \quad [\text{MPa}] \tag{2}$$

where:
σ – given stress value [MPa],
F – corresponding force [N],
A – initial moulding cross-section area [mm^2];

– maximum tensile force F_{max}, recorded by the measuring device at the moment when the sample is broken;
– deformation under tension (displacement), i.e., the linear elongation of the sample during the measurement, whose value was calculated from the following formula:

$$\varepsilon_t = \frac{L_t}{L} \tag{3}$$

where:
ε_t – nominal deformation, expressed in a dimensionless quantity,
L_t – increase in the distance between the clamps since the beginning of the test [mm],
L – distance between the clamps [mm].

Water sorption

Seven samples with dimensions of 15 mm × 2.5 mm × 1.4 mm were prepared. Each of the samples was stored in an incubator for 28 days, at a temperature of 37°C, in 20 mL of artificial saliva. The samples were weighed on the 1st and the 28th day of the experiment with an electronic balance accurate to 0.0001 g. The obtained results were marked W_1 and W_{28}, respectively. Each time before the measurement was made, the samples were dried with tissue paper until no traces of moisture were visible on their surfaces.

Results

In order to investigate the relationship between the variables taken into consideration in the study, statistical analyses were conducted with the use of the TIBCO Statistica® v. 13.3 software (TIBCO Software, Inc., Palto Alto, USA). The analysis of basic descriptive statistics together with the Shapiro–Wilk test as well as the analysis of the Pearson correlation coefficient, Spearman's *rho*, and the trend line adjustment analysis were carried out. The significance level was established at the classic threshold α = 0.05.

Basic descriptive statistics of the material properties

At the beginning, the basic descriptive statistics of the quantitative variables under study were calculated, along with performing the Shapiro-Wilk test, examining the normality of the distribution of these variables. This test showed that the distribution of the maximum tensile force value F_{max} did not differ significantly from the normal one. A different situation was observed for the other quantitative variables included in the study. Therefore, the skewness values were analyzed and were found to range from –2 to +2 for sorption ω, so it might be assumed that the distribution was similar to the normal one.[8] The distributions of the remaining variables examined in the study, i.e., Young's modulus E_t, tensile stress σ and tensile deformation ε_t, were significantly asymmetrical in relation to the average. That is why the correlations between sorption and the enumerated variables were subjected to non-parametric tests. In the case of the correlation between sorption and maximum tensile force, parametric tests were applied, having met the other assumptions. The results are presented in Table 2.

Table 2. Basic statistics of the parameters tested for the examined material

Variable	*M*	*Me*	*SD*	Skewness	Kurtosis	Lowest value of the distribution	Highest value of the distribution	Result of the Shapiro–Wilk test	*p*-value
E_t [MPa]	9,781.25	5,074.44	10,349.31	2.45	7.16	2,093.77	42,338.38	0.699	<0.001*
σ [MPa]	127.14	85.08	139.02	3.35	12.03	46.84	608.17	0.538	<0.001*
F_{max} [N]	74.99	70.45	38.61	0.73	–0.75	32.39	145.97	0.894	0.076
ε_t	0.03	0.02	0.02	2.73	9.00	0.01	0.09	0.695	<0.001*
ω [µg/mm^3]	56.63	51.43	82.15	–0.98	3.90	–167.62	200.00	0.862	0.025*

E_t – Young's modulus of elasticity; σ – tensile stress; F_{max} – maximum tensile force; ε_t – tensile deformation; ω – sorption; *M* – mean; *Me* – median; *SD* – standard deviation; * statistical significance.

Relationship between the value of maximum tensile force and sorption

Initially, the hypothesis stating that there was a relationship between the value of maximum tensile force and sorption was verified. In order to do that, the analysis of the Pearson correlation coefficient was conducted by comparing the value of maximum tensile force with the sorption value, calculated from the following formula:

$$\omega = \frac{W_{28} - W_1}{V} \text{ [µg/mm}^3\text{]} \quad (4)$$

where:
ω – sorption [µg/mm^3];
W_1 – weight of the sample on day 1 [µg];
W_{28} – weight of the sample on day 28 [µg];
V – volume [mm^3].

A statistically insignificant result was obtained. Then, it should be acknowledged that there was no relationship between the investigated variables. The relationship between maximum tensile strength and sorption is presented in Table 3.

Table 3. Relationship between maximum tensile strength and sorption

Statistics	F_{max} [N]	ω [µg/mm^3]
Pearson's correlation coefficient	–0.322	
p-value	0.241	

Relationship between sorption, the value of Young's modulus, tensile stress, and tensile deformation for the tested material

Next, it was checked whether or not there was a relationship between the value of Young's modulus, tensile stress and tensile deformation for the tested material and sorption. In order to determine whether there is a relationship between the examined variables and sorption, the correlation analysis was conducted, similarly to the previous stage. However, as the distributions of the aforementioned variables were significantly asymmetrical in relation to the average, nonparametric tests were carried out, i.e., the analysis of Spearman's rank correlation coefficient. A statistically significant result was obtained for the following pair of variables – tensile deformation and sorption, which meant that there was a statistically significant, strong negative relationship between the investigated variables. It should, then, be understood that the greater the sorption, the lower the tensile deformation values would be. The trend line adjustment analysis showed that the relationship between the 2 variables could be expressed by the following formula:

$$\varepsilon_t = \omega \times -4.1523 \times 10^{-5} + 0.0289$$

In the case of the other variables, statistically significant results were not obtained. Then, it should be assumed that the sorption value did not affect the values of the other variables – Young's modulus and tensile stress. The results are presented in Table 4 and Fig. 1.

Table 4. Relationship between Young's modulus, tensile stress and tensile deformation for the tested material and sorption

Statistics	E_t [MPa]	ω [µg/mm^3]	σ [MPa]	ω [µg/mm^3]	ε_t	ω [µg/mm^3]
Spearman's *rho* correlation	0.261		0.075		–0.539	
p-value	0.348		0.791		0.038*	

* statistical significance.

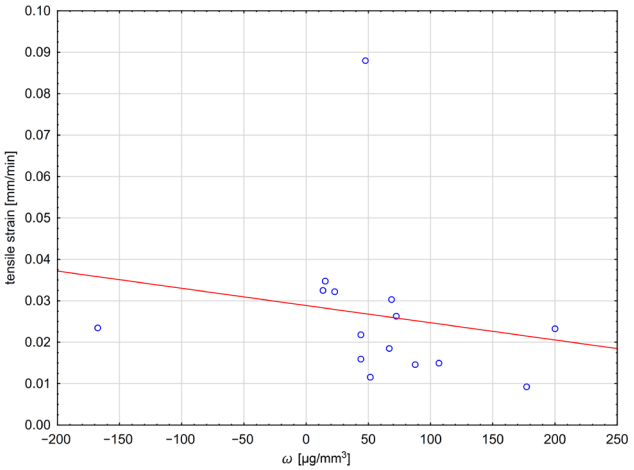

Fig. 1. Effect of sorption on the tensile strain of the selected material

Discussion

Fiber-reinforced composites are a group of prosthetic materials, which is increasingly treated as an alternative to traditional ceramic or metal restoration materials in dentistry. In the course of treatment with the use of a minimally invasive preparation technique, it has become possible to make lightweight prosthetic restorations, resembling natural dentition and, at the same time, ensuring desired strength and biocompatibility, cemented adhesively, not only mechanically. Lehmann et al.[9] as well as Behr et al.[10] admit that the incorporation of fibers in an organic matrix enhances the fracture resistance of the composite materials, and static tests have confirmed an increase in their tensile strength.[11] Some authors have shown that the location and orientation of the fibers in the material also affect its mechanical properties,[12] and the clinical effectiveness of such materials has been amply confirmed in the literature as well.[13,14]

Stress and the modulus of elasticity are parameters determining static mechanical properties. When external forces, generated, for example, during chewing, are transferred to a tooth or a dental restoration, i.e., there are stress conditions, energy is stored in the structure of the material. Due to the stress emerging within its structure, the material changes its shape or dimensions.[15]

The values of Young's modulus of elasticity and tensile stress obtained in the fiber unidirectional tensile test are presented in Table 2. On their basis, it may be stated that the material under study satisfies the requirements for polymer materials applied in dentistry to restore and make prosthetic crowns and bridges which are permanently attached to the pillar tooth, without the need for mechanical retention. In mechanical tests, tensile strength should be at least 50 MPa whereas the strength of the connection with the experimental tooth should not be less than 5 MPa.[6,16] The tested material is elastic and, at the same time, resistant to breaking.

Many factors influence the mechanical properties of FRC. These are the strength parameters of both the fibers and the polymer matrix in which they are embedded, the extent to which the fibers are integrated with the organic resin as well as their number, length, diameter, and spatial orientation in the material. On the basis of the images obtained with the use of a scanning electron microscope (SEM) and an optical microscope, it was concluded that the fibers were evenly embedded in the organic matrix. The attempt at breaking the material after having frozen it with liquid nitrogen, undertaken in order to make the composite fracture visible, was successful despite high strength parameters (Fig. 2).

Obtaining a fiber with an unusually ordered chain, as a result of forcing and elongating polyethylene of a molecular weight equal to approx. 300,000 Da, has been great technological progress. The polymer building the structure of a polyethylene fiber makes parallel chains

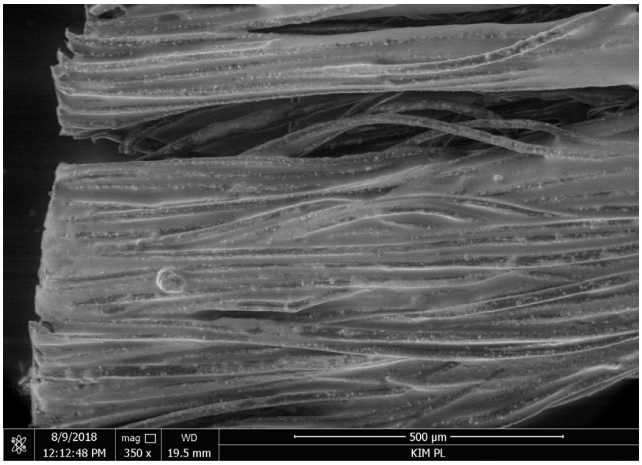

Fig. 2. Bundle of parallel fibers embedded in the composite
Magnification ×350.

of an orientation degree >95% and crystallinity >85%, which distinguishes it from para-aramid fibers, whose strength results mainly from a large number of intermolecular hydrogen bonds. Polymers containing aromatic groups have strong affinity for aromatic solvents whereas aliphatic UHMWPE is resistant to their activity.[5]

The process of the modification of the UHMWPE surface is aimed at improving the integration of the fibers with the organic matrix. It causes changes in the molecular structure of the fibers. At the initial stage, the phenomena also happen at the boundary of the individual phases, leading to an improvement in the material properties, in particular mechanical strength, which has been confirmed in the conducted studies. This happens through the additional cross-linking of the structure. In a longer time period, however, the depolymerization, destruction and decomposition of the polymer material to a monomer can be observed, so the material is degraded. Further research is, therefore, recommended in order to confirm a possible decrease in the mechanical properties with time.[17] Scanning electron microscopy confirms the high efficiency of the connection of the composite with the filaments in the tested samples (Fig. 3).

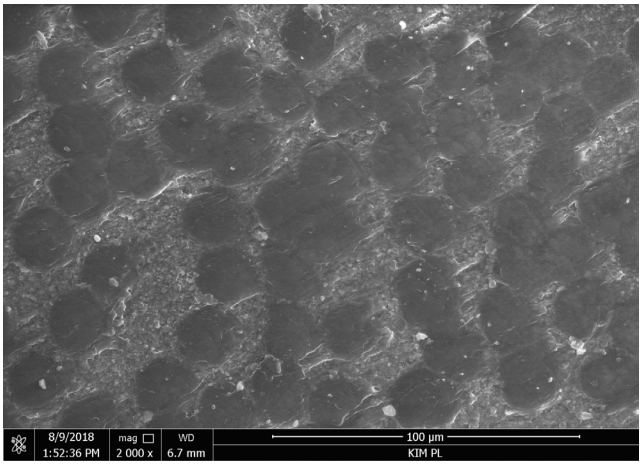

Fig. 3. Cross-section of a UHMWPE filament sealed with the composite material
Magnification ×2,000.

Water is absorbed into the organic matrix by diffusion. The bidirectional migration of water molecules and residual monomers – the unreacted products of the polymerization reaction – loosely connected with the matrix, is caused by the kinetic energy of the individual molecules and continues until the dynamic balance of the system is achieved. The weight of FRC remains constant then and, basically, does not undergo further changes.[18]

In the study, the phenomenon of water absorption took place in equal time periods, and the process was not statistically significant in all the analyzed time intervals. In the course of the experiment, the changes corresponded to the state of intermolecular forces, canceling each other out, not causing the mutual exchange of weight. The quantity of the absorbed water rose proportionally to the growth of the polymer volume of the organic matrix, and decreased together with an increase in the number of the reinforcing fibers embedded in it. The quantity of the water absorbed by FRC should, then, be smaller in comparison with resins, in which the fillers are not continuous fibers, but inorganic glass particles, silica, etc., of different geometry.[19] Storing a fiberglass-reinforced organic resin in artificial saliva for 180 weeks caused the strength of the material to deteriorate by 27%.[20]

A less effective connection between the reinforcing fibers and the organic matrix may lead to empty spaces, fractures and other defects in the structure of the material. Presumably, this phenomenon facilitates water penetration, which damages the links in the three-dimensional (3D) polymer grid, thus destabilizing the material.[21] According to Miettinen et al., an incoherent and non-homogeneous polymer bond with the fibers reinforcing the matrix in the structure of the material may result in empty spaces in the 3D spatial arrangement.[19] The images obtained by Behr et al. with the use of SEM confirmed that the damage to and the physical flaws of the material caused by water molecules led to the deterioration of its mechanical properties.[10] The study by Chai et al. showed that an improvement in the sorption properties might be achieved by prolonging the time of the irradiation of the material; a higher conversion level and a better density of the organic matrix cross-linking were then obtained.[22]

In the study, the phenomenon of water absorption took place in equal time periods, yet the process was not statistically significant. The examined material satisfied the assumptions of the following norm: ISO 10477:2018 Dentistry – Polymer-based crown and veneering materials, which states that water absorption should not exceed 40 μg/mm^3 within 1 month of the experiment.[23] The good sorption properties of the FRC material (low water sorption), in which the fibers are arranged unidirectionally in the form of a longitudinally oriented bundle, may prove the good preparation of the polyethylene fibers and the effective connection thereof with the dimethacrylate grid.

Conclusions

On the basis of the conducted strength tests, high and desired mechanical strength was observed in the tensile tests, which may justify the effective use of this type of fiber in clinical practice. The phenomena of saturation and the penetration of the resin into the spaces between the fiber bundles, occurring in the process of their physical modification, did not negatively influence the mechanical properties of the material under study. Water sorption did not negatively affect the mechanical properties of the FRC material. Fiber-reinforced composites can be an alternative to prosthetic restorations, whose retention is obtained only through mechanical interlocking to the abutment tooth.

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Comparison of intraoral digital radiography and cone-beam computed tomography in the measurement of periodontal bone defects

Porównanie radiografii cyfrowej i tomografii stożkowej w ocenie wielkości periodontologicznych ubytków kostnych

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D – writing the article; E – critical revision of the article; F – final approval of the article

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Abstract

Background. Periodontal disease has a high prevalence in many countries. Thus, the early detection of periodontal disease is important in order to obtain the most appropriate treatment plan to prevent tooth loss, and subsequently, to maintain the patient's general health.

Objectives. The aim of this study was to compare the accuracy of cone-beam computed tomography (CBCT) and intraoral parallel digital radiography in measuring the dimensions of periodontal bone defects.

Material and methods. In this in vitro study, 236 periodontal bone defects were artificially created in dry human mandibles using a burr. Defects included horizontal, one-, two-, and three-wall defects, craters, dehiscences, and fenestrations. Intraoral digital radiographs were obtained using the parallel technique with photostimulable phosphor plates (PSP) and CBCT scans were performed. Two calibrated observers evaluated the images and measured the dimensions of the defects. Clinical probing was performed and considered as the gold standard. The measurements of digital radiography and CBCT were compared to those achieved by probing to evaluate their accuracy.

Results. Cone-beam computed tomography had a significantly stronger correlation with the gold standard than intraoral parallel digital imaging. In the total assessment of the periodontal defects, the intraclass correlation coefficient (*ICC*) was calculated at 0.93 for CBCT–probe and at 0.78 for PSP–probe ($p < 0.05$).

Conclusions. The accuracy of CBCT was superior to that of intraoral digital radiography for measuring horizontal, one-, two-, and three-wall defects, craters, dehiscences, and fenestrations.

Key words: cone-beam computed tomography, radiography, alveolar bone loss, dental

Słowa kluczowe: tomografia stożkowa, radiografia, zanik wyrostka zębodołowego, dentystyczny

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Introduction

Periodontal disease has a high prevalence in many countries.[1] The early detection of periodontal disease is important in preventing tooth loss, and subsequently, maintaining the patient's general health.[2] Conventional diagnostic methods for periodontal disease include probing gingival tissues and performing radiographs to evaluate bony support.[3] Radiographs give us information about the amount and type of alveolar bone defect.[4] Hence, they are valuable in the detection of bone defects, the estimation of their severity, the evaluation of the treatment outcome, and making prognosis.[5]

The digitalization of intraoral radiographs has eliminated the processing of chemical compounds and lead foils. It made digital subtraction radiography (DSR) useful for lesion follow-up.[6] Also, digital radiography has a highly decreased radiation dose. It has some other advantages over conventional methods, including time efficiency and image enhancement.[7]

Using two-dimensional (2D) radiographic methods, we can only observe the interproximal surfaces, and as a result, bone loss may be underestimated due to having a 2D view of three-dimensional (3D) structures. Difficulty in finding a reliable reference point can be another outcome.[8] Moreover, the superimposition of anatomical structures in 2D imaging may cause errors in measuring the distance between the buccal and lingual cortical plates.[2] However, the parallel projection technique of performing periapical radiographs results in a minimal geometric distortion.[9] It also costs less than 3D imaging.

On the other hand, cone-beam computed tomography (CBCT) provides high-quality images. Structures can be assessed in 3 dimensions at different planes and at any angle, with no overlapping, making it possible to carry out an analysis without distortions and to measure bone defects even of the buccal and lingual plates.[10]

Measuring precisely the dimensions of a vertical periodontal defect is pivotal when planning an appropriate therapeutic intervention, such as regenerative therapy.[11–13]

Considering the high prevalence of periodontal disease and rapid advances in new imaging techniques, we need to compare their accuracy in measuring the dimensions of periodontal defects. A few studies with small sample sizes and limited types of periodontal defects have been done regarding this aspect, and more investigations are needed to show whether CBCT is a suitable modality for periodontal tissues.[14,15] The aim of this study was to compare the accuracy of CBCT and parallel periapical digital radiography in measuring simulated periodontal defects.

Material and methods

For this descriptive-analytic study, 11 mandibles of dry human skulls were used in 2017. A total of 236 artificial defects, including horizontal, one-, two-, and three-wall defects, craters, dehiscences, and fenestrations, were created with a No. 1/2 round burr and a No. 1 fissure burr. In all, 86 horizontal defects, 30 one-wall defects, 20 two-wall defects, 22 three-wall defects, 22 craters, 32 dehiscences, and 24 fenestrations were prepared in this study.

The cementoenamel junction (CEJ) was considered as the reference point. For one-, two- and three-wall defects as well as for dehiscences, the dimensional measurement of the maximum depth (from CEJ to the bottom of the defect) was done by a periodontist using the WHO (World Health Organization) periodontal probe. For craters, the maximum distance from the CEJ of the tooth, mesial to the crater, to the deepest point of the crater was measured. The mesiodistal width of fenestrations was recorded and the maximum distance from CEJ to the alveolar bone crest was measured in order to evaluate bone loss in horizontal defects. The dimensions were marked on the probe, and then measured by a digital caliper (Guilin Guanglu Measuring Instrument Co. Ltd, Guilin, China).

Before applying imaging modalities, the soft tissue was simulated by putting the mandibles into a plexiglass box full of water. The holder was anchored to the box and the teeth with tape.

Intraoral digital radiographs were taken with the parallel technique, using a size 2 photostimulable phosphor plate (PSP) (VistaScan®; Dürr Dental SE, Bietigheim-Bissingen, Germany), the XCP® sensor holder (Dentsply Rinn, Charlotte, USA), and an intraoral X-ray unit (Planmeca, Helsinki, Finland) at a focal spot–object distance (FOD) of 30 cm. The exposure was set up at 60 kvp with 0.8 mA. The dimensions were measured with the Scanora® 4.3.1.1 software (Soredex, Tuusula, Finland) (Fig. 1).

Then, CBCT scanning was carried out with a CBCT unit (Dentsply Sirona, Helsinki, Finland). The exposure setting was 89 kvp and 6 mA at a 12 × 8-centimeter field of view (FOV). The isotropic voxel size was 0.25 mm. Cone-beam computed tomography images were evaluated with the

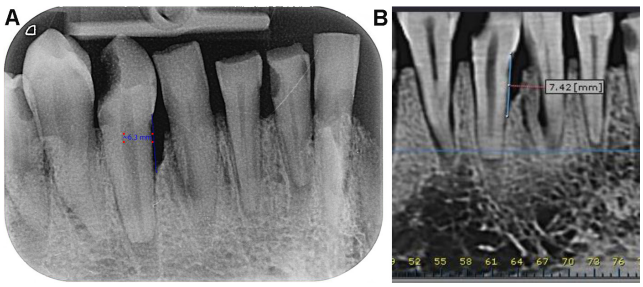

Fig. 1. Three-wall defect at the mesial side of a canine

A – intraoral digital radiograph; B – panoramic reconstruction view of the cone-beam computed tomography (CBCT) scan.

OnDemand3D® software (Cybermed Inc., Seoul, South Korea). They were reconstructed into 3D models to measure dehiscences and fenestrations whereas panoramic views (a slice thickness of 2 mm) were used for measuring the dimensions of other defects. The reason for this was that scrolling the panoramic reconstructions to find the deepest point of dehiscences and the maximum width of fenestrations was problematic, and could provide inaccurate measurements (Fig. 1,2).

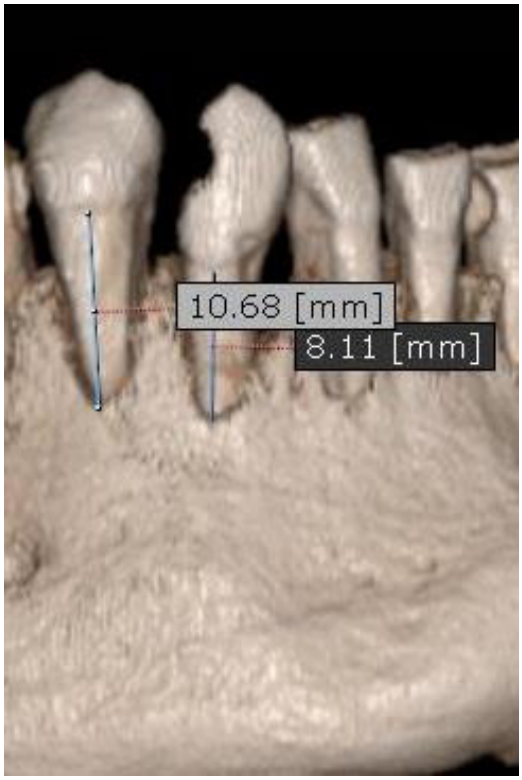

Fig. 2. Three-dimensional (3D) view of the cone-beam computed tomography (CBCT) scan illustrating dehiscences on a canine and on a first premolar

Measuring on radiographs followed the same protocol as measuring with a probe, considered here as the gold standard. Two calibrated observers (1 radiologist and 1 periodontist), who did not know where the defects were located, carried out the measurements. They assessed image sets at a 1-week interval and the assessment was repeated 1 week after first viewing. Inter- and intra-observer agreement was calculated with the intraclass correlation coefficient (*ICC*). It was also applied for CBCT–probe and PSP–probe to figure out which method had a higher correlation with the gold standard (according to the defect type and in total).

Results

According to *ICC*, the agreement degree between the observers who evaluated image sets was 0.93. Intra-observer agreement was calculated at 0.95 for the 1st observer and at 0.88 for the 2nd observer.

Based on the defect type, *ICC* was calculated for CBCT –probe, PSP–probe and CBCT–PSP. Table 1 shows that for all defect types, CBCT performed better in measuring the dimensions of the defects and had a higher correlation with the gold standard method (probe). Digital imaging was unable to detect dehiscences and fenestrations.

Based on the overall analysis of the data, CBCT showed a higher agreement degree and correlation with the probe than with digital imaging (Table 2).

Table 2. Intraclass correlation coefficient (*ICC*) in the evaluation of cone-beam computed tomography (CBCT) and photostimulable phosphor plates (PSP)

Image modality	*ICC*	*p*-value
CBCT–probe	0.93	0.00
PSP–probe	0.78	0.00
CBCT–PSP	0.77	0.00

Table 1. Intraclass correlation coefficient (ICC) and the mean defect dimensions [mm] calculated for each method according to the defect type

Defect type *N* = 236	*ICC*			Mean defect dimensions [mm]		
	CBCT –probe	PSP –probe	CBCT–PSP	probe	CBCT	PSP
Horizontal *n* = 86	0.92 *p* = 0.00	0.73 *p* = 0.00	0.66 *p* = 0.00	5.45 ±2.58	5.93 ±2.94	5.46 ±2.31
One-wall *n* = 30	0.94 *p* = 0.00	0.64 *p* = 0.00	0.62 *p* = 0.00	8.91 ±4.66	8.74 ±4.02	8.88 ±3.51
Two-wall *n* = 20	0.73 *p* = 0.00	0.62 *p* = 0.00	0.87 *p* = 0.00	10.52 ±2.88	10.25 ±2.13	10.81 ±2.12
Three-wall *n* = 22	0.82 *p* = 0.00	0.77 *p* = 0.00	0.78 *p* = 0.00	8.31 ±2.37	9.00 ±2.79	9.39 ±2.89
Crater *n* = 22	0.94 *p* = 0.00	0.71 *p* = 0.00	0.81 *p* = 0.00	7.63 ±2.73	7.15 ±2.97	8.01 ±2.70
Dehiscence *n* = 32	0.92 *p* = 0.00	–	–	8.09 ±1.83	8.93 ±1.78	–
Fenestration *n* = 24	0.81 *p* = 0.00	–	–	1.72 ±0.31	2.15 ±0.33	–

Data presented as mean (*M*) ± standard deviation (*SD*).
CBCT – cone-beam computed tomography; PSP – photostimulable phosphor plates.

Discussion

Many studies have confirmed that CBCT is advantageous in several fields, such as implant site imaging, orthodontics or craniofacial surgery.[15] Evaluating CBCT in the periodontal field, some studies have assessed the ability of CBCT just to detect periodontal defects[16–19] and some have evaluated the diagnostic accuracy of CBCT in measuring the dimensions of periodontal defects.[20,21]

Comparing the diagnostic accuracy of a charge-coupled device (CCD) and CBCT, Vandenberghe et al. examined both the panoramic reconstruction view and 0.4-millimeter cross-sectional slices of CBCT.[2] They reported no significant differences in linear measurements between the panoramic reconstruction view of CBCT and CCD; however, CBCT with 0.4-millimeter-thick cross-sections demonstrated values closer to the gold standard, indicating a more accurate assessment of periodontal bone loss.[2] Haghgoo et al. showed that CBCT was more accurate than CCD in evaluating the vertical dimensions of periodontal bone defects, but they reported no statistically significant differences.[20] Silveira-Neto et al. assessed detail registration in the peri-implant region with CBCT and CCD for periapical digital radiography.[22] They better detected buccal bone defects with CBCT and peri-implant bone defects with periapical digital radiography.[22]

Suphanantachat et al. compared conventional intraoral radiography and CBCT in assessing periodontal conditions and infrabony defects.[19] They stated that CBCT was superior to intraoral radiography in evaluating infrabony defect morphology and providing treatment.[19]

The present study compared intraoral digital imaging (using PSP) and CBCT. A major advantage of the PSP image receptor is that it is cordless. This subsequently impacts the ease of receptor placement. According to the results, CBCT performed better than PSP, with a statistically significant difference in detecting and measuring periodontal defects.

Particularly, in measuring the horizontal pattern of bone loss, there was a higher correlation between CBCT and the gold standard than between PSP and the gold standard. In another study, CBCT also accurately reproduced the clinical measurement of the horizontal periodontal bone defect[23]; however, Haghgoo et al. found no significant difference in horizontal bone loss patterns between CCD and CBCT.[20]

Vandenberghe et al. demonstrated that crater defects are depicted more accurately with CBCT than with intraoral digital imaging,[2] which is in agreement with our results.

Cone-beam computed tomography and intraoral digital imaging were compared with a direct surgical measurement in a study by Grimard et al.[24]; their conclusion is in agreement with ours, which is that CBCT shows a higher correlation with the gold standard.

Bayat et al. created defects in sheep mandibles and compared CBCT with PSP.[17] They reported that CBCT was significantly superior in detecting grade I furcation involvements, three-wall defects, fenestrations, and dehiscences ($p < 0.05$). No significant difference was found in the detection of grades II and III furcation involvements, one-wall, two-wall, and trough-like defects[17]; however, in our study, CBCT was substantially more accurate in detecting and measuring all the examined periodontal defects. Ruetters et al. investigated the accuracy of CBCT and periapical digital radiography in comparison with clinical measurements for the vertical dimensions of periodontal bone defects, and showed that CBCT had a higher agreement with the clinical results and fewer deviations than periapical images.[25]

The detection of lingual or buccal defects, such as fenestrations and dehiscences, is difficult if not impossible, using 2D radiographs because of the superimposition of the root image. In these cases, CBCT is significantly superior to intraoral digital radiography, as mentioned by Mish et al.[3] Similar to our study, in the results provided by Vandenberghe et al., 100% detectability of periodontal defects with CBCT was confirmed, while intraoral digital imaging was not able to identify all defects.[2] Fleiner et al.[26] and Fuhrmann et al.[27] also reported 100% detectability of periodontal defects. These findings differed from those of Braun et al.[28] and Bagis et al.[16] The percentage of the correct diagnoses of fenestration and dehiscence using 3D projections was very high, but not 100%; however, they reported a superior diagnostic accuracy of CBCT over PSP.[16,23] Mengel et al. also concluded that CBCT was closer to the histopathologic investigation.[29]

Noujeim et al. reported an excellent diagnostic accuracy of CBCT as compared to the 2D modality in the detection of inter-radicular bony defects.[12] Mol and Balasundaram[10] and Bagis et al.[16] also reported a better diagnostic and quantity accuracy of CBCT in comparison with PSP. Overall, the outcomes of this study revealed similar results to those of previous studies, indicating that CBCT exhibited a more accurate diagnostic ability than intraoral digital imaging with PSP sensors for detecting periodontal defects.

A substantial strength of this study was its comprehensiveness resulting from a large sample size (236 defects) and the evaluation of various types of periodontal defects. Using human mandibles was another advantage of the present study, while some other studies have used animal skulls, such as from pigs and sheep, whose anatomical differences may have affected diagnostic accuracy.

The in vitro design of the study can be considered a limitation, since there are differences between clinical conditions and in-vitro settings; however, Rost reported difficulty in measuring in vivo because of such factors as the patient's discomfort upon probing, inaccuracies in probing, probe angulation, and the impaired visualization due to the presence of subgingival calculus and inflamed gingivae.[30] Artificially created periodontal defects are another limitation of this study, since burrs usually make distinctive borders, which may facilitate detection in imaging.

Cone-beam computed tomography provided more diagnostic and quantity accuracy with regard to periodontal defects. It can be used as an additional tool for diagnosing and offering treatment plans for patients with periodontal bone defects. Even though the radiation dose of CBCT is higher in comparison to other modalities, nowadays the effective dosage of radiation can be decreased to 34 μS by choosing smaller FOVs.[31] If such progress continues and the radiation dose can be reduced to that of a panoramic view, the use of CBCT may be developed in the future. Further investigations are needed to examine other CBCT units and protocols with such factors as cost and conformance taken under consideration. Also, more studies should be conducted to assess and compare different resembling methods for soft tissue simulation.

Conclusions

CBCT is superior to digital intraoral radiography in detecting and measuring horizontal, one-, two- and three-wall defects, craters, dehiscences, and fenestrations.

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Extraction versus non-extraction orthodontic treatment: Soft tissue profile changes in borderline class I patients

Ekstrakcyjne a nieekstrakcyjne leczenie ortodontyczne – zmiany profilu tkanek miękkich u pacjentów z wątpliwą klasą I

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Abstract

Background. The decision regarding the selection of extraction or non-extraction orthodontic treatment is a common challenge in orthodontic treatment planning.

Objectives. The objective of this study was to compare the effects of extraction and non-extraction orthodontic treatment on the soft tissue profile of borderline class I patients.

Material and methods. In this retrospective study, 70 patients were selected from among those referred to the Department of Orthodontics of the Faculty of Dentistry at Hamadan University of Medical Sciences in Iran. The inclusion criteria were skeletal class I, 4–10 mm of space deficiency, and the possibility of applying both extraction and non-extraction orthodontic treatment. All patients underwent fixed orthodontic treatment with the use of 0.022-inch-slot edgewise brackets. The patients were divided into 2 groups ($n = 35$) according to the 4-premolar extraction or non-extraction treatment plan. The 2 groups were compared by means of the cephalometric analysis.

Results. There were 11 males and 24 females at a mean age of 17.46 years in the non-extraction group, and 9 males and 26 females at a mean age of 18.46 years in the extraction group. The upper and lower incisors as well as the lower lip moved forward in the non-extraction group (lower lip to E-plane = 0.87 ±1.39 mm, U1–SN = 2.83 ±8.03°, IMPA = 4.64 ±5.47°). The incisors and the lips moved backward in the extraction group (upper lip to E-plane = −1.42 ±2.08 mm, lower lip to E-plane = −1.56 ±1.97 mm, U1–SN = −7.63 ±9.02°, IMPA = −7.05 ±6.79°). The differences were statistically significant ($p < 0.05$). Mentolabial sulcus became more pronounced in the non-extraction group (1.92 ±2.73 mm; $p < 0.001$) and shallower in the extraction group (−1.90 ±4.2 mm; $p = 0.000$).

Conclusions. Orthodontic treatment can change the soft tissue appearance of the lower third of the face. The lips and the incisors moved forward in the non-extraction group and backward in the extraction group.

Key words: tooth extraction, orthodontics, cephalometry, Angle class I malocclusion

Słowa kluczowe: ekstrakcja zęba, ortodoncja, cefalometria, wada zgryzu klasy I wg Angle'a

Introduction

A large number of people seek orthodontic treatment to improve their dentofacial appearance.[1] In general, the purpose of orthodontic treatment is to improve dentofacial appearance, oral function and the stability of the dental arches. Choosing an appropriate treatment plan helps to maintain a balance between the 3 above-mentioned parameters.[2–4]

The decision regarding the creation of space is challenging in orthodontic treatment planning. In patients with the tooth size–arch size discrepancy, it is necessary to provide sufficient space for the teeth during orthodontic treatment. The conventional methods for creating the space include the distal movement of the posterior teeth, changes in the width and shape of the arch, the interproximal reduction of the teeth, the protrusion of the incisors, and tooth extraction. Tooth extraction may be required to achieve a coordinated dental arch, compensate moderate to severe dental protrusion or crowding, and camouflage mild to moderate jaw discrepancies.[1] The decision regarding tooth extraction depends on different factors, such as esthetic considerations, the stability of the teeth, and the preferences of patients or orthodontists.[5]

Non-extraction orthodontic treatment is indicated in patients with space excess or dental retroclination. In contrast, in the case of space shortage or dental proclination, the only treatment option is tooth extraction. The treatment plan in such orthodontic patients is relatively straightforward. In addition, post-treatment outcomes in such patients are highly predictable. However, there are some patients for whom both extraction and non-extraction orthodontic treatment can be considered. In such patients, the choice of treatment depends on several factors, and the treatment plan may vary, depending on the patient's soft and hard tissue components, and the preferences of orthodontists and patients. The choice of the treatment plan in these patients is considered to be borderline. No consensus has been reached regarding the effects of tooth extraction on the vertical dimension, facial profile changes, jaw position, temporomandibular joint health, and the periodontal status after treatment.[6,7]

The perspectives of patients and orthodontists regarding an ideal soft tissue profile have been continuously changing over the past decades.[8] Tooth extraction can change the soft tissue profile. However, there is controversy regarding the long-term effects of tooth extraction.[9] Although some studies have been conducted on this topic, no study could reach a definite conclusion regarding the effect of treatment on the appearance of the lower third of the face.[8,10–12] A limited number of available studies on this topic include borderline patients. The results may be overestimated or underestimated, depending on whether the chosen patients had space shortage or excess, or dental protrusion.

The primary objective of this study was to evaluate and compare the effects of extraction and non-extraction orthodontic treatment on the soft tissue profile of borderline class I patients.

Material and methods

In this retrospective study, cephalometric changes that occurred during the orthodontic treatment of the patients treated with extraction and non-extraction methods were evaluated. The patients were randomly selected from among those reporting to the Department of Orthodontics of the Faculty of Dentistry at Hamadan University of Medical Sciences in Iran.

The inclusion criteria were as follows: age between 18 and 30 years, skeletal class I relationship ($1° < ANB < 5°$), space deficiency of 4–10 mm, and the borderline treatment plan – the possibility of both extraction and non-extraction treatment.

The exclusion criteria were the following: patients with craniofacial deformities or syndromes, large discrepancies in the tooth size, a history of unsuccessful orthodontic or orthognathic treatment, a history of facial surgeries, an intake of medications that would affect the soft tissue volume.

In order to choose borderline patients, 6 factors were assessed according to Paquette et al.[13]: (1) the magnitude of space deficiency in the maxillary arch; (2) the magnitude of space deficiency in the mandibular arch; (3) maxillary incisor protrusion (U1–SN); (4) mandibular incisor protrusion (L1–NB); (5) the irregularity index; and (6) facial convexity (Z-angle).

Afterward, 3 orthodontists were asked to design the treatment plan according to the 6 above-mentioned factors. The patients were categorized in the borderline range in case of disagreement between the orthodontists regarding the selection of the extraction or non-extraction orthodontic treatment plan.

The sample size was calculated to be 34 in each group according to a previous study,[1] assuming a power of 0.85, type I error of 0.05, standard deviation (*SD*) of 1.2, and with the aim of finding a 0.5-millimeter true difference between the groups, using Power and Sample Size Calculator v. 3.1.2 (https://ps-power-and-sample-size-calculation.software.informer.com/3.1/).

The primary (baseline) and final cephalograms, casts and photographs of the patients were examined for space deficiency, and the soft tissue profile analysis was performed for case selection. All patients had been treated with 0.022-inch-slot edgewise brackets, and had complete pre-treatment and post-treatment diagnostic records.

The eligible patients were categorized as follows:

– the non-extraction group included patients who underwent non-extraction orthodontic treatment (except third molar extraction);
– the extraction group included patients who were treated with the extraction of the 4 first or second premolars.

The pre-treatment and post-treatment cephalograms were analyzed using the Dolphin Imaging software v. 11.8 (Patterson Dental Supply, Inc., St. Paul, USA). Thirty-seven landmarks were assessed (23 hard tissue and 14 soft tissue landmarks) (Fig. 1). Linear and angular measurements were made to evaluate the soft and hard tissue profiles of the patients (Table 1).

In order to assess the intra-class correlation coefficient, 11 cephalograms were traced by another calibrated researcher.

The data was analyzed using PASW Statistics for Windows v. 18 (SPSS, Inc., Chicago, USA). The paired *t* test was used to analyze changes in each treatment group, and the independent *t* test was utilized to compare the 2 kinds of treatment in the 2 groups. Pearson's correlation coefficient was used to assess the correlation of hard tissue and soft tissue changes. A p-value of <0.05 was considered statistically significant.

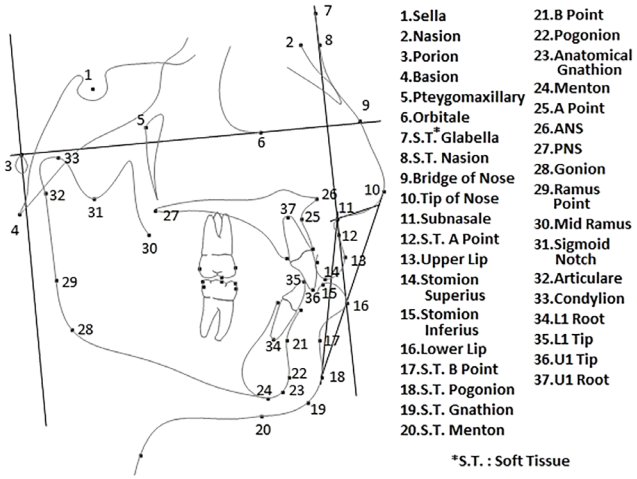

Fig. 1. Hard tissue and soft tissue cephalometric landmarks used for cephalometric tracing

Table 1. Linear and angular cephalometric measurements and their definitions

No.	Variable	Definition
1	nasolabial angle (Col–Sn–UL)	angle between the line tangent to the columella and the line tangent to the upper lip
2	E-plane	line passing through the tip of the nose and soft tissue pogonion
3	upper lip to E-plane	distance of the most anterior point of the upper lip to E-plane
4	lower lip to E-plane	distance of the most anterior point of the lower lip to E-plane
5	upper lip thickness	horizontal distance between the most anterior point of the upper lip and the labial surface of the upper central incisors
6	lower lip thickness	horizontal distance between the most anterior point of the lower lip and the labial surface of the lower central incisors
7	upper lip length	the shortest distance between subnasale and the most inferior point of the upper lip vermilion
8	lower lip length	the shortest distance between soft tissue menton and the most superior point of the lower lip vermilion
9	mentolabial sulcus	the shortest distance between the most posterior point in the lower lip contour (soft tissue B point) and the line passing through soft tissue pogonion and the most anterior point of the lower lip
10	Wits appraisal	distance between the points resulting from drawing perpendicular lines from A and B points to the functional occlusal plane
11	post.–ant. face height (S–Go / N–Me)	proportional ratio between the posterior facial height (S to gonion) and the anterior facial height (N to menton)
12	UFH / TFH (N–ANS / N–Me)	proportional ratio between the upper anterior facial height (N to ANS point) and the total anterior facial height (N to menton)
13	posterior facial height (S–Go)	distance between S and gonion
14	anterior facial height (N–Me)	distance between N and menton
15	upper face height (N–ANS)	distance between N and ANS point
16	Pog–NB	distance between pogonion and the line passing through N and B points
17	SN–GoMe	angle between SN line and the mandibular plane (gonion to menton line)
18	U1–SN	angle between the long axis of the most prominent upper incisors and SN line
19	interincisal angle	angle between the long axis of the upper and lower incisors
20	IMPA (L1–MP)	angle between the long axis of the most prominent lower incisors and the mandibular plane (gonion to menton line)
21	FH–SN	angle between Frankfort and SN lines
22	SNA	angle between S, N and A points
23	SNB	angle between S, N and B points
24	ANB	angle between A, N and B points
25	interlabial gap	vertical distance between the most inferior point of the upper lip vermilion and the most superior point of the lower lip vermilion

Results

This study was performed on 70 patients, including 35 patients in the extraction group (11 males and 24 females) and 35 patients in the non-extraction group (9 males and 26 females). The mean age of the patients at the onset of treatment was 17.45 ±4.66 years and 18.46 ±4.94 years in the non-extraction and extraction groups, respectively. The mean intra-class correlation coefficient was 0.79.

Tables 2 and 3 show the pre-treatment and post-treatment values of cephalometric variables in the non-extraction and extraction groups, respectively.

In the non-extraction group, changes in lower lip to E-plane ($p \leq 0.001$), mentolabial sulcus ($p \leq 0.001$), SN–GoMe ($p \leq 0.035$), U1–SN ($p \leq 0.044$), interincisal angle ($p \leq 0.001$), and IMPA ($p \leq 0.001$) were all statistically significant.

In the extraction group, nasolabial angle ($p \leq 0.048$), upper lip to E-plane ($p \leq 0.001$), lower lip to E-plane ($p \leq 0.001$), mentolabial sulcus ($p \leq 0.012$), Pog–NB ($p \leq 0.047$), U1–SN ($p \leq 0.001$), interincisal angle ($p \leq 0.001$), and IMPA ($p \leq 0.001$) changed significantly after treatment.

Table 4 compares the changes between the extraction and non-extraction treatment groups.

The comparison of the 2 groups revealed significant differences in the upper lip to E-plane, lower lip to E-plane, mentolabial sulcus, U1–SN, interincisal angle, and IMPA (Table 4).

Significant differences were noted between the extraction and non-extraction treatment groups regarding the change in the position of the upper and lower incisors and the lips, all moving backward in the extraction group. The upper and lower incisors and the lower lip moved forward in the non-extraction treatment group. Mentolabial sulcus became shallower in the non-extraction group and more pronounced in the extraction group.

Tables 5 and 6 show the results of Pearson's correlation test regarding the correlation between skeletal/dental changes and soft tissue changes.

As shown in Tables 5 and 6, the posterior and anterior facial height had a significant correlation with the upper and lower lip length and the mentolabial sulcus depth in both groups and with the upper lip thickness in the extraction group. The parameter Pog–NB had an inverse correlation with lower lip to E-plane in the extraction group , while there was a positive correlation between this parameter and the lower lip length, and U1–SN had a moderately positive correlation with the upper lip thickness and the mentolabial sulcus depth in the non-extraction group. The parameter IMPA positively correlated with the upper lip thickness and the mentolabial sulcus depth in the extraction group.

Table 2. Pre-treatment and post-treatment values of the variables in the non-extraction group

No.	Variable	Before treatment	After treatment	*p*-value
1	nasolabial angle (Col–Sn–UL) [°]	107.81 ±10.38	107.02 ±9.84	0.676
2	upper lip to E-plane [mm]	–3.20 ±2.16	–3.20 ±2.01	0.992
3	lower lip to E-plane [mm]	–0.37 ±2.12	0.50 ±2.33	0.001*
4	upper lip thickness [mm]	4.53 ±1.07	4.64 ±1.19	0.645
5	lower lip thickness [mm]	4.55 ±1.12	4.76 ±1.17	0.574
6	upper lip length [mm]	20.19 ±2.50	19.84 ±3.30	0.439
7	lower lip length [mm]	17.05 ±3.14	17.09 ±2.77	0.943
8	mentolabial sulcus [mm]	7.52 ±3.87	9.44 ±4.43	0.001*
9	Wits appraisal [mm]	2.18 ±3.41	2.00 ±2.53	0.129
10	post.–ant. face height (S–Go / N–Me)	63.73 ±3.37	63.86 ±3.64	0.757
11	UFH / TFH (N–ANS / N–Me)	44.28 ±1.98	44.50 ±2.11	0.401
12	posterior facial height (S–Go) [mm]	70.11 ±8.53	70.54 ±10.39	0.776
13	anterior facial height (N–Me) [mm]	121.62 ±12.71	123.17 ±15.80	0.533
14	upper face height (N–ANS) [mm]	47.76 ±5.34	48.59 ±6.13	0.427
15	Pog–NB [mm]	1.48 ±1.29	1.46 ±1.46	0.929
16	SN–GoMe [°]	34.06 ±4.50	35.21 ±4.74	0.035*
17	U1–SN [°]	102.91 ±7.17	105.74 ±6.85	0.044*
18	interincisal angle [°]	125.15 ±10.37	116.55 ±9.44	0.001*
19	IMPA (L1–MP) [°]	95.08 ±6.00	99.72 ±6.87	0.001*
20	FH–SN [°]	7.36 ±3.02	6.96 ±3.18	0.467
21	SNA [°]	82.31 ±4.59	81.68 ±4.38	0.265
22	SNB [°]	76.84 ±3.04	77.00 ±3.11	0.694
23	ANB [°]	4.47 ±2.54	4.69 ±2.35	0.115
24	interlabial gap [mm]	2.09 ±1.53	1.95 ±0.67	0.594

Data presented as mean (*M*) ± standard deviation (*SD*).
* statistical significance.

Table 3. Pre-treatment and post-treatment values of the variables in the extraction group

No.	Variable	Before treatment	After treatment	*p*-value
1	nasolabial angle (Col–Sn–UL) [°]	107.12 ±13.75	111.15 ±11.28	0.048*
2	upper lip to E-plane [mm]	–2.27 ±2.06	–3.69 ±2.05	0.001*
3	lower lip to E-plane [mm]	0.80 ±2.25	–0.76 ±2.08	0.001*
4	upper lip thickness [mm]	4.40 ±1.15	4.55 ±1.10	0.674
5	lower lip thickness [mm]	4.43 ±1.63	4.62 ±1.53	0.703
6	upper lip length [mm]	19.84 ±3.52	20.00 ±3.25	0.806
7	lower lip length [mm]	16.66 ±3.22	17.29 ±2.68	0.312
8	mentolabial sulcus [mm]	9.04 ±5.42	7.14 ±3.56	0.012*
9	Wits appraisal [mm]	1.63 ±3.52	1.19 ±3.32	0.434
10	post.–ant. face height (S–Go / N–Me)	62.72 ±3.48	63.40 ±3.64	0.193
11	UFH / TFH (N–ANS / N–Me)	44.00 ±2.08	43.94 ±1.96	0.806
12	posterior facial height (S–Go) [mm]	69.27 ±10.99	71.80 ±9.28	0.245
13	anterior facial height (N–Me) [mm]	121.26 ±17.78	125.98 ±14.76	0.212
14	upper face height (N–ANS) [mm]	47.25 ±6.70	49.09 ±5.61	0.218
15	Pog–NB [mm]	0.86 ±1.21	1.24 ±1.21	0.047*
16	SN–GoMe [°]	35.05 ±5.15	35.96 ±5.54	0.057
17	U1–SN [°]	105.96 ±7.59	98.33 ±9.04	0.001*
18	interincisal angle [°]	119.76 ±11.43	133.39 ±8.29	0.001*
19	IMPA (L1–MP) [°]	96.22 ±6.90	89.17 ±7.26	0.001*
20	FH–SN [°]	7.34 ±3.35	7.06 ±3.41	0.647
21	SNA [°]	81.32 ±3.53	81.21 ±3.87	0.798
22	SNB [°]	76.89 ±3.14	76.76 ±4.05	0.692
23	ANB [°]	4.43 ±2.71	4.46 ±2.50	0.947
24	interlabial gap [mm]	2.28 ±2.07	2.13 ±1.18	0.648

Data presented as mean (*M*) ± standard deviation (*SD*).
* statistical significance.

Table 4. Comparison of the treatment changes between the extraction and non-extraction groups

Parameter	Group	*M*	*SD*	*p*-value
nasolabial angle (Col–Sn–UL) [°]	non-extraction extraction	–0.789 4.031	11.05049 11.63786	0.080
upper lip to E-plane [mm]	non-extraction extraction	–0.003 –1.423	1.76993 2.08144	0.003*
lower lip to E-plane [mm]	non-extraction extraction	0.874 –1.569	1.39439 1.97153	0.001*
upper lip thickness [mm]	non-extraction extraction	0.209 0.204	1.28941 1.34009	0.439
lower lip thickness [mm]	non-extraction extraction	0.274 0.191	2.02068 2.61745	0.461
upper lip length [mm]	non-extraction extraction	–0.351 0.166	2.65766 3.96002	0.523
lower lip length [mm]	non-extraction extraction	0.037 0.631	3.03858 3.64206	0.461
mentolabial sulcus [mm]	non-extraction extraction	1.911 –1.891	2.73354 4.20423	0.001*
Wits appraisal [mm]	non-extraction extraction	–1.186 –0.443	3.07630 3.31044	0.334
post.–ant. face height (S–Go / N–Me)	non-extraction extraction	–0.129 –0.671	2.44078 2.98847	0.408
UFH / TFH (N–ANS / N–Me)	non-extraction extraction	0.214 –0.054	1.49098 1.29985	0.425
posterior facial height (S–Go) [mm]	non-extraction extraction	0.431 2.526	8.90640 12.63386	0.426
anterior facial height (N–Me) [mm]	non-extraction extraction	1.557 4.723	14.63691 21.94631	0.480
upper face height (N–ANS) [mm]	non-extraction extraction	0.834 1.843	6.13615 8.68671	0.577
Pog–NB [mm]	non-extraction extraction	–0.014 0.380	0.93969 1.09270	0.110
SN–GoMe [°]	non-extraction extraction	1.157 0.911	3.11847 2.74084	0.727
U1–SN [°]	non-extraction extraction	2.834 –7.631	8.03587 9.02848	0.001*
interincisal angle [°]	non-extraction extraction	–8.603 13.626	11.00036 12.33518	0.001*
IMPA (L1–MP) [°]	non-extraction extraction	4.637 –7.051	5.47379 6.79945	0.001*
FH–SN [°]	non-extraction extraction	–0.397 –0.274	3.19333 3.50466	0.878
SNA [°]	non-extraction extraction	–0.626 –0.117	3.26914 2.68892	0.480
SNB [°]	non-extraction extraction	0.154 –0.131	2.30298 1.94766	0.577
ANB [°]	non-extraction extraction	–0.780 0.029	1.80274 2.50301	0.126
interlabial gap [mm]	non-extraction extraction	–0.146 –0.149	1.60374 1.90593	0.995

M – mean; *SD* – standard deviation; * statistical significance.

Table 5. Pearson's correlation between skeletal/dental changes and soft tissue changes in the non-extraction group

Changes in parameters	Nasolabial angle (Col–Sn–UL)	Upper lip to E-plane	Lower lip to E-plane	Upper lip thickness	Lower lip thickness	Upper lip length	Lower lip length	Mentolabial sulcus
Posterior facial height (S–Go)	0.022	–0.197	0.251	0.321	–0.088	0.767*	0.464*	0.540*
Anterior facial height (N–Me)	0.062	–0.235	0.122	0.254	–0.081	0.819*	0.554*	0.416*
Pog–NB	0.011	–0.016	0.157	0.097	0.005	0.094	0.309	0.237
U1–SN	–0.289	0.155	0.289	0.441*	0.308	–0.002	0.218	0.385*
IMPA	0.024	–0.012	0.173	–0.022	–0.096	0.147	0.184	0.211

* statistical significance.

Table 6. Pearson's correlation between skeletal/dental changes and soft tissue changes in the extraction group

Changes in parameters	Nasolabial angle (Col–Sn–UL)	Upper lip to E-plane	Lower lip to E-plane	Upper lip thickness	Lower lip thickness	Upper lip length	Lower lip length	Mentolabial sulcus
Posterior facial height (S–Go)	–0.190	–0.275	0.078	0.358*	–0.730	0.895*	0.829*	0.346*
Anterior facial height (N–Me)	–0.258	–0.229	0.169	0.396*	–0.032	0.922*	0.823*	0.411*
Pog–NB	–0.130	–0.225	–0.347*	0.240	0.002	0.324	0.409*	–0.050
U1–SN	–0.085	–0.115	0.005	0.203	0.293	0.048	0.034	0.122
IMPA	–0.156	–0.067	0.229	0.176	0.051	0.382*	0.197	0.369*

* statistical significance.

Discussion

In general, dental and skeletal changes that occur during orthodontic treatment affect the soft tissue structures. Soft tissue changes do not completely coincide with hard tissue changes, and may be greater or lesser depending on the treatment plan.[5,13–16] The purpose of the present study was to compare the treatment outcomes between the extraction and non-extraction orthodontic treatment groups.

Soft tissue variables

In both the extraction and non-extraction groups, lower lip to E-plane changed significantly. In the extraction group, the lower lip moved backward whereas in the non-extraction group, the lower lip moved forward. In a study by Xu et al., the lower lip moved backward in relation to E-plane in both extraction and non-extraction treatment, but this movement was greater in the extraction group.[17] However, in extraction and non-extraction treatment, the lower lip moved backward and forward in relation to Sn–Pog line (the line passing through subnasale and the chin prominence), respectively. Thus, it seems that the change in the lower lip position was similar to that reported in the present study. The reason for the difference in the results regarding lower lip to E-plane can be attributed to the age range and malocclusion of the patients in the study by Xu et al. In their study, the mean age of patients was 12 years and a mixed group of patients with different malocclusion types was evaluated.[17] Large changes in the nasal tip prominence can make E-line an unstable plane. In addition, Momeni Danaei et al. examined the skeletal, dental and soft tissue changes following orthodontic treatment with or without tooth extraction in patients with class II division I malocclusion, and reported results similar to the results of the extraction group in the present study.[15] However, in the non-extraction group, the lower lip was not significantly altered. This difference in the outcome is due to the difference in the malocclusion type (class I vs class II). In other words, in class II patients, both extraction and non-extraction treatment caused similar changes in the dental position.[15] These results were similar to those of Bravo.[18] Also, Bishara et al. reported the forward movement of the lower lip during non-extraction treatment.[19]

The comparison of the 2 groups revealed that changes in the position of the lower lip in the extraction group were significantly different from those in the non-extraction group, which is similar to the findings of Xu et al.[17]

Upper lip to E-plane experienced significant changes in the extraction group. It seems that the upper lip moved backward in the extraction group in our study. This finding is similar to that of Bravo.[18]

There was a significant difference between the groups in the position of the upper lip in relation to E-plane in our study. Our results are in contrast to those of Xu et al., which can be attributed to the treatment mechanics.[17]

In our study, nasolabial angle in the extraction group significantly increased, which suggests that the upper lip moved backward. This angle decreased very slightly in the non-extraction group after treatment, but the change was not statistically significant and may indicate that the upper lip position did not change significantly.

This finding confirms the results regarding the position of the lips in relation to E-plane. It is also similar to the results of Talass et al.,[20] Lo et al.[21] and Diels et al.[22] Changes in this angle did not differ significantly between the 2 groups.

In our study, mentolabial sulcus increased significantly in the non-extraction group after treatment, but decreased significantly in the extraction group. This finding shows that mandibular incisor retroclination in the extraction group can retract the lower lip relative to the sagittal plane. Also, in the non-extraction group, as the mandibular incisors moved forward, the lower lip also moved toward the sagittal plane, causing a deeper mentolabial sulcus.[1] These changes are in line with significant changes in IMPA, which were observed in both groups after treatment. The mentolabial sulcus changes also coincided with the lower lip to E-plane changes. In the non-extraction group, lower lip to E-plane significantly decreased after treatment, which indicated the protrusion of the lower lip. In the extraction group, the distance between the lower lip and E-plane significantly increased, which indicated the retrusion of the lower lip. The mentolabial sulcus changes were different between the 2 groups.

The lip thickness and length did not change in any group. The results of other studies in this regard have been controversial.[5,9] Such contradictory findings indicate that multiple factors, other than orthodontic treatment, can affect the thickness of the lips, such as age, race and the lip structure.

No significant difference was observed in the interlabial gap in any group. Due to the fact that the patients in this study were in the borderline spectrum, none of them had a severe protrusion or retrusion of the lips. Hence, achieving this finding seems logical.

Skeletal variables

In the anteroposterior aspect, ANB and Wits appraisal did not change significantly in any group. Considering the fact that all patients had class I malocclusion before treatment, this finding appears to be logical.

In the extraction group, Pog–NB significantly increased after treatment. This finding suggests that in the extraction group, the chin seems to be more prominent in the profile view. This variable did not change significantly in the non-extraction group. Although point B is a skeletal point, a change in the position of the teeth can affect the position of this point.[23] The retraction of the lower teeth could retract NB line and make Pog–NB larger in the extraction group.

In the vertical dimension, the posterior and anterior facial height did not change significantly in either group. The only significant change in the vertical dimension was in the mandibular plane and the cranial base angle (SN–GoMe) in the non-extraction group. The measurements showed that this angle increased slightly after treatment in the non-extraction group. However, the linear variables of the vertical facial height did not change significantly.

Dental variables

In the extraction group, U1–SN decreased significantly after treatment, indicating the retraction of the maxillary incisors. This finding is consistent with a significant decrease in upper lip to E-plane in the extraction group. This may indicate that with the retraction of the maxillary incisors, the upper lip also moved backward. The parameter U1–SN significantly increased in the non-extraction group, which caused the upper lip to move forward relative to the sagittal plane. It should be noted that upper lip to E-plane increased in the non-extraction group, but this increase was not large enough to cause a statistically significant change. It also shows that the upper lip changes did not fully coincide with dental changes.

Changes in the upper incisor inclination in the extraction group were significantly different from those in the non-extraction group. The parameter IMPA significantly increased in the non-extraction group, but significantly decreased in the extraction group. This finding is in agreement with the findings regarding lower lip to E-plane. Following the retraction of the incisors, the lower lip moved backward in the extraction group whereas in the non-extraction group, the lower lip moved forward due to the protraction of the incisors. The differences between the 2 treatment groups in the angle between the lower incisors and the mandibular plane were significant.

Interincisal angle increased significantly in the extraction group, which can be attributed to a significant reduction in U1–SN and IMPA in the extraction group. Interincisal angle decreased significantly in the non-extraction group, which explains the maxillary and mandibular incisor protrusion. There was a significant difference between the 2 groups in the interincisal angle variations.

Correlation between the variables

In the present study, the inclination of incisors did not show a strong correlation with the upper lip position. This angle did not have a significant correlation with nasolabial angle, either. In fact, the position of the upper lip was not significantly correlated with any of the evaluated variables. However, the position of the lower lip in relation to E-plane had a significant inverse correlation with Pog–NB in the extraction group. The variable Pog–NB did not have a positive correlation with lower lip to E-plane in the non-extraction group. The lower lip thickness did not have a significant correlation with any of the vertical or dental variables, but the upper lip thickness had a significant positive correlation with the angle of the maxillary incisors (U1–SN) in the non-extraction group as well as with the posterior and anterior facial height in the extraction group. Nasolabial angle did not correlate with any hard tissue variable. This finding is similar to that of Fitzgerald et al.[24]

Upper lip to E-plane did not have any correlation with the hard tissue variables. However, lower lip to E-plane had an inverse correlation with the chin position (Pog–NB) in the extraction group. As the chin moves forward, E-plane is also displaced forward, increasing the lower lip-to-E-plane distance.

The lower lip thickness did not have any significant correlation with the hard tissue variables. However, the upper lip thickness had a positive correlation with the upper incisor angulation (U1–SN) in the non-extraction group, and the posterior and anterior facial height in the extraction group. Shirvani et al. also revealed a correlation between the incisor angulation and the lip thickness.[25] The lip structure and its initial thickness can affect this correlation. Oliver showed that in patients with thicker lips or in people who have lips with low traction, the lips follow hard tissue changes to a lesser degree in comparison with patients with thin lips or high-traction lips.[26] A lack of a correlation between the upper lip thickness and the incisor angulation in the extraction group can be attributed to this fact. In addition, Momeni Danaei et al. revealed that, although lip retraction had a correlation with dental retraction, this correlation was not strong.[15] According to Talass et al., the upper lip changes during orthodontic treatment are less predictable, and they can be attributed to the lip anatomy and the complex dynamics of the upper lip.[20]

In both the extraction and non-extraction groups, a significant positive correlation existed between the vertical facial changes and the upper and lower lip length. It is interesting to note that in both groups, the facial height changes had a stronger correlation with the upper lip than with the lower lip.

In the extraction group, the chin prominence had a positive correlation with the lower lip length. The lower lip length is measured as the distance between soft tissue menton and the most superior point of the lower lip. It seems logical that by increasing the chin prominence, the lower lip length would increase.

The lower incisor angulation had a significant correlation with the upper lip length in the extraction group. It seems that the retraction of the lower incisors decreases the traction of the upper lip, leading to lip shortening.[25]

There was a significant positive correlation between the facial height and mentolabial sulcus. Mentolabial sulcus had a positive correlation with the angle of the maxillary incisors in the non-extraction group and the angle of the mandibular incisors in the extraction group. This finding is similar to that of Bloom.[27]

Conclusions

According to the results of the present study, extraction and non-extraction orthodontic treatment has different effects on the soft tissue profile of borderline class I orthodontic patients. In general, skeletal changes were similar in the 2 groups. The greatest difference was in the lips and the upper and lower incisors. In the patients with the extraction treatment plan, the anterior teeth and the upper and lower lips were retracted relative to the sagittal plane, but in the patients with the non-extraction treatment plan, the anterior teeth and the lower lip moved forward relative to the sagittal plane.

Mentolabial sulcus also became shallower after treatment in the extraction group and deeper in the non-extraction group. Considering these findings along with the patients' facial features can be beneficial to the orthodontic treatment planning of borderline patients.

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Evaluation of patient-centered outcomes associated with the acceleration of canine retraction by using minimally invasive surgical procedures: A randomized clinical controlled trial

Ocena korzyści pacjenta związanych z akceleracją cofania kłów po zastosowaniu minimalnie inwazyjnych technik chirurgicznych – randomizowane badanie kliniczne z grupą kontrolną

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Abstract

Background. Only a few studies in the literature have reported patient-centered outcomes associated with minimally invasive corticotomy, and thus, related scientific evidence is limited.

Objectives. The objective of this study was to evaluate patient-centered outcomes associated with upper canine retraction assisted with piezocision or laser-assisted flapless corticotomy (LAFC).

Material and methods. Thirty-two patients (19 females, 13 males) at a mean age of 18.25 ±3.05 years were randomly divided into 2 equal groups: the LAFC group (LG; $n = 16$) and the piezocision group (PG; $n = 16$). In each group, the surgical procedure was randomly assigned to one side of the maxillary arch, and the other side served as the control. Standardized questionnaires using the numerical rating scale (NRS) were distributed to all patients during the 1st month after the surgical procedure at 4 time points: 24 h (T1); 3 days (T2); 7 days (T3); and 14 days (T4). The patients' responses were obtained, regarding their feelings of pain, discomfort, swelling, eating difficulty, jaw movement restriction, analgesic consumption, and satisfaction.

Results. The levels of pain, discomfort, swelling, and difficulty in chewing were significantly greater at the experimental sides as compared to the control sides only at T1 in both groups ($p < 0.05$). The levels of pain and discomfort in LG were significantly lower than those in PG only at T1 ($p = 0.013$ and $p = 0.009$, respectively) whereas there were no significant differences between the groups regarding swelling, eating difficulty, jaw movement restriction, and analgesic consumption. The patients in both groups reported high levels of satisfaction, with no significant differences. The levels of pain, discomfort, swelling, eating difficulty, and jaw movement restriction were dramatically decreased 1 day after flapless corticotomy treatment in both groups ($p < 0.05$).

Conclusions. Both LAFC and piezocision were associated with high levels of pain, discomfort, swelling, and difficulty in chewing at T1. Laser-assisted flapless corticotomy caused less pain and discomfort than piezocision.

Key words: piezosurgery, orthodontic tooth movement, minimally invasive surgical procedures, patient-centered care

Słowa kluczowe: piezochirurgia, ortodontyczny ruch zębów, minimalnie inwazyjne techniki chirurgiczne, opieka skoncentrowana na pacjencie

Introduction

Due to esthetic concerns, the reduction of orthodontic treatment time is considered one of the most important needs of both patients and orthodontists.[1] Corticotomy-assisted orthodontic treatment (CAOT) has been recently introduced as an effective solution for adults who seek accelerated orthodontic tooth movement,[2,3] but it has not met with general approval from patients because of the aggressive nature of corticotomy, and the attendant anxiety and fear of pain.[4] Therefore, several forms of minimally invasive corticotomy have been developed as alternative procedures to traditional corticotomy; these procedures do not need the extensive removal of the cortical bone or full mucoperiosteal flaps, and use innovative tools which cause less trauma. One example is piezocision – a minimally invasive procedure introduced in 2009 by Dibart et al. to overcome the disadvantages of corticotomy.[5] This technique involves performing vertical cuts in the attached gingiva and the alveolar cortical bone without flap elevation using a piezosurgery knife.[5] It has also been suggested that laser-assisted flapless corticotomy (LAFC) might cause less trauma to hard and soft tissues, and result in fewer complications.[6,7]

One of the most important disadvantages of surgical techniques used to accelerate tooth movement is the patient's pain and discomfort.[8] Furthermore, studies have shown that pain is considered a deterrent for orthodontic treatment and an important reason to stop it.[9] It has been claimed that minimally invasive surgical procedures could accelerate orthodontic tooth movement with minimal levels of pain and discomfort, but only a few studies in the literature have reported patient-centered outcomes associated with minimally invasive corticotomy,[10] and related scientific evidence is limited.[11–13] Therefore, the aim of the current trial was to evaluate and compare patient-centered outcomes associated with canine retraction accelerated by using piezocision or LAFC.

Material and methods

Subjects and study design

The local ethics committee of the Dental School at the University of Damascus in Syria approved the protocol of the current trial (UDDS-372-07042015/SRC-2744). The trial was conducted between February 2017 and December 2018. This study was a compound parallel-group randomized controlled trial. Thirty-two patients were allocated randomly to the LAFC group (LG; n = 16) and the piezocision group (PG; n = 16); then, a split-mouth design was applied in each group so that patients could receive canine retraction facilitated with either LAFC or piezocision at the experimental side, with the contralateral side serving as the control (without any intervention). Computer-generated randomization lists with an allocation ratio 1:1 were created by one of the co-authors (O.H.) using Minitab®, v. 17 (Minitab Inc., State College, USA). Allocation was concealed by using a sequentially numbered, opaque, sealed envelope. Blinding was applied only for the outcome assessor, as blinding of the principal researcher and the patients was not possible.

Thirty-two adult patients (19 females, 13 males) at a mean age of 18.25 ±3.05 years who visited the Department of Orthodontics of the Dental School at the University of Damascus, Syria, were recruited into this study. All the patients met the following inclusion criteria: class II division I malocclusion with an indication for the extraction of the upper first premolars (an overjet of 5–10 mm, normal or long face growth patterns); age range between 16 and 29 years; healthy patients with no prior orthodontic treatment; and good oral hygiene (probing depth ≤3 mm, no alveolar bone loss assessed radiographically).

The teeth were leveled and aligned using MBT™ prescription brackets with 0.022-inch slots (JISCOP Co., Ltd., Gunpo-si, South Korea). The upper first premolars were extracted before the fixed appliances were applied and moderate anchorage (soldered transpalatal arch) was used. After the completion of leveling and alignment, and before canine distalization, flapless corticotomy was performed at the experimental side. Once local anesthesia had taken effect, in PG, 2 vertical incisions, each of a length of 10 mm, were made using a No. 15 blade in the attached gingiva distal to the upper canines; then, cortical incisions were made using a piezosurgery knife (BS1, Piezotome®, Implant Center™ 2; Satelec, Mérignac, France) in the alveolar cortical bone with a depth of 3 mm. In LG, an erbium-doped yttrium aluminum garnet (Er:YAG) laser (LightWalker® ST-E; Fotona, Ljubljana, Slovenia) with a R14C handpiece and the Cylindrical Sapphire Tip (diameter: 1.3 mm, length: 8 mm) in the non-contact mode was used to perform both gingival and cortical perforations. Five perforations were conducted distal to the upper canines; each perforation was 1.3 mm wide and away from the other perforation at least 1.5 mm, with a depth of 3 mm. The device settings were as follows: 100 mJ, 10 Hz and 2 W for soft tissue perforations, and then the settings were changed to 200 mJ, 12 Hz and 3 W for cortical perforations. No sutures were applied and antibiotics (Augmentin®, 625-milligram tablets) were prescribed for 5 days in both groups,[14,15] although recent guidelines of the American Dental Association (ADA) indicate that it is not necessary

to administer a prophylactic antibiotic cover following minor surgery in patients with good health and immunity.[16] The patients were instructed to take analgesics (paracetamol, 500-milligram tablets) only when necessary and at least 6 h before filling out the questionnaire. The patients were also asked to record and inform the researcher about the number of paracetamol tablets they took.

Canine retraction was initiated immediately on 0.019 × 0.025-inch stainless steel (SS) wires using 150-gram NiTi closed-coil springs and continued until class I relationship was achieved as shown in Fig. 1. The same researcher (A.M.H.A.) treated all patients in both groups.

Questionnaires

Standardized questionnaires were answered by the patients at chairside as shown in Table 1. The researcher was present to answer any questions raised by the patients while filling out the questionnaire without affecting their responses. The patients' responses were obtained, regarding their perception of pain, discomfort, swelling, eating difficulty, jaw movement restriction, and analgesic consumption at 4 assessment time points: 24 h (T1), 3 days (T2), 7 days (T3), and 14 days (T4) after the onset of canine retraction. The patients were also asked about their levels of satisfaction, whether they would advise a friend to undergo the same surgical intervention, and whether the extraction of the premolars or the surgical intervention was the most annoying experience at the end of the canine retraction stage (T5).

The first 10 questions were related to the perception of pain, discomfort, swelling, difficulty in chewing, difficulty in swallowing, and restriction in jaw movement. The patients recorded their responses using the numerical rating scale (NRS), with 0 and 10 placed at the opposite ends of this scale. With regard to pain assessment, the patients were instructed that 0 would mean 'no pain' and 10 would mean 'the worst pain imaginable'.

Table 1. Questions given to the patients at 5 assessment time points

No.	Question
1	Do you have pain in your mouth or teeth at the surgical intervention side?
2	Do you have pain in your mouth or teeth at the non-operated side?
3	Do you experience discomfort in your mouth or teeth at the surgical intervention side?
4	Do you experience discomfort in your mouth or teeth at the non-operated side?
5	Do you experience swelling in your mouth at the surgical intervention side?
6	Do you experience swelling in your mouth at the non-operated side?
7	Do you experience difficulty in chewing food at the surgical intervention side?
8	Do you experience difficulty in chewing food at the non-operated side?
9	Do you experience difficulty in swallowing?
10	Do you experience restriction in jaw movement?
11	Have you used analgesics for pain from your teeth or jaws? If yes, what dosage did you use?
12	Are you satisfied with your treatment?
13	Would you advise a friend to undergo the same treatment?
14	What was more disturbing to you – the extraction of the premolars or the surgical intervention?

Questions 1–11 were asked at 1 day (T1), 3 days (T2), 7 days (T3), and 14 days (T4) after the onset of canine retraction whereas questions 12–14 were asked at the end of canine retraction (T5).

The same method of recording the patients' experiences on this scale was explained for the rest of the questions. Question 11 was answered with 'yes/no' and a space was provided for writing the amount of consumption in grams. Question 12 was also answered using NRS, but 0 meant 'no satisfaction' and 10 meant 'the best satisfaction'. The questionnaires were analyzed by one of the co-authors (M.A.A.), who was blinded to treatment allocation.

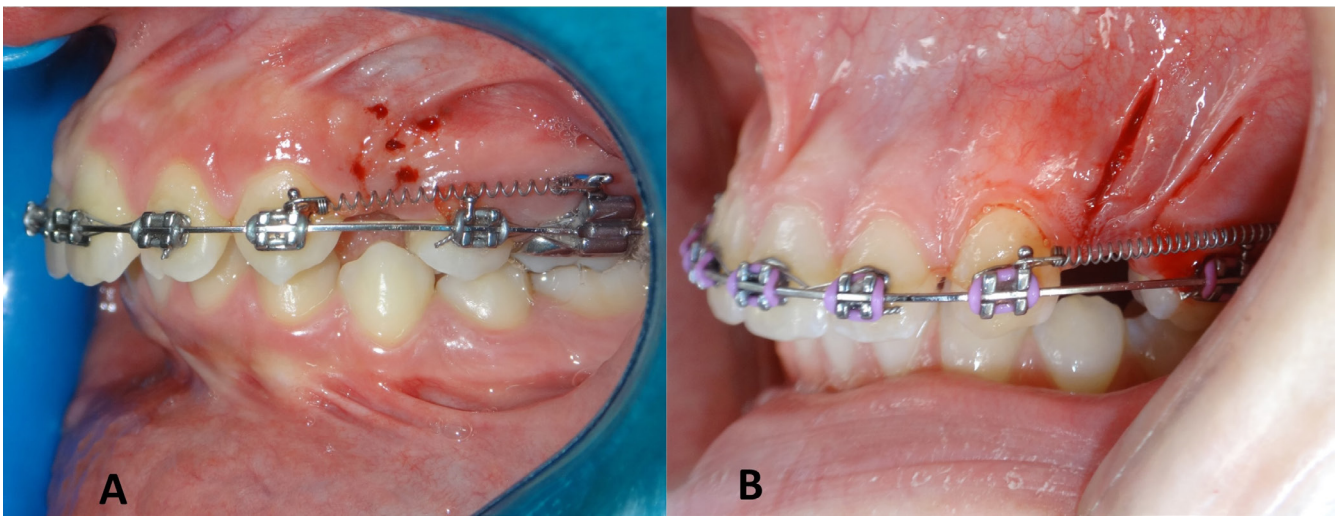

Fig. 1. Canine retraction using NiTi closed-coil springs, facilitated by laser-assisted flapless corticotomy (LAFC) (A) or piezocision (B)

Statistical analysis

The Minitab software, v. 17 was used to calculate the sample size and conduct all statistical analyses by one of the co-authors (M.Y.H.), who was blinded to the data collected in the questionnaires.

The non-parametric Wilcoxon signed-rank tests were used to assess differences within each group between the control and experimental sides. The Mann–Whitney *U* tests were used to detect differences between the 2 groups regarding pain, discomfort, swelling, difficulty in chewing, difficulty in swallowing, restriction in jaw movement, and satisfaction. The χ^2 tests were used to assess differences between the groups concerning the consumption of analgesics, the recommendation of the procedure to a friend, and whether the extraction of the premolars or the surgical intervention was the most disturbing experience. To evaluate changes in the studied variables over time, Friedman's test was used. When a result was significant, the post-hoc Wilcoxon matched-pairs signed-rank tests were employed. Statistical significance was considered when a *p*-value was found less than 5%. For the multiplicity of tests, the Bonferroni correction was employed.

Results

All patients completed their questionnaires and no patient was lost to follow-up. Consequently, LG involved 16 patients (10 females, 6 males) at a mean age of 18.44 ±3.38 years whereas PG involved 16 patients (9 females, 7 males) at a mean age of 18.06 ±2.79 years. There were no significant differences between both group regarding age ($p = 0.711$) and gender ($p = 0.719$). Patient allocation and follow-up are presented in Fig. 2.

Pain and discomfort

The levels of experienced pain and discomfort were significantly greater at the experimental sides as compared to the control sides at T1 in LG ($p = 0.005$ and $p < 0.001$, respectively) and also PG ($p = 0.001$ and $p < 0.001$, respectively) as shown in Table 2 and Fig. 3.

Then, the levels of pain and discomfort perception greatly decreased at the experimental sides to the extent that the differences between the 2 sides were not significant at T2, T3 and T4 in both groups. The levels

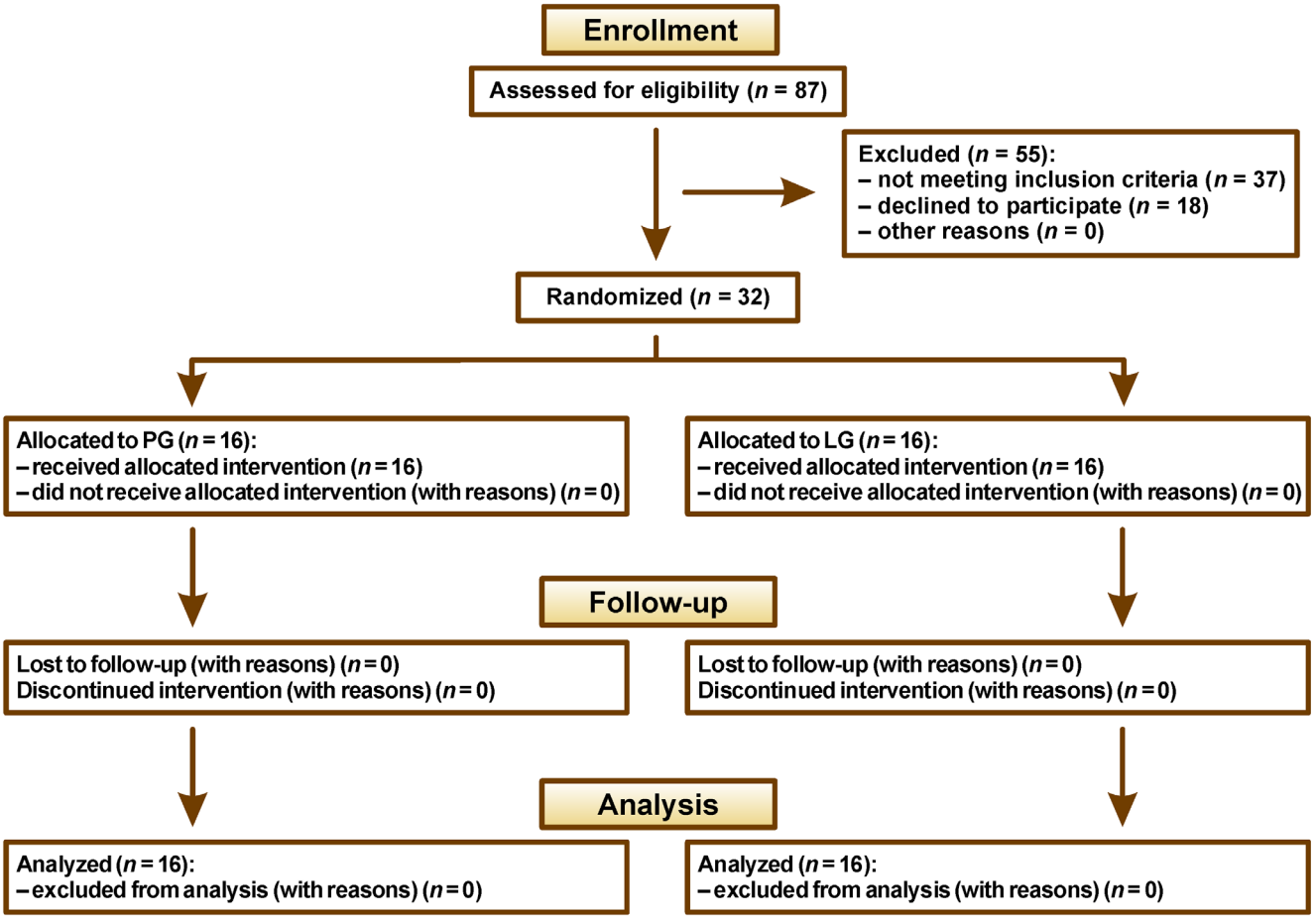

Fig. 2. CONSORT (Consolidated Standards of Reporting Trials) participants' flow diagram

PG – piezocision group; LG – LAFC group.

of pain and discomfort perception in LG were significantly lower than those in PG only at T1 (p = 0.013 and p = 0.009, respectively) whereas there were no significant differences between both groups at the subsequent assessment time points.

Swelling and difficulty in chewing

The levels of swelling and difficulty in chewing were significantly higher at the experimental sides than in the control sides only at T1 in both groups (p < 0.001).

Table 2. Descriptive statistics of the levels of pain, discomfort, swelling, and difficulty in chewing perceived by the patients as well as the *p*-values of significance tests

Time point	Variable	LG (n = 16)					PG (n = 16)					LG vs PG
		experimental side		control side		*p*-value†	experimental side		control side		*p*-value†	*p*-value††
		Me	*IQR*	*Me*	*IQR*		*Me*	*IQR*	*Me*	*IQR*		
T1	pain	4	2–5	2	1–2.75	0.005*	5.5	4–7	1.5	0.25–2.75	0.001**	0.013*
	discomfort	5.5	5–7	3	2–4	<0.001***	8	6–9	4	3–5	<0.001***	0.009**
	swelling	2	1.25–3	1	0–1	<0.001***	3	2–4	1	0.25–2	<0.001***	0.118
	difficulty in chewing	4	3–5	1	1–2	<0.001***	4.5	4–6	2	1–3	<0.001***	0.082
T2	pain	1	0–2	1	0–1	0.106	1.5	1–2.75	1	0.25–1.75	0.100	0.338
	discomfort	3	1.25–4	2	1–2.75	0.096	3	2–4.75	2	1–3	0.065	0.528
	swelling	1	0–2	0.5	0–1	0.070	2	1–2	1	0–2	0.078	0.109
	difficulty in chewing	1	0-2	0.5	0–1	0.073	2	0.25–3	1.5	0–2	0.119	0.194
T3	pain	0	0–1	0	0–1	0.157	1	0–1	0	0–1	0.157	0.695
	discomfort	0	0–1.75	0	0–0.75	0.167	0	0–2	0	0–1	0.121	0.983
	swelling	0	0–0	0	0–0	0.480	0	0–1	0	0–0.75	0.405	0.281
	difficulty in chewing	0	0–1	0	0–0.75	0.272	0.5	0–2	0	0–1	0.155	0.415
T4	pain	0	0–0	0	0–0	0.157	0	0–0	0	0–0	0.317	0.632
	discomfort	0	0–0.75	0	0–0.75	1.000	0	0–0.75	0	0–0	0.317	0.920
	swelling	0	0–0	0	0–0	0.317	0	0–0	0	0–0	0.157	0.551
	difficulty in chewing	0	0–0.5	0	0–0	0.414	0	0–1	0	0–0	0.102	0.544

Me – median; *IQR* – interquartile range; * p < 0.05; ** p < 0.01; *** p < 0.001; † Wilcoxon signed-rank test; †† Mann–Whitney *U* test.

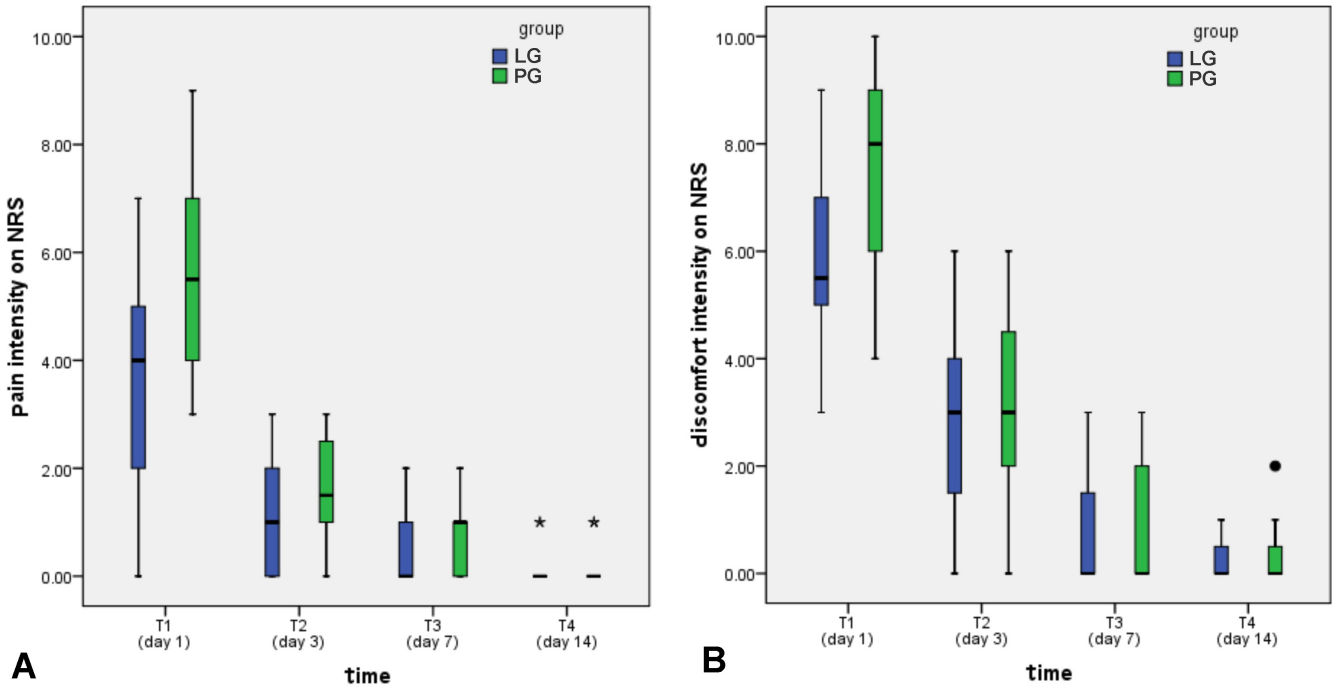

Fig. 3. Box plot showing the levels of pain (A) and discomfort (B) assessed on the numerical rating scale (NRS) in both groups
The asterisks indicate extreme outliers whereas dots indicate outliers.

There were no significant differences between both sides at T2, T3 and T4. There were no significant differences between both groups at all evaluated time points as shown in Table 2 and Fig. 4.

Difficulty in swallowing and jaw movement restriction

There were no significant differences between LG and PG at all evaluated time points (Table 3 and Fig. 5).

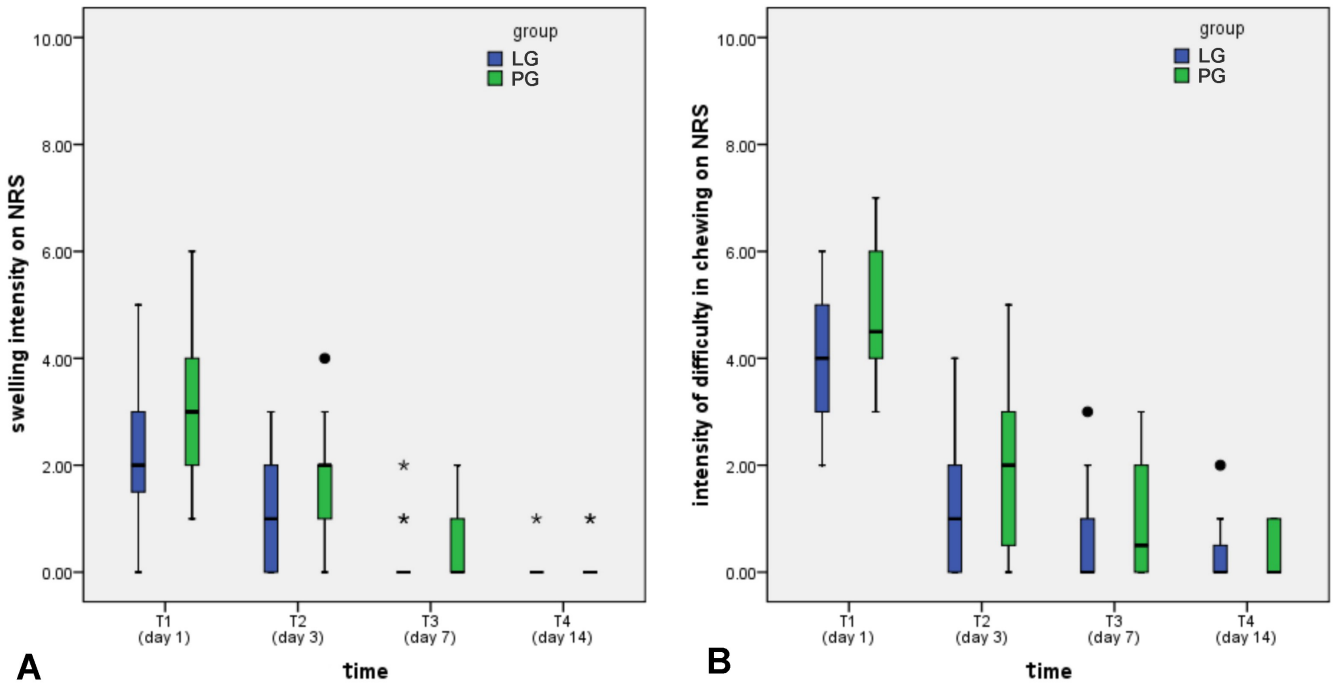

Fig. 4. Box plot showing the levels of swelling (A) and difficulty in chewing (B) assessed on NRS in both groups
The asterisks indicate extreme outliers whereas dots indicate outliers.

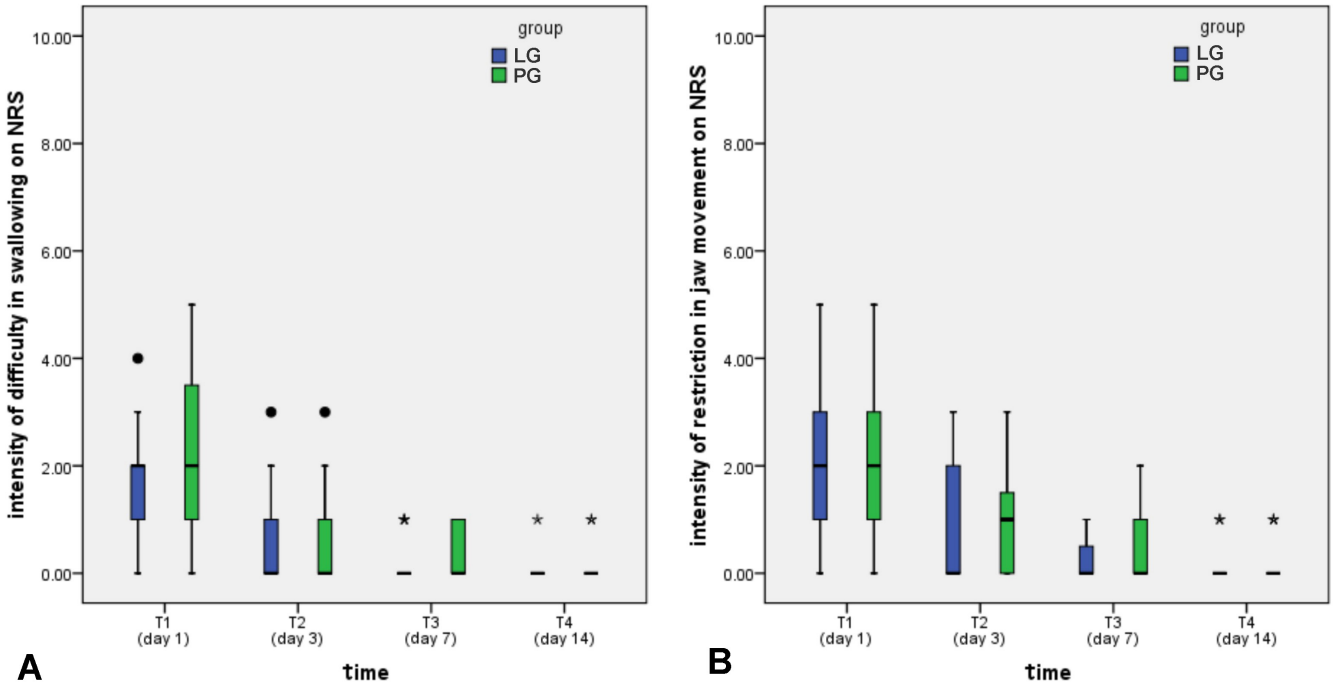

Fig. 5. Box plot showing the levels of difficulty in swallowing (A) and restriction in jaw movements assessed on NRS in both groups
The asterisks indicate extreme outliers whereas dots indicate outliers.

Table 3. Descriptive statistics of the difficulty in swallowing and restriction in jaw movement perceived by the patients as well as the *p*-values of significance tests

Time point	Variable	LG (n = 16)		PG (n = 16)		LG vs PG
		Me	*IQR*	*Me*	*IQR*	*p*-value†
T1	difficulty in swallowing	2	1–2	2	1–3.75	0.236
	restriction in jaw movement	2	1–3	2	1–3	0.877
T2	difficulty in swallowing	0	0–1	0	0–1	0.687
	restriction in jaw movement	0	0–2	1	0–1.5	0.427
T3	difficulty in swallowing	0	0–0	0	0–1	0.422
	restriction in jaw movement	0	0–0.5	0	0–1	0.630
T4	difficulty in swallowing	0	0–0	0	0–0	0.551
	restriction in jaw movement	0	0–0	0	0–0	0.632

† Mann–Whitney *U* test.

Analgesic consumption

The amount of paracetamol consumption was low in both groups, with a maximum of 1g at T1, and did not differ significantly between both groups (Table 4).

Satisfaction and acceptance

The patients reported high levels of satisfaction in both groups; the median value for LG was 10 (interquartile range (*IQR*): 8.25–10) and it was 9 (*IQR*: 7–10) for PG, with no significant differences between the 2 groups. A great proportion of patients in both groups (i.e., 87.5% in LG and 81.3% in PG) reported that they would advise a friend to undergo the same treatment and the difference in proportions between both groups was insignificant (p = 0.626). Additionally, the majority of patients in both groups (i.e., 75% in LG and 68.8% in PG) found that the extraction of premolars was more disturbing than flapless corticotomy and the difference in proportions between both groups was insignificant (p = 0.828).

Changes within groups

The results of Friedman's test showed that there were significant differences between the 4 evaluated time points regarding the levels of pain (p < 0.001, p < 0.001), discomfort (p < 0.001, p < 0.001), swelling (p < 0.001, p < 0.001), difficulty in chewing (p = 0.001, p = 0.001), difficulty in swallowing (p < 0.001, p < 0.001), and restriction in jaw movement (p = 0.001, p = 0.001) for LG and PG, respectively. There were no significant differences in analgesic consumption between the 4 evaluated time points within LG (p = 0.164) whereas the differences were significant within PG (p = 0.002). Post-hoc pairwise comparisons are demonstrated in Tables 5 and 6.

Table 4. Descriptive statistics of analgesic consumption as well as the *p*-values of significance tests

Time point	Amount of paracetamol [g]					Patients taking/not taking analgesics *n* (%)				
	LG (n = 16)		PG (n = 16)		*p*-value†	LG (n = 16)		PG (n = 16)		*p*-value††
	Me	*IQR*	*Me*	*IQR*		yes	no	yes	no	
T1	0	0–0.5	0.5	0–1	0.137	5 (31.3)	11 (68.8)	9 (56.3)	7 (43.8)	0.154
T2	0	0–0	0	0–0.37	0.695	3 (18.8)	13 (81.3)	4 (25.0)	12 (75.0)	0.669
T3	0	0–0	0	0–0	0.551	1 (6.3)	15 (93.8)	2 (12.5)	14 (87.5)	0.544
T4	0	0–0	0	0–0	0.317	1 (6.3)	15 (93.8)	0 (0)	16 (100)	0.310

† Mann–Whitney *U* test; †† χ^2 test. Question 11: Have you used analgesics for pain from your teeth or jaws? If yes, what dosage did you use?

Table 5. Results of the significance tests of pairwise comparisons between the 4 evaluated time points for patient-centered outcomes in the laser-assisted flapless corticotomy group (LG)

Time points	Pain	Discomfort	Swelling	Difficulty in chewing	Difficulty in swallowing	Restriction in jaw movement	Analgesic consumption
T1–T2	0.003*	0.001*	0.017	0.001*	0.033	0.051	0.319
T1–T3	0.001*	<0.001*	0.001*	<0.001*	0.003*	0.003*	0.071
T1–T4	0.001*	<0.001*	0.001*	<0.001*	0.002*	0.002*	0.071
T2–T3	0.097	0.006*	0.018	0.133*	0.129	0.068	0.257
T2–T4	0.006*	0.001*	0.007*	0.019	0.066	0.040	0.083
T3–T4	0.038	0.103	0.257	0.059	0.317	0.414	1.000

The Wilcoxon signed-ranks tests were employed for pairwise comparisons, with the Bonferroni adjustment of alpha level (i.e., 0.05 / 6 = 0.008).
* p < 0.008 (significant difference).

Table 6. Results of the significance tests of pairwise comparisons between the 4 evaluated time points for patient-centered outcomes in the piezocision group (PG)

Time points	Pain	Discomfort	Swelling	Difficulty in chewing	Difficulty in swallowing	Restriction in jaw movement	Analgesic consumption
T1–T2	<0.001*	0.001*	0.004*	0.001*	0.003*	0.026	0.041
T1–T3	<0.001*	<0.001*	0.001*	0.001*	0.002*	0.005*	0.008
T1–T4	<0.001*	<0.001*	0.000*	<0.001*	0.001*	0.001*	0.007*
T2–T3	0.015	0.001*	0.003*	0.039	0.236	0.038	0.180
T2–T4	0.003*	0.001*	0.001*	0.003*	0.039	0.018	0.059
T3–T4	0.046	0.130	0.096	0.101	0.180	0.366	0.157

The Wilcoxon signed-ranks tests were employed for pairwise comparisons, with the Bonferroni adjustment of alpha level (i.e., 0.05 / 6 = 0.008).
* $p < 0.008$ (significant difference).

Discussion

According to our knowledge, this is the first trial in the literature comparing patient-centered outcomes during upper canine retraction associated with piezocision vs LAFC. There were no significant differences between both groups regarding age and gender. Therefore, both groups were homogeneous and comparable. The numerical rating scale was used to answer most of the questions, since this scale has been shown to possess high reliability in comparison with the visual analog scale (VAS).[17–19] The patients' responses were first taken 1 day after flapless corticotomy treatment in both groups. Immediate recording of pain following the intervention was deemed unsuitable due to the possible interference of pain relief resulting from the use of local anesthesia. The main finding was that patients in LG experienced significantly less pain and discomfort at T1 as compared to PG.

The levels of pain and discomfort at the experimental sides were significantly higher than those at the control sides in both groups at T1. These slightly higher levels can be explained by the trauma of the gingiva and the alveolar bone during the implementation of LAFC and piezocision. The levels of pain and discomfort were significantly lower in LG as compared to PG and this could be attributed to the fact that soft tissue incisions in PG were performed with a blade whereas in LG, an Er:YAG laser was used to perform both soft tissue and alveolar bone perforations, which is characterized by less painful cuts in addition to little postoperative pain.[20,21] One of the theories that explains this is that protein coagulation caused by laser cutting seals the sensory nerve endings, and thus relieves the sensation of pain.[22] Furthermore, the fiber tip used in LG was in the non-contact mode; thus, no mechanical pressure was applied to the gingival tissue, as opposed to the traditional blade used in PG.

A significant reduction in pain and discomfort levels was observed after 1 day following the surgical intervention in both groups. Therefore, the differences between the experimental and the control sides were no longer significant. This could be explained by rapid recovery associated with the use of a piezosurgery knife[23] and an Er:YAG laser.[24] Consequently, analgesic consumption was low in both groups. There are no trials in the literature evaluating pain and discomfort while accelerating canine retraction in conjunction with piezocision or LAFC; therefore, a direct comparison with other trials is not straightforward. The levels of pain and discomfort associated with micro-osteoperforations accomplished with the Propel® device were not significant 1 day after canine retraction in Alikhani et al.'s trial,[25] but in the present trial, they were significant. This difference between the 2 studies could be explained by different designs of the surgical intervention as well as different devices employed.

High levels of swelling perception were observed at the experimental sides at T1 for both techniques, which could be attributed to edema resulting from surgical trauma that is associated with such procedures. Additionally, difficulty in chewing was significantly higher at the experimental sides than at the control sides in both groups at T1, and this could be correlated with the encountered pain and discomfort following the surgical intervention. The levels of difficulty in swallowing and restriction in jaw movement were low in both groups, with no significant differences. This can be explained by the conservative nature of the surgical intervention in both groups.

Patients reported high levels of satisfaction and acceptance of the surgical intervention, with negligible differences between both groups. This might be due to the minimally invasive nature of piezocision and LAFC, as they did not require flap raising or suturing like conventional corticotomy. Another factor could be related to the use of innovated tools, which resulted in less trauma and morbidity as compared to the traditional use of surgical burs. These findings are in line with those of Uribe et al.[26] and Charavet et al.,[27] who found that high levels of satisfaction were achieved in patients subjected to piezocision during the leveling and alignment of their teeth. In the present study, the majority of patients in both groups indicated that the extraction of the upper premolars was a more disturbing experience than flapless corticotomy. This could have resulted from the fact that the extraction

of the premolars was performed bilaterally whereas piezocision/LAFC was conducted only at one side of the upper arch. Another factor is the conservative nature of flapless corticotomy employed in this trial.

One of the limitations of this study is its split-mouth design. The patients experienced oral pain or discomfort only from one side of the mouth, which would not reflect the actual picture if the surgical intervention had been carried out at both sides. Therefore, the results of this study cannot be generalized unless a complete procedure mimicking the actual scenario in the daily practice is carried out for patients undergoing canine retraction in the context of orthodontic treatment.

Conclusions

Both piezocision and LAFC were associated with significantly high levels of pain, discomfort, swelling, and difficulty in chewing at 1 day following the intervention. Laser-assisted flapless corticotomy was associated with significantly lower levels of pain and discomfort than piezocision. The levels of pain, discomfort, swelling, eating difficulty, and jaw movement restriction dramatically decreased 24 h after LAFC and piezocision. Both piezocision and LAFC were associated with high levels of satisfaction and acceptance.

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Pharmacological and non-pharmacological management of burning mouth syndrome: A systematic review

Leczenie farmakologiczne i niefarmakologiczne zespołu pieczenia jamy ustnej – przegląd piśmiennictwa

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Abstract

Burning mouth syndrome (BMS) is idiopathic chronic oral pain, associated with depression, anxiety and pain symptoms. The BMS symptoms include a burning sensation in the tongue and/or other oral mucosa with no underlying medical or dental reasons. As many BMS patients suffer from psychiatric comorbidities, several psychotropic drugs are included in the management of BMS, reducing the complaint, while managing anxiety, depression and pain disorders.

In this review, a search of the published literature regarding the management of BMS was conducted. We discuss the BMS etiology, clinically associated symptoms and available treatment options. The current evidence supports some BMS interventions, including alpha-lipoic acid (ALA), clonazepam, capsaicin, and low-level laser therapy (LLLT); however, there is a lack of robust scientific evidence, and large-scale clinical trials with long follow-up periods are needed to establish the role of these BMS management options. This knowledge could raise the awareness of dentists, psychiatrists and general practitioners about these challenges and the available kinds of treatment to improve multidisciplinary management for better health outcomes.

Key words: burning mouth syndrome, neuropathic pain, orofacial pain, clonazepam, oral conditions

Słowa kluczowe: zespół pieczenia jamy ustnej, ból neuropatyczny, ból twarzoczaszki, klonazepam, warunki w jamie ustnej

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Introduction

Burning mouth syndrome (BMS) is oral dysesthesia characterized by a burning sensation in the tongue and/or other oral mucosa. It is associated with dry mouth and taste changes in the absence of clinical/laboratory findings or underlying medical or dental reasons, and it can be debilitating in some patients.[1–3] Burning mouth syndrome is a painful cranial neuropathy, similar to trigeminal neuralgia,[4] with mostly unknown etiology. As described by the international classification of headache disorders, BMS recurs daily for more than 2 h/day over more than 3 months without clinically evident causative lesions; the pain is usually bilateral with fluctuating intensity.[5] The syndrome can also lead to sleep disturbances, especially in the elderly.[6]

Burning mouth syndrome is commonly associated with depression and anxiety.[7] It has a prevalence of 0.7–5% and appears to be more frequent in females,[8] especially in post-menopausal women, where its prevalence is 12–18%.[9] Females report more paresthesia, oral mucosal pain, dysgeusia and xerostomia, while taste changes are less common in males.[10]

Burning mouth syndrome is common in psychiatric patients; there are reports that it affects up to 20% of the older hospitalized psychiatric patients[11–13] and 10–20% of elderly outpatients.[14] It could be associated with oral or systemic abnormalities, such as changes in hormone levels, infections, nutritional disturbances, denture-related lesions, and pharmacological treatment.[15] The BMS characteristics include changes in the mucosal blood flow.[16]

Burning mouth syndrome has been described as a psychosomatic disorder predisposed by psychological stress or neuropathic pain, affecting the peripheral and central nervous system in the trigeminal pathways,[3] the prefrontal cortex and the hippocampus.[17] Patients with BMS process thermal stimulation differently, with changes in tactile sensory functions, including a lower threshold for cold detection, while warmth, heat and pain detection thresholds are higher.[18–20]

Immune and endocrine functions are also involved in BMS; a lower level of plasma adrenaline, a low level of $CD8^{(+)}$ cells and a high $CD4^{(+)}/CD8^{(+)}$ ratio represent a suppressed immune system.[21] A significant increase in the genetic polymorphisms associated with interleukin-1β (IL-1β) has also been suggested.[22]

Changes in scores on psychiatric assessment scales have been identified. With the Temperament and Character Inventory(TCI), BMS patients have lower novelty-seeking scores and self-directedness scores, while their harm-avoidance scores are higher.[23] A Visual Analog Scale (VAS) study supported higher frequencies of depression, anxiety and cancer phobia in BMS patients.[24] This is reflected in the F3 classification of BMS as a mood/affective disorder.[25]

Risk factors for developing BMS include stroke, a low level of education, depression, life events, anxiety, personality disorders, the excessive use of hexetidine mouthwashes, and vitamin deficiency.[26,27] Burning mouth syndrome is common in Parkinson's disease, characterized by dopamine dysregulation, especially in the nigrostriatal dopaminergic pathway, as confirmed by positron emission tomography (PET).[28,29]

Material and methods

A literature search for studies investigating different forms of BMS management was performed in PubMed, European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials (CENTRAL), using the Population/Interest/Context (PICO) framework and the following search terms: "burning mouth syndrome", "BMS", "alpha-lipoic acid" AND "burning mouth syndrome", and "clonazepam" AND "burning mouth syndrome".[30] No restrictions on the study size, year or duration were set. Titles were screened for relevance and duplicates were removed, while abstracts were screened according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[31] Trials that investigated the efficacy of different management approaches for BMS were included (Tables 1,2). The study populations included adult patients undergoing pharmacological or non-pharmacological treatment compared to placebos/controls for BMS management, with randomized controlled trials (RCTs) and case studies screened for relevancy.

Outcome measures

The primary efficacy outcome was the improvement in the VAS and Oral Health Impact Profile (OHIP) scores. Pharmacological management included alpha-lipoid acid (ALA), clonazepam, capsaicin, amisulpride, fluoxetine, trazodone, milnacipran, St. John's wort (*Hypericum perforatum* extract), melatonin, bupivacaine, benzydamine, and lidocaine lingual nerve injection (Table 1).

Results

Pharmacological management of burning mouth syndrome

As BMS appears to be associated with psychiatric comorbidities, a number of psychotropic drugs are used in its management, including antidepressants and clonazepam (Table 1)[2]; psychotherapy has also been used (Table 2).

Table 1. Pharmacological management of burning mouth syndrome (BMS)

Medication	Study	Dose	Efficacy assessment	Control	No. of patients	Main findings	Side effects
Alpha-lipoic acid	Carbone 2009[33]	400 mg BID	– change in VAS – responders	Pla	16 ALA 20 Pla	– ALA: 2.00 ±2.59 vs Pla: 1.60 ±2.41 – ALA: 4/16 vs Pla: 5/20	–
	López-Jornet 2009[34]	800 mg/day	change in VAS	Pla	23 ALA 16 Pla	ALA: 2.2 ±2.6 vs Pla: 3.8 ±3.7 no sign differences	ALA: 1 case of GI side effects
	Marino 2010[35] (open-label study)	800 mg/day	– change in VAS – improvement	Pla	14 in each group	– ALA: –2.1 ±2.5 vs Pla: 0.5 ±2.2 – ALA: 8/14 vs Pla: 0/14	no side effects reported
	Femiano 2000[36]	600 mg/day for 20 days, then 200 mg/day	improvement	Pla	21 in each group	ALA: 16/21 Pla: 3/21 crossover to ALA 63% improved	–
	Femiano 2002[37]	200 mg TID	improvement	Pla	30 in each group	ALA: 29/30 Pla: 12/30	–
	Femiano 2002[38]	200 mg TID	improvement	Pla	22 in each group	ALA: 20/22 Pla: 8/22 definite ALA: 16/22 Pla: 0/22	–
	Femiano 2002[39]	200 mg TID	improvement	Bet Lac Pla	20 in each group	ALA: 18/20 Bet: 0% Lac: 0% Pla: 0%	ALA: GI side effects (4/20) Bet: nausea, dizziness, blood pressure fall
	Femiano 2004[40]	600 mg/day	improvement	ALA Psy Com Pla	48 in each group	ALA: 39/58 Psy: 19/48 Com: 43/48 Pla: 6/48	–
	López-D'Alessandro 2011[41]	ALA: 600 mg/day Gab: 300 mg/day	improvement	ALA Gab Com Pla	20 ALA 20 Gab 20 Com 60 Pla	ALA: 11/20 Gab: 10/20 Com: 14/20 Pla: 9/60	–
	Palacios-Sánchez 2015[42]	200 mg TID for 2 weeks	improvement	Pla	25 ALA 29 Pla	ALA: 16/25 Pla: 8/29	–
	Cavalcanti 2009[43]	200 mg TID	improvement	Pla	17 ALA 14 Pla	ALA: 14/17 Pla: 11/14	ALA: gastric headache
Clonazepam	Gremeau-Richard 2004[47]	topical 3 mg/day	change in VAS	Pla	24 in each group	a significant decrease in pain scores Clo: –2.4 ±0.6 vs Pla: –0.6 ±0.4	–
	Heckmann 2012[48]	0.5 mg/day	BDI	Pla	10 in each group	a significant decrease regarding pain Clo: –3.5 ±2.9 vs Pla: –1.4 ±2.4	–
	Rodríguez de Riveira Campillo 2010[49]	0.5 mg mouth-dissolving tablet	– change in VAS – improvement	Pla	33 in each group	– a decrease in pain scores Clo: 4.8 vs Pla: 3.3 – Clo: 70% vs Pla: 13%	–
	Barker 2009[50] (follow-up study)	Clo: 0.25 mg BID Dia: 2 mg BID	improvement	–	21 Clo 70 Dia	Clo: partial or complete resolution of symptoms in 71.4% of patients Dia: partial or complete resolution of symptoms in 55.1% of patients	–
	Fenelon 2017[98]	–	VNS	Amit	23 Clo drops 16 Amit	Clo: –2.7 ±2.0 vs Amit: –3.4 ±2.7 both effective (no difference between the 2 kinds of treatment)	–
	De Castro 2014[99]	oral rinse 1 mg/10 mL	change in VAS	–	16	a decrease in the VAS scores from 5.56 ±2.77 to 3.50 ±3.19	–

Continued Table 1

Medication	Study	Dose	Efficacy assessment	Control	No. of patients	Main findings	Side effects
Capsaicin	Marino 2010[35] (open-label study)	oral rinse TID	change in VAS	Pla	14 in each group	Cap: –3.2 ±2.6 vs Pla: 0.5 ±2.2	–
	Petruzzi 2004[53]	oral rinse 0.25% TID	– change in VAS – improvement	Pla	25 in each group	– Cap: a greater decrease in VAS scores – Cap: 76% vs Pla: 4%	Cap: gastric pain (8/25)
	Lauritano 2003[54]	3× 50 mg of red pepper powder with 0.25% of Cap	change in VAS	Pla	42 in each group	high VAS scores (8–10) Cap: 5% (2/42) Pla: 57% (24/42)	–
	Toida 2009[55]	Laf 10 mg BID	improvement	Pla	34 Laf 30 Pla	Laf: a greater decrease in VAS scores	Laf: mild abdominal pain (2/34)
	Jørgensen 2017[96]	Cap gel at 2 different doses 0.01% or 0.025%	change in VAS	–	9 in each group, no Pla	0.01%: –1.7 ±2.3 vs 0.025%: –1.0 ±2.8	4 cases of GI side effects
	Silvestre 2012[97]	oral rinse TID	change in VAS	Pla	15 in each group	significant differences (data not extractable)	–
Amisulpride	Maina 2002[73]	Ami: 50 mg/day Par: 20 mg/day Ser: 50 mg/day	– change in VAS – Ham-D – responders	Ami Par Ser	27 Ami 26 Par 23 Ser	– Ami: –4.0 ±1.2 vs Par: –3.7 ±1.2 vs Ser: –4.4 ±1.0 – Ami: –3.3 ±2.4 vs Par: –3.1 ±2.4 vs Ser: –3.5 ±2.6 – Ami: 19/27 vs Par: 16/26 vs Ser: 13/23	Ami: no withdrawal Par: 3 (11.5%) Ser: 5 (21.7%) insomnia: Ami: 3/27 Par: 1/26 Ser: 1/23 Ami: anxiety (4/27), tremor (3/27)
Fluoxetine	Zoric 2018[100]	20 mg/day	– change in VAS – BDI – improvement – Ham-D	Pla	50 in each group	– Flu: –4.0 ±2.5 vs Pla: –3.3 ±2.8 – Flu: –5.6 ±6.0 vs Pla: –1.8 ±5.6 – Flu: 39/50 vs Pla: 25/50 – Flu: –5.4 ±5.3 vs Pla: –2.4 ±8.1	Flu: nausea, dizziness, headache
Trazadone	Tammiala-Salonen 1999[101]	100 mg/day, then 200 mg/day	change in VAS	Pla	11 Tra 17 Pla	no significant differences	Tra: dizziness, drowsiness
Milnacipran	Kato 2011[65] open-label study	30 mg/day, increasing to 90 mg/day for 12 weeks	improvement	–	56 females	at 30 mg/day – 28.6%, and it rose as the daily dose increased (50.8–67.9%)	–
	Ito 2010[66]	–	change in VAS	–	22	a significant decrease in VAS scores	–
	Sugimoto 2011[67]	60 mg/day	– Ham-D – change in VAS	–	12	– a significant decrease in Ham-D – no changes in pain, VAS and GOHAI scores	–
St. John's wort	Sardella 2008[102]	900 mg/day	change in VAS	Pla	21 SJ 22 Pla	fewer oral sites affected by symptoms SJ: –2.30 vs Pla: –1.25 no sign differences	SJ: 1 case of headache
Melatonin	Varoni 2018[103]	–	change in VAS	Pla	20 in each group	Mel: 0.6 ±0.4 vs Pla: 1.2 ±0.5	–
Bupivacaine	Treldal 2016[104]	5 mg TDI	change in VAS	Pla	18 in each group	treatment more effective –6.8 (–8.6, –4.9)	–
Benzydamine	Sardella 1999[105]	oral rinse 0.15%	improvement	Pla	30 in each group	Ben: 1/10 vs Pla: 2/10 no significant differences	–
Lidocaine lingual nerve injection	Grémeau-Richard 2018[106]	–	change in VAS	Pla	20 in each group	Lid: –2.7 ±3.9 vs Pla: 2.0 ±2.6 no significant improvement	–

BID – twice a day; VAS – Visual Analog Scale; ALA – alpha-lipoic acid; Pla – placebo; GI – gastrointestinal; TID – 3 times a day; Bet – bethanol; Lac – lactoperoxidase; Psy – psychotherapy; Com – combination; Gab – gabapentin; Clo –clonazepam; BDI – Beck Depression Inventory; Dia – diazepam; VNS – Visual Numeric Scale; Amit – amitriptyline; Cap – capsaicin; Laf – lafutidine (capsaicin analog); Ami – amisulpride; Par – paroxetine; Ser – sertraline; Ham-D – Hamilton Depression Rating Scale; Flu – fluoxetine; Tra – trazadone; GOHAI – General Oral Health Assessment Index; SJ – St. John's wort; Mel – melatonin; Ben – benzydamine; Lid – lidocaine.

Table 2. Non-pharmacological management of burning mouth syndrome (BMS)

Medication	Study	Efficacy assessment	Control	No. of patients	Main findings	Side effects
Lasers	Barbosa 2018[45]	– changes in VAS – salivary flow	ALA	10 LLLT 5 ALA	– LLLT: −2.0 vs ALA: −3.5 – LLLT: 0.2 vs ALA: 0.1	no side effects reported
	Arbabi-Kalati 2015[78]	– changes in VAS – QoL	Pla	10 females in each group	– LLLT: −4.4 ±3.0 vs Pla: −0.2 ±1.5 – LLLT: −15.0 ±11.4 vs Pla: 0.3 ±11.5	–
	Spanemberg 2015[79]	– change in VNS – change in VAS – OHIP	3 groups vs Pla	20 LLLT I 20 LLLT II 19 LR 19 Pla	– LLLT I: −5.00 ±2.52 vs LLLT II: −5.00 ±2.31 vs LR: −3.76 ±2.68 vs Pla: −2.95 ±1.70 – LLLT I: −53.95 ±27.20 vs LLLT II: −48.05 ±24.00 vs LR: −35.79 ±28.30 vs Pla: −18.90 ±19.80 – LLLT I: −5.23 ±5.10 vs LLLT II: −5.98 ±4.05 vs LR: −4.69 ±4.95 vs Pla: −3.41 ±3.62	no side effects reported
	Spanemberg 2019[80]	change in VAS	Pla	12 LLLT 9 Pla	LLLT: −4.2 vs Pla: −3.2	–
	Valenzuela 2017[81]	– change in VAS – OHIP	2 groups vs Pla	16 LLLT I 16 LLLT II 12 Pla	– LLLT I: −1.18 ±1.60 vs LLLT II: −1.32 ±1.80 vs Pla: −0.18 ±1.60 – LLLT I: −1.30 ±3.10 vs LLLT II: −1.30 ±6.10 vs Pla: −0.08 ±5.10	no side effects reported
	Bardellini 2019[82]	– changes in VAS – OHIP	Pla	43 LLLT 42 Pla	– significant improvement – LLLT: 9.00 ±4.20 vs Pla: −4.87 ±3.75	–
	Sugaya 2016[109]	complete remission	Pla	13 LLLT 10 Pla	LLLT: 6/13 vs Pla: 4/10	–
	Antonić 2017[110]	change in VAS	2 lasers 660 nm and 810 nm	20 in each group	−2.5 vs −2.0 improvement in both cases	–
	dos Santos 2015[111]	change in VAS	prospective study	20	LLLT effective	–
	dos Santos 2011[112]	change in VAS	10 patients follow-up	–	a reduction in the VAS scores by 58%	–
	Brailo 2013[113]	change in VAS	16 patients follow-up	–	a decrease in burning by 55.2%	–
	Arduino 2016[114]	– change in VAS – MPQ – OHIP	topical Clo	18 LLLT 15 Clo	– LLLT: −2.78 ±4.80 vs Clo: −1.15 ±1.80 – LLLT: −10.05 ±4.80 vs Clo: −11.00 ±4.80 – LLLT: −11.06 ±32.10 vs Clo: 4.40 ±43.00	Clo: fever, dizziness and headache in 32% of patients
	Sikora 2018[115]	change in VAS	data not extractable	–	–	–
Psychotherapy	Femiano 2004[40] CBT (two 1-hour sessions per week)	improvement	ALA Psy Com Pla	48 in each group	ALA: 39/48 Psy: 19/48 Com: 43/48 Pla: 6/48	–
	Miziara 2009[83]	improvement	Pla	24 Psy 20 Pla	Psy: 17/24 Pla: 8/20	–
	Bergdahl 1995[116] 1 h/week	pain symptoms using VAS	Pla	15 in each group	Psy: 27% symptom-free (4 pts) vs Pla: none a decrease in pain scores Psy: 2.8 vs Pla: 0.3	–
	Komiyama 2013[117] (not a trial)	pain symptoms	no comparison	–	group intervention helpful in persistent pain	–
Acupuncture	Juriscic Kvesic 2015[107]	– change in VAS – BDI	Clo	19 in each group	– Acu: −3.0 ±3.0 vs Clo: 3.0 ±2.0 – Acu: −5.0 ±4.1 vs Clo: 7.0 ±4.8	Clo: nausea, dizziness, drowsiness
	Zavoreo 2017[108]	– change in VAS – OHIP – Ham-D	vitamin C	21 in each group	– Acu: 1.5 ±2.7 vs Vit.C: 0.8 ±2.7 – Acu: 9.9 ±7.4 vs Vit.C: 3.1 ±8.4 – Acu: 3.9 ±4.7 vs Vit.C: 3.9 ±4.8	–

LLLT – low-level laser therapy; QoL – quality of life; OHIP – Oral Health Improvement Profile; LR – Laser Red; MPQ – Multiple Personality Questionnaire; CBT – cognitive behavioral therapy; Acu – acupuncture; Vit.C – vitamin C.

Alpha-lipoic acid

Alpha-lipoic acid is a free-radical scavenger, and its metabolite – dihydrolipoic acid – has antioxidant properties and can regenerate endogenous antioxidants (vitamin E, vitamin C and glutathione).[32] Alpha-lipoic acid is considered an effective medication for BMS management, as highlighted by the evidence obtained from trials measuring its efficacy by means of various methods,[33–44] with some heterogeneity among the studies (Table 1). An interesting comparison with low-level laser therapy (LLLT) showed that both LLLT and ALA were efficient in treating BMS.[45]

Benzodiazepines

Benzodiazepines are hypnotics/sedatives that potentiate the action of the inhibitory neurotransmitter gamma aminobutyric acid (GABA).[46] We found 3 trials that compared the efficacy of clonazepam against a placebo using the VAS scores.[47–49] The overall results proved the effectiveness of clonazepam, as highlighted by a significant reduction in the VAS scores. Systemic clonazepam presented the best efficacy, with more than 70% of patients showing the partial or complete resolution of their oral symptoms as compared to just over 55% of patients on diazepam.[50] Topical clonazepam was also effective, and considered more cost-effective than amisulpride, paroxetine and sertraline,[51] while prazepam showed some efficacy as well.[52]

Capsaicin

We found 4 studies that measured the efficacy of capsaicin.[35,53–55] The overall results showed a positive effect and a possible beneficial role of capsaicin in BMS management.

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) have low side-effect profiles and are particularly efficient in psychogenic BMS management.[56] At low doses, they inhibit serotonin reuptake, and at high doses, they may inhibit noradrenaline reuptake as well.[46] There have not been many trials pitting SSRIs against a placebo or control medication (Table 1), and most of the available evidence comes from case studies. Sertraline, a widely used antidepressant, resulted in a reduction in the severity of stomatodynia.[57] Paroxetine proved to be efficacious, with complete pain remission in more than 70% of patients.[58] In 1 study, painful burning sensations were elicited with fluoxetine treatment, and citalopram used as an alternative led to the remission of BMS associated with depression.[59] On the other hand, clomipramine reduced pain in BMS patients at a level similar to a placebo.[60]

Venlafaxine and duloxetine are serotonin-norepinephrine reuptake inhibitors (SNRIs). Venlafaxine with clonazepam were successful in patients unresponsive to anticonvulsants and antidepressants.[11] Duloxetine was observed to significantly relieve pain in case reports, and led to symptom remission and improvement in the quality of life (QoL).[61,62] Moclobemide is a reversible inhibitor of monoamine oxidase, and it reduced anxiety, depression and the VAS scores among BMS patients.[63]

Milnacipran blocks serotonin and norepinephrine reuptake. It has a simple pharmacokinetics profile and no inhibitory effects on cytochrome P450 enzymes, so it is recommended for patients with multiple treatment regimens.[64] Low-dose milnacipran (30 mg daily) had a poor response; the cumulative improvement rate increased to 68% when the daily dose was increased from 60 mg to 90 mg.[65] Milnacipran reportedly brought about significant reductions in the VAS scores,[66] reduced depression and improved patients' QoL,[67] but there have not been enough trials comparing milnacipran to a placebo or control medication (Table 1). Most of the available evidence of the efficacy of milnacipran comes from case studies, such as that of a 71-year-old with no satisfactory response to psychotropic drugs who recovered from BMS when sertraline was replaced with milnacipran.[68]

Antipsychotics and anti-Parkinson medications

For antipsychotics and anti-Parkinson drugs, there is not enough data comparing a placebo or control medication with these medications, and most of the evidence comes from case studies. Olanzapine, an antipsychotic, caused rapid significant improvement in treating BMS,[69] even in patients unresponsive to milnacipran or paroxetine.[70] Aripiprazole ameliorated chronic burning pain,[71] while levosulpiride and amisulpride alleviated oral symptoms.[72,73] A case of refractory BMS showed complete relief after treatment with pramipexol.[74] The BMS symptoms also responded to levodopa.[7]

Anticonvulsants

Pregabalin was successful in patients unresponsive to milnacipran or duloxetine.[75] Gabapentin – a structural analog of GABA – reduced oral burning, while nortriptyline and sertraline were contraindicated.[76] However, another study failed to confirm the efficacy of gabapentin in BMS.[77]

Non-pharmacological management of burning mouth syndrome

The most common non-pharmacological interventions are LLLT, psychotherapy and acupuncture.

We found 4 trials measuring the efficacy of LLLT using the VAS scores[78–81] and 3 trials measuring its efficacy

using OHIP (Table 2).[79,81,82] The overall results showed positive effects on both VAS and OHIP. Interestingly, a comparison with ALA showed similar efficacy.[45]

Two trials measured the efficacy of psychotherapy in alleviating the BMS symptoms,[40,83] but there have not been enough trials studying the efficacy of acupuncture as compared to a placebo or control medication (Table 2).

Discussion

Both the diagnosis and management of BMS are unclear.[3] Burning mouth syndrome is known as a chronic condition with pain intensity increasing from morning to evening.[84] The tongue is the most commonly affected site, followed by the lower lip and the hard palate.[84] Burning mouth syndrome could be due to immunological or endocrine etiology, and some recent evidence suggests neurophysiological mechanisms, such as a peripheral small-fiber neuropathy or central neuropathic disturbances.[9] Risk factors include metabolic disorders, vitamin deficiencies[85] or medications, i.a., angiotensin-converting enzyme inhibitors and anticoagulants.[86]

The prevalence of BMS can be especially high in psychiatric patients,[87] and it is associated with comorbidities such as depression and anxiety.[88] Assessment and outcome measurements include the VAS scores, QoL ratings, taste, and the salivary flow.[2]

Multiple kinds of pharmacological treatment have been tried, including ALA, milnacipran, benzodiazepines, antidepressants, anticonvulsants, and atypical antipsychotics (Table 3).[87] Topical clonazepam is used for peripheral BMS, while central BMS is managed with antidepressants, anti-seizure medications or antipsychotics,[89] but the evidence of their efficacy is weak, as the power of the studies and the numbers of patients have been relatively low, and most studies have had short follow-up periods with high variability.

Burning mouth syndrome could have a neuropathic origin, and experts recommend neuropathic pain agents, such as amitriptyline, gabapentin, benzodiazepines, antipsychotics,[90] or mood-altering interventions.[91] Our study highlights that ALA, clonazepam and capsaicin may bring promising results (Table 4); however, more studies are needed, with longer follow-up periods and larger numbers of patients. Alpha-lipoic acid and clonazepam have shown modest evidence of decreasing BMS.[92] The overall quality of the evidence of effectiveness remains low for all pharmacological and non-pharmacological interventions.

Our review has some limitations. There was high heterogeneity among the studies and there were few clinical trials for most of the management options. Different methods were used to present the findings, while some trials had missing data (Tables 1,2).

Combination treatment has shown promising results. Alpha-lipoic acid with gabapentin,[41] sertraline with cognitive behavioral therapy,[93] and tranylcypromine with low-dose anxiolytics and psychotherapy have been effective in refractory BMS.[94] Non-pharmacological interventions, such as LLLT or psychotherapy, have shown some efficacy. However, large-scale clinical trials with long follow-up periods are still needed to confirm these findings.[89] Treatment should be tailored with careful history-taking and consultations among a variety of health professionals, including psychiatrists, dentists, pain specialists, and neurologists with a special interest in headaches, to avoid potential delays in diagnosis.[85,95] A clinical diagnosis should include the assessment of the nutritional status and comprehensive dental evaluation.[96] The management of BMS should include managing anxiety, depression and pain disorders, ruling out treatable conditions,

Table 3. Summary of the available evidence for the pharmacological management of burning mouth syndrome (BMS)

Medication	As per current clinical research
Alpha-lipoic acid	Positive outcome demonstrated with improvement in the VAS scores in several trials; however, RCT failed to support its role – further research needed.
Milnacipran	Weak scientific evidence that milnacipran (60–90 mg) could result in a significant reduction in the VAS scores.
Benzodiazepines	Research suggests the efficacy of systemic clonazepam or its application in the form of oral rinse – large clinical trials still needed to confirm.
Antidepressants	Scientific evidence mostly from case studies. Sertraline and paroxetine were efficacious with a reduction in the severity of BMS. In case reports, venlafaxine and duloxetine significantly relieved pain. Moclobemide reduced anxiety, depression and the VAS scores.
Antipsychotics and anti-parkinsonism medications	In case studies, olanzapine and aripiprazole caused improvement – RCTs lacking. Weak scientific evidence for the efficacy of amisulpride. Case studies highlighted pramipexol and levodopa as promising medications.
Anticonvulsants	Case studies highlighted gabapentin and pregabalin as promising medications despite the presence of some contradictory results. One clinical trial highlighted the possible efficacy of gabapentin, especially in combination with ALA.

RCT – randomized clinical trial.

Table 4. Characteristics of the main pharmacological therapies for the management of burning mouth syndrome (BMS)

Medication	Dosage	Duration	Possible side effects
Alpha-lipoic acid	600–800 mg/day in 2–3 divided doses	2–4 weeks	rare minor abdominal pain, headache, and rarely hypersensitivity
Clonazepam	oral tablets 0.5 mg/day	2–4 weeks	fatigue, muscle weakness, nausea, somnolence, rash, headache, and impaired concentration
	oral rinse 1 mg/10 mL	2–4 weeks	
Capsaicin	systemic 0.25%	2–4 weeks	mild abdominal pain, and rarely hypersensitivity
	oral rinse 0.025% TID	2–4 weeks	
Milnacipran	30–90 mg/day	2–4 weeks	dizziness, hot flash, nausea, insomnia, palpitations, rash, headache, and xerostomia

and discussing different management options with the patient.[97] Non-pharmacological interventions could be tried first, if clinically appropriate, and compatible with the patient's preferences and the severity of the symptoms. If pharmacotherapy is appropriate, ALA or capsaicin could be first choice because of favorable side-effect profiles, while clonazepam or milnacipran could be second-line medications for BMS management due to their side effects – particularly cognitive ones – and an increased risk of dependence associated with benzodiazepines.

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Effectiveness of different adjunctive interventions in the management of orthodontically induced white spot lesions: A systematic review of systematic reviews and meta-analyses

Skuteczność różnych metod leczenia poortodontycznych białych plam próchnicowych – przegląd systematyczny z przeglądów systematycznych i metaanaliz

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Abstract

The purposes of this review were to appraise the current evidence on the management of orthodontically induced white spot lesions (OIWSLs) and to choose the best evidence from among conflicting systematic reviews.

The published literature was searched from inception through November 2019 in 5 databases. Only systematic reviews and/or meta-analyses were eligible for inclusion. Methodological quality was assessed using A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2). The Jadad decision algorithm was applied to choose the best available evidence from among discordant reviews.

Thirteen publications were included. The interventions reported in the management of OIWSLs were topical fluorides, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP)-containing products, fluoride-containing bonding materials, laser therapy, resin infiltration, and micro-abrasion. The methodological quality of the reviews ranged between moderate and critically low according to the AMSTAR-2 tool. Based on the Jadad decision algorithm criteria, topical fluorides yielded a 25–30% prevention of OIWSLs; however, their effect on reversing OIWSLs was unclear. The CPP-ACP products were effective in both preventing and reversing OIWSLs. No differences were noted between fluoride-releasing adhesives and conventional adhesives. Laser irradiation was effective in preventing OIWSLs, with some concerns about the argon laser at a certain setting. Finally, there is a lack of reliable evidence supporting the efficacy of resin infiltration or micro-abrasion due to the limited number of available studies.

Based on the currently available information, topical fluorides and laser irradiation are effective in preventing OIWSLs. The CPP-ACP products are effective in preventing and reversing OIWSLs. Fluoride-releasing adhesives have no effect on OIWSL prevention.

Key words: orthodontics, dental care, tooth demineralization, tooth remineralization, white caries spot

Słowa kluczowe: ortodoncja, opieka stomatologiczna, demineralizacja zębów, remineralizacja zębów, biała plama próchnicowa

Introduction

Achieving optimal occlusion with minimal treatment complications is an essential demand for orthodontic treatment.[1] Orthodontically induced white spot lesions (OIWSLs) are considered one of the most prominent complications, with a prevalence of 68.4% in patients undergoing multi-bracketed fixed orthodontic treatment.[2] This high percentage of prevalence is due to the irregular and non-uniform surfaces of fixed appliances, which can encourage plaque stagnation and limit natural self-cleansing mechanisms (Fig. 1,2).[3–5]

Primarily, patients seek orthodontic treatment in an attempt to improve function and esthetics.[4] However, these common white, chalky, opaque spots with limited spontaneous reversibility may seriously jeopardize esthetic appearance and the patient's satisfaction with the results of treatment.[4,6,7] Worse still, untreated white spot lesions (WSLs) may lead to tooth cavitation, requiring a subsequent restorative procedure.[8]

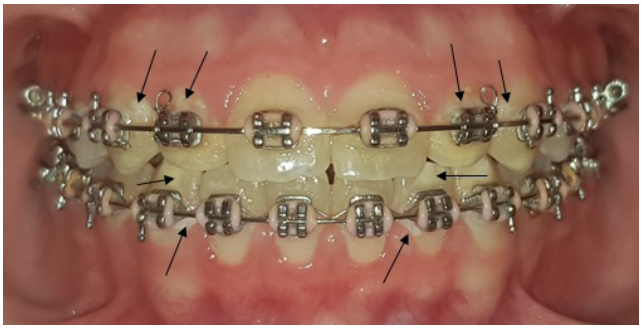

Fig. 1. Clinical case undergoing multi-bracketed fixed orthodontic treatment and developing several orthodontically induced white spot lesions (OIWSLs)

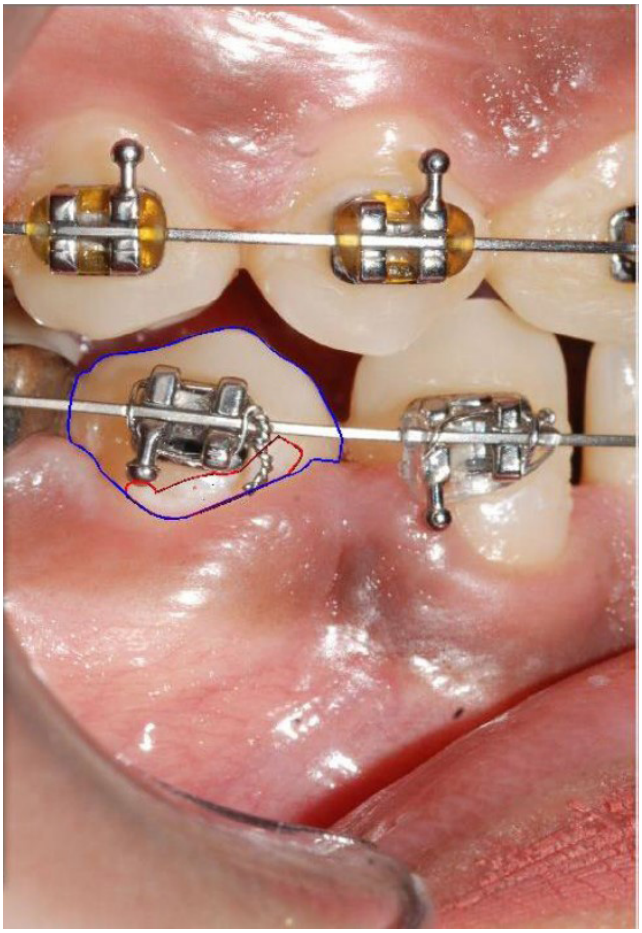

Fig. 2. Orthodontically induced white spot lesion (OIWSL)

It is important to differentiate OIWSLs from other, non-carious white spots, such as fluorosis, developmental enamel hypomineralization or enamel hypoplasia. Firstly, OIWSLs are typically found on the buccal tooth surfaces and around the perimeter of orthodontic brackets whereas non-carious spots usually cover the entire tooth surface and are not associated with orthodontic treatment.[9,10] Secondly, the consistency and texture of the surface of a clean, dry tooth can be gently assessed with a periodontal probe. Orthodontically induced white spot lesions appear rough, opaque and porous, while non-carious lesions appear mostly smooth and shiny.[10]

Numerous research projects have been conducted on the effectiveness of various interventions in the management of OIWSLs. Mainly, the approaches involved either preventing the formation of lesions or reversing the existing ones through 2 basic strategies – remineralizing the enamel or masking the lesions.[7]

Recently, exponential growth in the systematic reviews focusing on this issue has been noticed. However, given the breadth of this topic area, decision-makers have become overwhelmed by a plethora of reviews reporting contradictory conclusions. Thus, a systematic review of the published reviews (an overview or umbrella review) was a logical and appropriate next step, in order to summarize the body of evidence and choose from among the disparate findings of various reviews.

Methods

Protocol and registration

The methodology of this review was formulated in advance by strictly adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. The systematic review protocol was written during the first phase of this review and registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42019135137, which is freely available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=135137.

Question

The research question with regard to the effectiveness of different adjunctive interventions in the management of OIWSLs was defined according to the PICO format:

– P (population) – healthy patients of any age and from any ethnic group who underwent multi-bracketed fixed orthodontic treatment;

– I (intervention) – any adjunctive intervention that would prevent or reverse (manage) OIWSLs;
– C (comparison) – a control group that was not exposed to an adjunctive intervention;
– O (outcome) – any measurement that would reflect the efficacy of the applied intervention, such as changes in the incidence or size of the lesions, or any quantitative assessment of enamel mineral loss.

Eligibility criteria

The following criteria were used to consider articles eligible for this review:
– only systematic reviews and/or meta-analyses were eligible for inclusion;
– only interventions that involve remineralizing the enamel or masking the lesions were included;
– due to the scarcity of randomized controlled trials (RCTs) on this subject, the design of the primary studies of the eligible reviews were either controlled clinical trials (CCTs) (randomized or non-randomized) or prospective observational studies with concurrent comparison.

Trials, narrative literature reviews, reviews including the methods of improving patients' oral hygiene, reviews including laboratory primary studies, and reviews discussing the management of naturally developed WSLs (i.e., without orthodontic treatment) were excluded.

Search strategy

A comprehensive electronic search was performed from inception through November 2019 in the following databases: Cochrane Library, Scopus, Web of Science, CINAHL via EBSCO, and PubMed. Additionally, the bibliographies of the relevant reviews were screened for further possible reviews. No restrictions were applied on the search strategy with regard to the language, the publication date or the publication status. More details on the search strategy can be found in Supplementary Table 1.

Study selection and data extraction

The authors of the present study independently assessed the identified results of the search and extracted necessary data. The screening process was initiated by assessing titles and abstracts. Then, the full text of each relevant article was evaluated in depth. Articles that failed to meet one or more of the eligibility criteria were eliminated. After filtration, the required data was extracted from the studies using a standardized form that included the authors' names, setting, the number of primary studies, interventions, the number of participants, outcomes, the quality of primary studies, and main findings. Any disagreement between the 2 reviewers was discussed until a resolution was reached.

Quality assessment of the selected reviews

The methodological quality of the obtained systematic reviews was assessed independently by the 2 reviewers utilizing A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2).[11] The AMSTAR-2 checklist includes 16 domains that assess the multiple steps of conducting a systematic review, of which 7 domains are considered critical.

Supplementary Table 1. Search strategy

Database	Search strategy	Results
Cochrane Library from inception up to November 30, 2019 Title Abstract Key Word with no limits	#1 orthodontic* OR "orthodontic treatment" #2 "White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz* #3 manag* OR reduc* OR prevent* OR revers* #4 "systematic review" OR "meta-analysis" #5 #1 AND #2 AND #3 AND #4	#5 = 33 (reviews)
Scopus from inception up to November 30, 2019 Title Abstract Key Word with no limits	#1 orthodontic* OR "orthodontic treatment" #2 "White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz* #3 manag* OR reduc* OR prevent* OR revers* #4 "systematic review" OR "meta-analysis" #5 #1 AND #2 AND #3 AND #4	#5 = 33
Web of Science from inception up to November 30, 2019 TS – Topic with no limits	#1 TS = (orthodontic* OR "orthodontic treatment") #2 TS = ("White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz*) #3 TS = (manag* OR reduc* OR prevent* OR revers*) #4 TS = ("systematic review" OR "meta-analysis") #5 #1 AND #2 AND #3 AND #4	#5 = 24
CINAHL via EBSCO from inception up to November 30, 2019 TX – All Text with no limits	(orthodontic* OR "orthodontic treatment") AND ("White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz*) AND (manag* OR reduc* OR prevent* OR revers*) AND ("systematic review" OR "meta-analysis")	15
PubMed from inception up to November 30, 2019 All fields with no limits	(orthodontic* OR "orthodontic treatment") AND ("White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz*) AND (manag* OR reduc* OR prevent* OR revers*) AND ("systematic review" OR "meta-analysis")	36

The overall confidence of the results of a systematic review was reported according to the following categories:
– high confidence of the results – no or only one non-critical weakness was found;
– moderate confidence – more than one non-critical weakness was found;
– low confidence – one critical flaw with/without a non-critical weakness was found;
– critically low confidence – more than one critical flaw with/without a non-critical weakness was found.

The overall confidence of the results of the selected systematic reviews was rated electronically by filling out the online AMSTAR-2 checklist (https://amstar.ca/Amstar_Checklist.php).

Choice of the best body of evidence

The Jadad decision algorithm is a simple guide that was designed to interpret discordant reviews and to help decision-makers select the most relevant and valid ones from among them.[12] In this review, when an intervention was addressed by numerous systematic reviews with conflicting results, the Jadad decision algorithm was applied independently by the 2 reviewers. The results were then compared in order to robustly determine the systematic review which provided the best available evidence.

Results

Search results

A total of 141 references were retrieved through the search. After removing duplicates, 82 references were screened for eligibility by titles and abstracts. As a result, 33 articles were considered potentially relevant, and therefore checked in depth. Ultimately, 13 reviews were included. The detailed literature search process is provided in Fig. 3. The excluded reviews are presented in Supplementary Table 2 with the reasons for exclusion.

Characteristics of the selected reviews

The 13 reviews included in this review were published between 2004 and 2019; 4 of them were integrated into meta-analyses.[4,13–15] The addressed adjunctive interventions were topical fluoride application (assessed by 10 systematic reviews),[4,6,8,13–19] the application of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) or other casein derivatives (assessed by 4 systematic reviews),[6,17,18,20] fluoride-releasing bonding materials (assessed by 4 systematic reviews),[13–15,21] laser therapy (assessed by 1 systematic review),[3] resin infiltration (assessed by 1 systematic review),[6] and micro-abrasion (assessed by 1 systematic review).[6] The characteristics of the systematic reviews are summarized in Table 1.

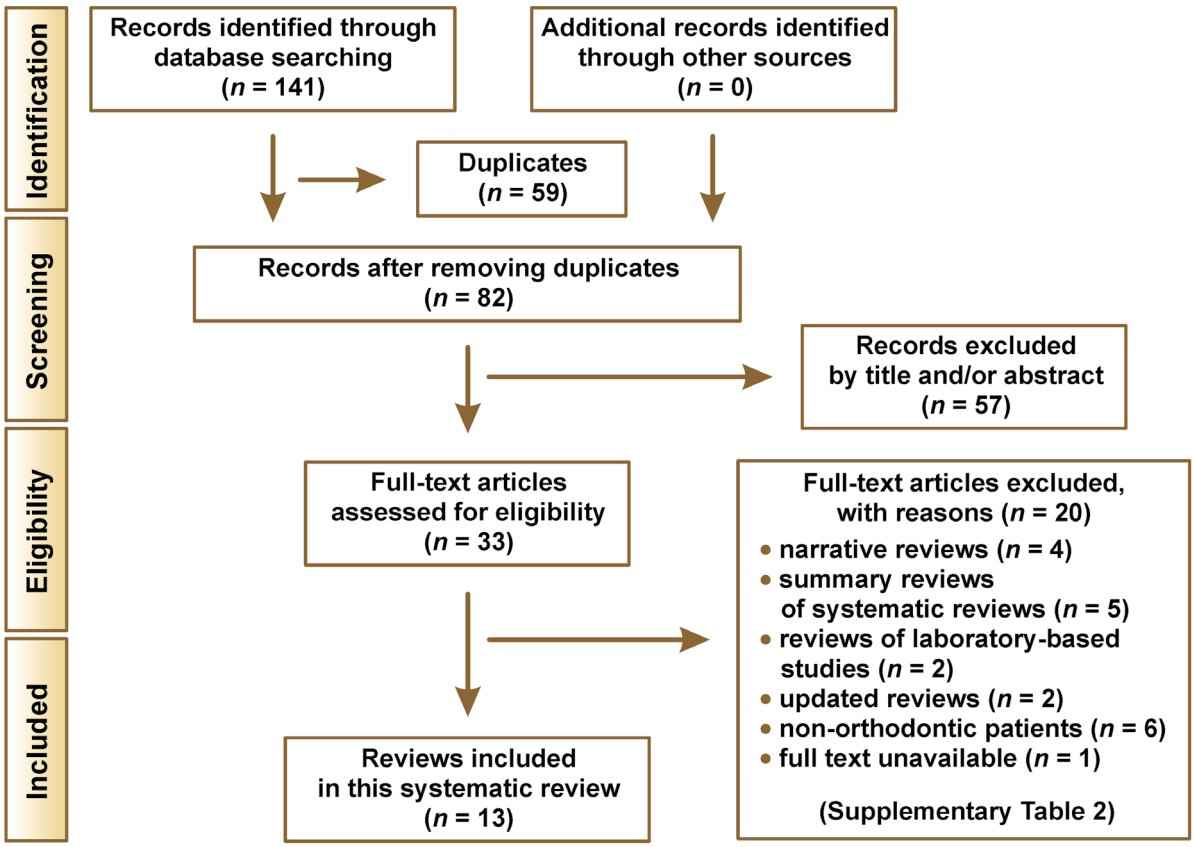

Fig. 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

Supplementary Table 2. Excluded studies and the reasons for exclusion

No.	Study	Reason for exclusion
1	Aravind N, Pandiyan S. Demineralisation around orthodontic brackets – A review. *Res J Pharm Technol.* 2016;9(9):1536–1540.	narrative review
2	Raj BJR, Pradeep S. Remineralising agents in dentistry. *Res J Pharm Technol.* 2016;9(10):1734–1736.	narrative review
3	Faghihian R, Shirani M, Tarrahi MJ, Zakizade M. Efficacy of the resin infiltration technique in preventing initial caries progression: A systematic review and meta-analysis. *Pediatr Dent.* 2019;41(2):88–94.	non-orthodontic patients
4	Hani TB, O'Connell AC, Duane B. Casein phosphopeptide-amorphous calcium phosphate products in caries prevention. *Evid Based Dent.* 2016;17(2):46–47.	summary review of a systematic review (Raphael S, Blinkhorn A. Is there a place for Tooth Mousse in the prevention and treatment of early dental caries? A systematic review. *BMC Oral Health.* 2015;15(1):113.)
5	Martinez-Mier EA. Fluoride-containing orthodontic adhesives may reduce the occurrence of enamel demineralization in patients with fixed orthodontic appliances. *J Evid Based Dent Pract.* 2011;11(3):132–134.	summary review of a systematic review (Rogers S, Chadwick B, Treasure E. Fluoride-containing orthodontic adhesives and decalcification in patients with fixed appliances: A systematic review. *Am J Orthod Dentofacial Orthop.* 2010;138(4):390.e1–e390.e8.)
6	Kalha AS. Topical fluorides and decalcification around fixed orthodontic appliances. *Evid Based Dent.* 2006;7(2):38–39.	summary review of a systematic review (Chadwick BL, Roy J, Knox J, Treasure ET. The effect of topical fluorides on decalcification in patients with fixed orthodontic appliances: A systematic review. *Am J Orthod Dentofacial Orthop.* 2005;128(5):601–606.)
7	O'Neill J. Little evidence exists about optimal caries-prevention strategies during orthodontic treatment. *Evid Based Dent.* 2004;5(4):97.	summary review of a systematic review (Derks A, Katsaros C, Frencken JE, van't Hof MA, Kuijpers-Jagtman AM. Caries-inhibiting effect of preventive measures during orthodontic treatment with fixed appliances. *Caries Res.* 2004;38(5):413–420.)
8	Cheng LL. Limited evidence indicates fluoride may prevent demineralized white lesions during orthodontic treatment. *J Am Dent Assoc.* 2015;146(9):699–701.	summary review of a systematic review (Benson PE, Parkin N, Dyer F, Millett DT, Furness S, Germain P. Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment. *Cochrane Database Syst Rev.* 2013;12:CD003809.)
9	Taha AA, Patel MP, Hill RG, Fleming PS. The effect of bioactive glasses on enamel remineralization: A systematic review. *J Dent.* 2017;67:9–17.	review of laboratory-based studies
10	Rahimi F, Sadeghi M, Mozaffari HR. Efficacy of fluoride varnish for prevention of white spot lesions during orthodontic treatment with fixed appliances: A systematic review study. *Biomed Res Ther.* 2017;4(8):1513–1526.	review of laboratory-based studies
11	Cosma LL, Şuhani RD, Mesaroş A, Badea ME. Current treatment modalities of orthodontically induced white spot lesions and their outcome – a literature review. *Med Pharm Rep.* 2019;92(1):25–30.	narrative review
12	Bergstrand F, Twetman S. Evidence for the efficacy of various methods of treating white-spot lesions after debonding of fixed orthodontic appliances. *J Clin Orthod.* 2003;37(1):19–21.	neither abstract nor full-text available (a request was sent to the corresponding author and the journal to get the article; however, no response was received)
13	Li J, Xie X, Wang Y, et al. Long-term remineralizing effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) on early caries lesions in vivo: A systematic review. *J Dent.* 2014;42(7):769–777.	non-orthodontic patients
14	Paula ABP, Fernandes AR, Coelho AS, et al. Therapies for white spot lesions – a systematic review. *J Evid Based Dent Pract.* 2017;17(1):23–38.	non-orthodontic patients
15	Raphael S, Blinkhorn A. Is there a place for Tooth Mousse in the prevention and treatment of early dental caries? A systematic review. *BMC Oral Health.* 2015;15(1):113.	non-orthodontic patients
16	Borges AB, Caneppele TMF, Masterson D, Maia LC. Is resin infiltration an effective esthetic treatment for enamel development defects and white spot lesions? A systematic review. *J Dent.* 2017;56:11–18.	non-orthodontic patients
17	Indrapriyadharshini K, Madan Kumar PD, Sharma K, Iyer K. Remineralizing potential of CPP-ACP in white spot lesions – a systematic review. *Indian J Dent Res.* 2018;29(4):487–496.	non-orthodontic patients
18	Benson PE, Parkin N, Millett DT, Dyer F, Vine S, Shah A. Fluorides for the prevention of white spots on teeth during fixed brace treatment. *Cochrane Database Syst Rev.* 2004;3:CD003809.	updated in 2013; the updated version is included in this review
19	Sudjalim TR, Woods MG, Manton DJ. Prevention of white spot lesions in orthodontic practice: A contemporary review. *Aust Dent J.* 2006;51(4):284–289;quiz 347.	narrative review
20	Bergstrand F, Twetman S. A review on prevention and treatment of post-orthodontic white spot lesions – evidence-based methods and emerging technologies. *Open Dent J.* 2011;5:158–162.	updated in 2016; the updated version is included in this review

Table 1. Characteristics of the included reviews assessing the effectiveness of different interventions in managing orthodontically induced white spot lesions (OIWSLs)

Study/setting	Study design	No. of primary studies	Age of participants*	Interventions/ No. of studies in each	No. of participants
Tasios et al.[15] 2019, Greece	systematic review and meta-analysis	23	mean age of 14.4 years	– fluoride varnish (4) – fluoride varnish under banding cement (2) – fluoride-releasing adhesives (8) – flat-surface sealants (5) – active reminders (4)	1,473 in total
Sardana et al.[16] 2019, China	systematic review	3	mean age of 13.3 years (for 1 study) range of 11–16 years/13–21 years (for 2 studies)	self-applied topical fluorides	505 (prevention of OIWSLs) 26 (reversal of OIWSLs)
Pithon et al.[20] 2019, Brazil	systematic review	11	mean age of 14.87 years	CPP-ACP	not addressed
Sardana et al.[4] 2019, China	systematic review and meta-analysis	11	mean age of 15.21 years	professional topical fluoride application in order to prevent or reverse OIWSLs	518 (prevention of OIWSLs) 693 (reversal of OIWSLs)
Raghis et al.[3] 2018, Syria	systematic review	8	mean age of 13.45 years	laser irradiation: – CO_2 laser – Nd:YAG laser – argon laser – Optodan laser	183
Nascimento et al.[13] 2016, Brazil	systematic review and meta-analysis	7	NA	fluoride-releasing materials (cementation materials, varnish and sealant)	1,867 teeth
Lapenaite et al.[17] 2016, Lithuania	systematic review	11	NA	fluoride products or casein derivatives	998 (studies on fluoride) 314 (studies on casein derivatives)
Sonesson et al.[6] 2016, Denmark	systematic review	7	≤30 years	– remineralizing agents (fluoride, CCP-ACP) – micro-abrasion – resin infiltration	not addressed
Chen et al.[18] 2013, China	systematic review	7 (3 – fluoride vs control; 2 – CPP-ACP vs control; 2 – fluoride vs CPP-ACP)	NA	remineralizing agents (fluoride, CCP-ACP)	173 (studies on fluoride) 110 (studies on CPP-ACP) 86 (studies on fluoride vs CPP-ACP)
Benson et al.[8] 2013, UK	systematic review	3	mean age of 15 years (for 2 studies) adults up to 45 years (for 1 study)	fluorides	458
Rogers et al.[21] 2010, UK	systematic review	10	NA	fluoride-containing adhesives	not addressed
Chadwick et al.[19] 2005, UK	systematic review	6	NA	topical fluorides	not addressed
Derks et al.[14] 2004, the Netherlands	systematic review and meta-analysis	15	NA	fluorides, chlorhexidine, polymeric coating or fluoride-releasing sealant, and bonding material	847 (fluorides) 111 (chlorhexidine) 59 (polymeric coating or fluoride-releasing sealant) 297 (bonding material)

CPP-ACP – casein phosphopeptide-amorphous calcium phosphate; Nd:YAG laser – neodymium-doped yttrium aluminum garnet laser;
QLF – quantitative light-induced fluorescence; *M* – mean; *SD* – standard deviation; *CI* – confidence interval;
SEM – scanning electron microscopy; NA – not applicable.
* The mean age of the participants was calculated based on the available data (mean age) provided in the included reviews.

Outcomes	Quality of primary studies	Results
– incidence of OIWSLs – severity of OIWSLs	unclear risk (7) high risk (16)	– Fluoride varnish, flat-surface sealants and active reminders were associated with a reduced development and magnitude of lesions; however, the strength of this recommendation is mostly low. – No statistically significant difference was found for fluoride varnish under banding cement. – No statistically significant improvement was found for fluoride-releasing adhesives.
– changes in the incidence of OIWSLs as the primary outcome (studies on prevention) – reduction in the size of OIWSLs or mean fluorescence values or the prevalence of OIWSLs as the primary outcomes (studies on reversal)	low risk(1) high risk (2)	Although the review did not confirm the effectiveness of self-applied fluorides in the reversal of OIWSLs, it did partially substantiate the positive role (although indirectly) of self-applied fluorides in the prevention of OIWSLs based on a single trial with a low risk of bias.
prevention or treatment of OIWSLs around orthodontic braces	low risk (9) unclear risk (2)	The CPP-ACP products were effective in the prevention and treating of OIWSLs.
– difference in the incidence of OIWSLs – change in the mean QLF scores or the mean DIAGOdent scores	low risk (5) medium risk (4) high risk (2)	– Professional topical fluoride application brought about a 25–30% reduction in the incidence of OIWSLs (pooling 3 studies). – The standardized mean difference was found to be 0.57 less in the professional topical fluoride application group than in the control group (95% *CI*: from 0.23 to –0.91) in the studies evaluating the reversal of OIWSLs (pooling 3 studies); however, the effect of professional topical fluoride application on the reversal of OIWSLs was unclear due to concerns in interpreting the DIAGNOdent values.
– formation or non-formation of OIWSLs assessed clinically or with digital images – degree of decalcification – changes in the enamel structure after laser application	unclear risk (all studies)	Laser irradiation was effective in inhibiting demineralization during orthodontic treatment.
– risk of patients developing OIWSLs – the *M* and *SD* values of the extent of OIWSLs acc. to the Gorelick scale	high risk (all studies)	– The pooled relative risk of developing OIWSLs when using cementation materials as compared to control was 0.35 (95% *CI*: 0.15–0.81); hence, patients using fluoride-releasing materials were at a lower risk of developing OIWSLs (pooling 4 studies). The risk reduction was statistically significant for fluoride varnish, but not for sealant (only 1 study was included for each intervention). – The pooled mean difference in the extent of OIWSLs between the experimental and control groups was statistically significant for cementation materials, but not for varnish and sealant.
prevention of OIWSLs	not addressed	The results showed positive effects of the fluoride products and casein derivatives on preventing OIWSLs (4 out of 6 studies revealed the effectiveness of the fluoride products in preventing OIWSLs; 3 out of 5 studies revealed the effectiveness of casein derivatives in preventing OIWSLs).
extent, hardness or appearance of OIWSLs with a follow-up period of at least 8 weeks, as assessed with visual clinical scores, photographs, caries detection devices, or patient/therapist satisfaction	low risk (2) high risk (5)	There is a lack of reliable scientific evidence to support remineralizing or camouflaging strategies to manage OIWSLs (2 out of 4 trials revealed a significant effect of fluoride, 1 out of 3 trials revealed a significant effect of CCP-ACP, the 2 included trials on resin infiltration revealed a significant effect, and 1 trial revealed a significant effect of micro-abrasion).
difference in the severity of OIWSLs between the experimental and control groups as the primary outcome (severity was expressed in terms of the area over the whiteness of the lesion or as the amount of mineral loss or the lesion depth)	medium risk (1) high risk (6)	There is a lack of reliable evidence to support the effectiveness of remineralizing agents in the treatment of OIWSLs (1 out of 3 studies revealed the ineffectiveness of fluorides in managing OIWSLs; 1 study indicated that CPP-ACP was effective in managing OIWSLs, while another one found no significant difference as compared to control; 1 study indicated that fluoride was more effective than CPP-ACP, while another one found no difference).
– presence or absence of new lesions by participant – differences in the size and severity of OIWSLs between the experimental and control groups – any quantitative assessment of enamel mineral loss, such as fluorescent light techniques or microradiography, used with in situ caries models – any participant-assessed outcomes, such as the perception of the lesions and oral health-related quality of life data – adverse effects	low risk (1) medium risk (1) high risk (1)	– Applying fluoride varnish every 6 weeks at the time of the orthodontic review during treatment is effective, but this finding is based on a single study. – None of the included studies reported data on the size and severity of OIWSLs, the quantitative assessment of enamel mineral loss, patient's perception, oral health-related quality of life, and adverse effects.
any outcome measures of decalcification and the presence of OIWSLs	not addressed	It is impossible to make recommendations on the use of fluoride-containing adhesives during fixed orthodontic treatment. However, there is evidence to suggest that glass ionomer cement is more effective than composite resin in the prevention of OIWSLs, but the evidence is weak.
any valid outcome measure of decalcification, both before and after treatment	not addressed	The use of topical fluorides in addition to a fluoride toothpaste reduced the incidence of decalcification in populations with both fluoridated and non-fluoridated water supplies (all the included studies found a significant difference). Different preparations and formats appear to decrease decalcification, but there is no evidence that any method is superior. There is some evidence that the potency of fluoride preparations might be important.
any demineralization scores	not addressed	The use of a toothpaste and gel with a high fluoride concentration of 1,500–5,000 ppm, or complementary chlorhexidine during orthodontic treatment showed a demineralization-inhibiting effect. The use of a polymeric tooth coating on the tooth surface around the brackets or a fluoride-releasing bonding material showed almost no demineralization-inhibiting effect. Pooling data was only applied for the studies assessing fluoride-releasing bonding materials, where the overall prevented fraction was 20% (SEM 0.09). However, this effect was not statistically significant.

Methodological quality of the included reviews

The methodological quality of the reviews ranged between a critically low to moderate confidence of the results. In other words, all the reviews were fraught with some methodological shortcomings. The AMSTAR-2 questions and the results for the reviews are presented in Table 2. The detailed supporting reasons for each assessment are provided in Supplementary Table 3. With regard to the 7 critical domains of the AMSTAR-2 tool, most reviews failed to contain an explicit statement that the review methods were established prior to the conduct of the review (69.23% of the included reviews), did not use a satisfactory technique to assess the risk of bias in each individual study (53.84% of the included reviews), and did not account for the risk of bias in individual studies when interpreting and discussing the results (46.15% of the included reviews).

Effects of interventions

Effect of topical fluorides in the management of OIWSLs

Ten systematic reviews provided the results from studies evaluating the effectiveness of topical fluorides in the management of OIWSLs: Tasios et al. 2019,[15] Sardana et al. 2019,[16] Sardana et al. 2019 (Epub 2018),[4] Nascimento et al. 2016,[13] Lapenaite et al. 2016,[17] Sonesson et al. 2016,[6] Chen et al. 2013,[18] Benson et al. 2013,[8] Chadwick et al. 2005,[19] and Derks et al. 2004.[14] Different forms were utilized to apply topical fluorides, including fluoride varnish, fluoride gel, fluoridated mouth rinse, fluoridated toothpaste, fluoridated water, and fluoride chewing sticks.

Some of these reviews deduced that topical fluorides were effective in managing OIWSLs,[4,8,13–15,17,19] while others failed to find reliable significant evidence.[6,16,18] All the reviews were addressing the same review question, but the recruited trials and the selection criteria varied among them. In this case, the Jadad algorithm suggests that the best available review be selected according to the superiority in its publication status, the methodological quality of its primary studies, language restrictions, and the analysis of data on individual patients. As a result, Sardana et al. 2019[4] was selected (Fig. 4). The detailed steps of the Jadad decision algorithm used from the beginning until the final constructive decision are presented in Supplementary Table 4.

Sardana et al. 2019[4] addressed the use of professional fluorides and recruited 11 RCTs published between 2007 and 2017. All primary studies used a parallel-arm design. The results indicated that fluorides led to a 25–30% reduction in the incidence of OIWSLs; however, their effect on reversing lesions was unclear due to concerns in interpreting the DIAGNOdent values.

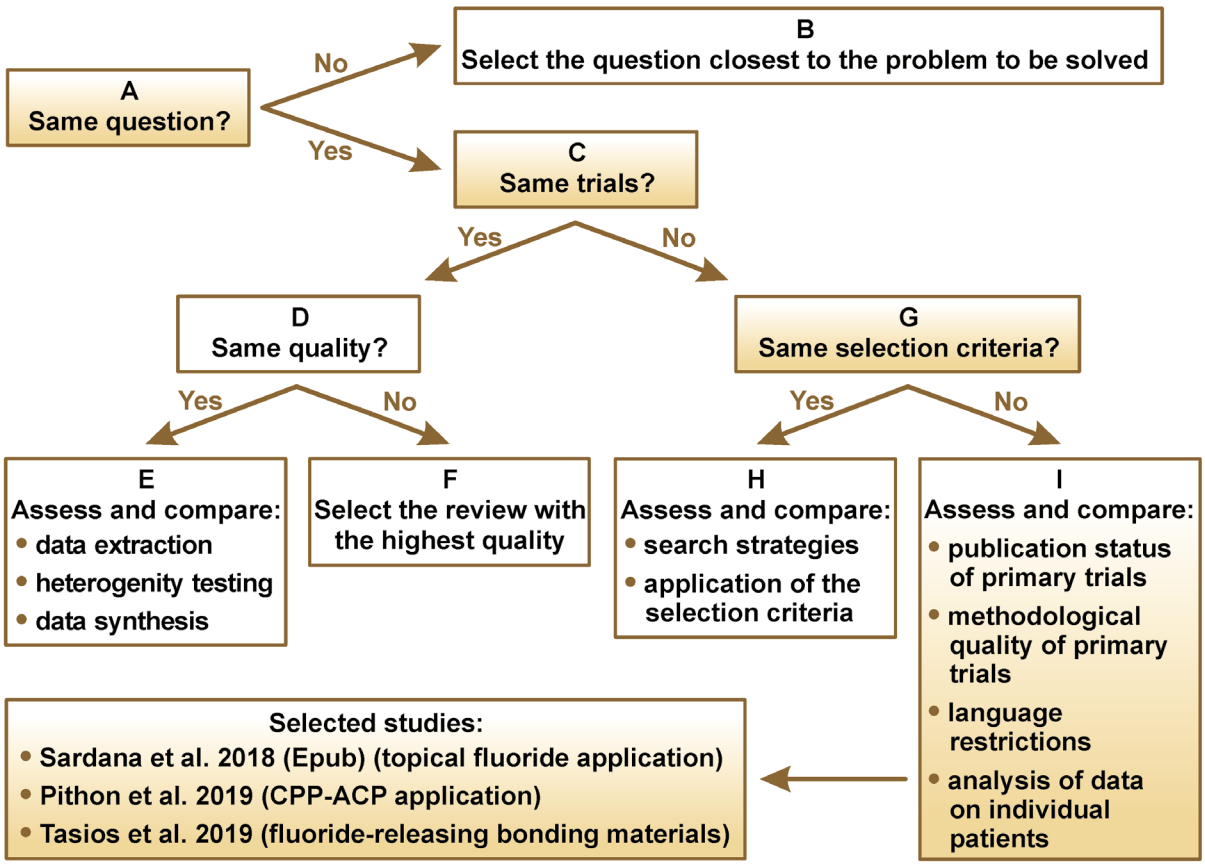

Fig. 4. Flow diagram of the Jadad decision algorithm for conflicting reviews on efficacy of topical fluorides, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and fluoride-releasing adhesives

Table 2. The AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews-2) criteria for the included reviews

Domains	Tasios 2019[15]	Sardana 2019[16]	Pithon 2019[20]	Sardana 2019[4]	Raghis 2018[3]	Nascimento 2016[13]	Lapenaite 2016[17]	Sonesson 2016[6]	Chen 2013[18]	Benson 2013[8]	Rogers 2010[21]	Chadwick 2005[19]	Derks 2004[14]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	no	no	no
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no
3. Did the review authors explain their selection of the study designs for inclusion in the review?	yes	no	no	no	no	no	no	no	no	no	no	no	no
4. Did the review authors use a comprehensive literature search strategy?	yes	yes	yes	yes	yes	no	P yes	P yes	P yes	P yes	yes	no	P yes
5. Did the review authors perform study selection in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
6. Did the review authors perform data extraction in duplicate?	yes	yes	no	yes	yes	yes	no	yes	yes	yes	yes	yes	no
7. Did the review authors provide a list of the excluded studies and justify the exclusions?	yes	yes	yes	yes	yes	no	no	yes	yes	yes	yes	no	yes
8. Did the review authors describe the included studies in adequate detail?	yes	yes	P yes	yes	P yes	P yes	no	P yes	P yes	yes	P yes	P yes	P yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	– RCTs: yes – non-RCTs: no	yes	– RCTs: yes – non-RCTs: yes	yes	– RCTs: yes – non-RCTs: no	yes	no	– RCTs: yes – non-RCTs: no	yes	yes	no	no	no
10. Did the review authors report on the sources of funding for the studies included in the review?	no	no	no	no	no	no	no	no	no	yes	no	no	no
11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of the results?	– RCTs: yes – non-RCTs: no	–	–	yes	–	yes	–	–	–	–	–	–	no
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	yes	–	–	yes	–	no	–	–	–	–	–	–	no
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	yes	yes	no	yes	no	yes	no	yes	yes	yes	no	no	no
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	no	no	yes	yes	no	no	no	no	yes	no	no
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the results of the review?	no	–	–	yes	–	no	–	–	–	–	–	–	no
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	no	yes	yes	no	no	no	yes	yes	yes	no	no
Quality results	CL	M	L	M	CL	L	CL	L	M	M	CL	CL	CL

RCT – randomized critical trial; P yes – partial yes; M – moderate; L – low; CL – critically low.

Supplementary Table 3. Detailed supporting reasons for the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews-2) assessment of each included review

Domains	Tasios 2019[15]	Sardana 2019[16]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes: As stated on page 2 in the "Eligibility criteria" section: "According to the Participants-Intervention-Comparison-Outcome study design (PICOS)..."	Yes: As stated on page 2: "The Population-Intervention-Control-Outcome (PICO) schema was used to direct the inclusion of studies as follows: . . ."
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes: As stated on page 2: "The review protocol was made a priori, registered in PROSPERO (CRD42017079352) and all post hoc changes were appropriately noted".	Yes: As stated on page 2: "The methodology of the review was formulated in advance by strictly adhering to the PRISMA guidelines".
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes: As stated on page 2: "due to the scarcity of RCTs on this subject, included were randomized or quasi-randomized prospective controlled human trials".	No: Authors did not provide the explanation for including RCTs and quasi-randomized CCTs only.
4. Did the review authors use a comprehensive literature search strategy?	Yes: – Authors searched 9 databases. – Authors searched trial registries: metaRegister of Controlled Trials. – Authors searched DOAJ and PQDT. – The reference lists and Google Scholar citation lists of the eligible full-text articles as well as the reference lists of relevant systematic reviews were screened manually for additional studies. – Key words and the search strategy were provided in Appendix Table 1. – No restrictions were applied on the language, publication year or status.	Yes: – Authors searched 4 databases. – Grey literature (www.opengrey.com) was searched to find any registered trial or unpublished material. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided in Table 1. – No restrictions were applied on the publication year or status. However, only articles written in English were included.
5. Did the review authors perform study selection in duplicate?	Yes: As stated in the abstract: "Study selection, data extraction and risk of bias assessment were done independently in duplicate".	Yes: As stated on page 3: "After the removal of duplicates, 2 authors (DS and MS) independently screened titles and their respective abstracts in a standardized manner to determine their inclusion/exclusion in the review".
6. Did the review authors perform data extraction in duplicate?	Yes: As stated in the abstract: "Study selection, data extraction and risk of bias assessment were done independently in duplicate".	Yes: As stated on page 3: "The characteristics of the respective studies and their data were extricated individually by 2 authors (DS and MS) on a piloted pro forma".
7. Did the review authors provide a list of the excluded studies and justify the exclusions?	Yes: The list of the studies identified from the literature and their inclusion/exclusion status with reasons was provided in Appendix Table 2.	Yes: As stated on page 3: "The detailed reasons for the exclusion of the remaining 70 articles are presented in Supplementary Appendix 2".
8. Did the review authors describe the included studies in adequate detail?	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow-up were all described in details in Tables 1 and 2 as well as in the text.	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow-up were all described in Table 2.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. No: Non-randomized controlled trials were assessed by the RoB tool rather than the ROBINS-I tool.	Yes: Randomized controlled trials were appropriately assessed by the RoB-2 tool. Non-randomized trials were not included.
10. Did the review authors report on the sources of funding for the studies included in the review?	No: Funding for primary studies was not reported in the review or in the "Other bias" section referring to the RoB tool.	No: Funding for primary studies was not reported in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of the results?	Yes: For RCTs, authors used an appropriate technique to combine the study results and adjusted for heterogeneity. No: Authors did not report separate summary estimates for NRSIs.	Meta-analysis was not performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes: Authors performed sensitivity analyses and presented them in Appendix Table 8.	Meta-analysis was not performed.
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes: The risk of bias in individual studies was accounted for, especially when applying the GRADE criteria.	Yes: The risk of bias was accounted for when interpreting results such as: "Since this deduction is made based on 2 trials – 1 with a low risk of overall bias and 1 with a high risk of bias – this conclusion should be interpreted with caution, and the present review recommends further trials to confirm this". Moreover, the risk of bias was accounted for when evaluating the overall quality of evidence.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes: The impact of heterogeneity was accounted for when discussing the results of the review.	Yes: As stated: "All 3 trials were quite heterogeneous in regards to the intervention (high-fluoride vs low-fluoride toothpaste; the composition of the fluoride agent), control group and outcome (2 assessed prevention at debonding and 1 assessed reversal at 26 weeks). Hence, it is quite difficult to give any recommendation by pooling the results qualitatively" and "The trials included in the review were of considerable heterogeneity, and this hampers providing the recommendations/guidelines pertaining to the concentration of fluoride, the fluoride carrier or the fluoride agent in the carrier".
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the results of the review?	No: Publication bias was not considered in the review.	Meta-analysis was not performed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes: As stated on page 10: "All authors declare that there is no conflict of interest".	Yes: As stated in the abstract: "This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors".

Continued Supplementary Table 3

	Pithon 2019[20]	Sardana 2019[4]	Raghis 2018[3]
1.	Yes: As stated on page 2: "To be included in the review, studies needed to comply with the following selection criteria, according to the PICOS strategy…"	Yes: As stated on page 2: "The PICO schema for individual studies was used to determine the eligibility criteria and is presented in Table 1".	Yes: As stated on page 323: "These review questions were developed according to the population, intervention, comparison, and outcome (PICO) study design".
2.	Yes: As stated on page 2: "The protocol used for the systematic review of the effectiveness of CPP-ACP-containing products was recorded in the International Prospective Register of Systematic Reviews".	Yes: As stated on page 2: "The present review was devised a priori by following the PRISMA guidelines".	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including both RCTs and CCTs.	No: Authors did not provide the explanation for including RCTs and quasi-randomized CCTs only.	No: Authors did not provide the explanation for including both RCTs and CCTs.
4.	Yes: – Authors searched 5 databases. – Authors searched trial registries: ClinicalTrials. – Grey literature was searched by www.opengrey.com. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided within the text. – No restrictions were applied on the language, publication year or status.	Yes: – Authors searched 4 databases. – Grey literature (www.opengrey.com) was searched to find any registered trial or unpublished material. – The reference lists of the eligible articles and relevant reviews were screened manually for additional studies. – Key words were provided in Table 2. – Restrictions were applied on the language, including only the English language. – No limits were applied to the search strategy regarding the publication year or the current stage of the trial.	Yes: – Authors searched 5 databases. – Authors searched trial registries: ClinicalTrials and ICTRP. – Grey literature was searched by www.opengrey.com. – PQDT was searched for dissertations. – The reference lists of the eligible articles were screened manually for additional studies. – Key words and the search strategy were provided in Supplementary Material 1. – No restrictions were applied on the language, publication year or status.
5.	Yes: As stated on page 2: "The selections were performed by 2 independent researchers".	Yes: As stated in the abstract: "Two reviewers independently selected studies, extracted data and assessed the risk of bias".	Yes: As stated on page 323: "The obtained articles were independently subjected to clear inclusion and exclusion criteria by 2 authors."
6.	No: It was not stated that data was extracted in duplicate.	Yes: As stated in the abstract: "Two reviewers independently selected studies, extracted data and assessed the risk of bias".	Yes: As stated on page 323: "The data was extracted from studies according to the aims of the systematic review by the same 2 authors independently".
7.	Yes: The potentially relevant studies that were read in the full-text form, but excluded from the review were stated and cited within the text in the "Results" section (page 3) with the justification for exclusion.	Yes: The details of the reasons for the exclusion of studies after full-text reading was presented in Appendix 2.	Yes: The details of the reasons for the exclusion of studies after full-text reading was presented in Supplementary Material 2.
8.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described. However, the study setting and follow-up were not addressed.	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow-up were all described in details in Table 3 and within the text.	Partial Yes: Though populations, interventions, comparators, outcomes, the study design, and follow-up were described, the study setting was not addressed.
9.	Yes: Randomized controlled trials were appropriately assessed by the RoB-2 tool. Yes: Non-randomized controlled trials were appropriately assessed by the ROBINS-I tool.	Yes: Randomized controlled trials were appropriately assessed by the RoB-2 tool. Non-randomized trials were not included.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. No: Non-randomized controlled trials were assessed by the RoB tool rather than the ROBINS-I tool.
10.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review or in the "Other bias" section referring to the RoB tool.
11.	Meta-analysis was not performed.	Yes: Authors used an appropriate weighted technique to combine the study results and adjusted for heterogeneity if present.	Meta-analysis was not performed.
12.	Meta-analysis was not performed.	Yes: Sensitivity analysis was performed by excluding 'high-risk' trials and trials with 'some concerns' from quantitative synthesis.	Meta-analysis was not performed.
13.	No: Authors did not account for the moderate risk of bias found in the 2 included studies when interpreting the results.	Yes: The risk of bias in individual studies was accounted for when discussing the results.	No: Authors did not account for the unclear risk of bias found in all the included studies when interpreting the results.
14.	No: Heterogeneity was not addressed.	No: Though authors performed an investigation for heterogeneity among studies, they did not discussed its impact on the results of the review.	Yes: As stated on page 325: "Heterogeneity was observed due to the study designs, treatment protocols and the assessed outcomes of the included studies".
15.	Meta-analysis was not performed.	Yes: Though funnel plots and statistical analysis were not provided, publication bias was discussed in the review as follows: "the unpublished study did not find any significant effect of 1.23% APF gel on the prevention of EWSLs during orthodontic treatment, which might have resulted in publication bias".	Meta-analysis was not performed.
16.	No: Neither funding nor conflicting interests were stated in the review.	Yes: As stated on page 9: "This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Conflicts of interest: None to be declared".	Yes: As stated on page 321: "Funding: None declared. Conflict of interest: None declared".

Continued Supplementary Table 3

	Nascimento 2016[13]	Lapenaite 2016[17]	Sonesson 2016[6]
1.	Yes: As stated on page 102: "The eligibility criteria and search strategy were based on the PICO elements (population, intervention, comparison, and outcome)".	No: The PICO components were not all included when addressing the inclusion criteria (comparison and outcome were not stated).	Yes: As stated on page 2: "The PICO was set up as follows…"
2.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including only RCTs.	No: Authors did not provide the explanation for including both RCTs and quasi-RCTs.	No: Authors did not provide the explanation for including both RCTs and CCTs.
4.	No: – Authors searched only 1 database. – Trial registries and grey literature were not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided on page 102. – No restrictions were applied on the language, publication year or status.	Partial Yes: – Authors searched 5 databases. – Trial registries and grey literature were not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided on page 4. – Restrictions were applied on the language (only articles written in English) and publication year (articles published between 2008 and 2013).	Partial Yes: – Authors searched 4 databases. – Authors searched trial registries: ClinicalTrials. – Grey literature was not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words and the search strategy were provided in Supplement 1. – Restrictions were applied on the language (only articles written in English) and publication year (articles published between 2011 and Oct 31, 2015).
5.	Yes: As stated on page 102: "Two independent reviewers screened the search results".	Yes: As stated on page 4: "Three researchers independently reviewed the titles and abstracts of the potentially relevant studies".	Yes: As stated in the abstract: "Abstract lists and selected full-text papers were independently examined by 2 reviewers, and any differences were solved by consensus".
6.	Yes: As stated on page 102: "To record the study characteristics, methodological quality and results, the reviewers used a data extraction form according to the CONSORT 2010 statement. Disagreement between the 2 reviewers was solved either by consensus or by a third reviewer".	No: The review did not contain an explicit statement that authors performed data extraction in duplicate.	Yes: As stated on page 2: "Key data from the accepted studies were extracted independently by 2 authors".
7.	No: The list of the excluded studies and the reasons for exclusion were not provided. Figure 1 provided the number of the excluded studies without providing the authors' names for each study.	No: The list of the excluded studies and the reasons for exclusion were not provided.	Yes: As stated on page 3: "The excluded studies with the main reason for exclusion are shown in Table 3".
8.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described, but not in details. Moreover, the study setting and follow-up were not addressed.	No: Though populations, interventions and comparators were described (not in details), outcomes, the study design, the study setting, and follow-up were not addressed.	Partial Yes: Populations, interventions, comparators, outcomes, the study design, and follow-up were described, but not in details. Moreover, the study setting was not addressed.
9.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. Not-randomized trials were not included.	No: The risk of bias was not assessed.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. No: Non-randomized controlled trials were assessed by the RoB tool rather than the ROBINS-I tool.
10.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.
11.	Yes: Authors used an appropriate technique to combine the study results and adjusted for heterogeneity.	Meta-analysis was not performed.	Meta-analysis was not performed.
12.	No: All studies were at a high risk of bias and were all included in evidence synthesis.	Meta-analysis was not performed.	Meta-analysis was not performed.
13.	Yes: As stated: "all the included studies presented a high risk of bias, indicating that the evidence is weak".	No: The risk of bias was not assessed.	Yes: The risk of bias in individual studies was accounted for when interpreting the results, especially when applying the GRADE criteria.
14.	Yes: As stated on page 106: "The subgroup analysis showed a 65% heterogeneity between the materials, indicating that the type of material partially explained the heterogeneity. Thus, different approaches for delivering fluorides near brackets could be related to the observed heterogeneity".	No: Heterogeneity was not addressed.	No: Authors just stated in the abstract that: "No pooling of the results was possible due to study heterogeneity", without providing any further explanation.
15.	No: Publication bias was not assessed.	Meta-analysis was not performed.	Meta-analysis was not performed.
16.	No: Neither funding nor conflicting interests were stated in the review.	No: Neither funding nor conflicting interests were stated in the review.	No: Though authors mentioned their funding sources: "Funding: The project was funded through the authors' academic institutions", they did not explain how they managed the potential conflict of interest.

Continued Supplementary Table 3

	Chen 2013[18]	Benson 2013[8]	Rogers 2010[21]
1.	Yes: The PICO elements were mentioned on page 377 in the "Material and methods" section.	Yes: The PICO components were mentioned in the "Criteria for considering studies for this review" section.	No: The PICO components were not all included when addressing the inclusion criteria.
2.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including only RCTs.	No: Authors did not provide the explanation for including only RCTs.	No: Authors did not provide the explanation for including all of the following: RCTs, clinical trials, and prospective observational studies with concurrent or historic comparison groups.
4.	Partial Yes: – Authors searched 4 databases. – Trial registries and grey literature were not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words and the search strategy were provided in Appendix 1. – No restrictions were applied on the language, publication year or status.	Partial Yes: – Authors searched 3 databases. – Authors searched trial registries: Cochrane Oral Health Group's Trials Register and US NIH Trials Register. – Grey literature was not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided in Appendices 1–5. – No restrictions were applied on the language.	Yes: – Authors searched 5 databases. – Authors searched trial registries: Current Controlled Trials Register and National Research Register. – Grey literature was searched by SIGLE and ISI Conference Proceedings. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided in Table 1. – No restrictions were applied on the language, publication year or status.
5.	Yes: As stated on page 377: "The full texts of the relevant studies were scrutinized by 2 reviewers (HC and TG) independently to select the eligible studies".	Yes: As stated on page 9: "Two review authors independently examined the title, key words and abstract of the reports identified through electronic searching".	Yes: As stated on page 390.e3: "all the selected articles were examined by 2 independent reviewers (SR and BC) to determine whether the eligibility criteria were met".
6.	Yes: As stated on page 377: "Data from all the eligible studies was extracted by 2 reviewers (HC and TG) independently, in duplicate".	Yes: As stated on page 9: "Data was extracted by 2 review authors independently, in duplicate, using specially designed data extraction forms".	Yes: As stated on page 390.e3: "data was extracted and methodological quality was assessed by 2 reviewers independently, in duplicate, using specially designed data extraction forms".
7.	Yes: As stated on page 378: "The list of the excluded articles and the reasons for exclusion are in Appendix II".	Yes: Authors provided the list of the excluded studies with the reasons for exclusion in Table "Characteristics of excluded studies".	Yes: Authors mentioned within the text on page 390.e3 in the "Results" section the relevant studies that were excluded from the review with the justification for exclusion.
8.	Partial Yes: Populations, interventions, comparators, outcomes, the study design, and follow-up were described, but not in details. Moreover, the study setting was not addressed.	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow up were all described in details in Table "Characteristics of included studies".	Partial Yes: Populations, interventions, comparators, outcomes, the study design, and follow-up were described, but not in details. Moreover, the study setting was not addressed.
9.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. Not-randomized trials were not included.	Yes: Randomized controlled trails were appropriately assessed by the RoB tool. Non-randomized trials were not included.	No: The risk of bias was not assessed.
10.	No: Funding for primary studies was not reported in the review.	Yes: The sources of funding for primary studies were reported in Table "Characteristics of included studies".	No: Funding for primary studies was not reported in the review.
11.	Meta-analysis was not performed.	Meta-analysis was not performed.	Meta-analysis was not performed.
12.	Meta-analysis was not performed.	Meta-analysis was not performed.	Meta-analysis was not performed.
13.	Yes: The risk of bias of studies was discussed with the reasons beyond this bias. Noteworthy, most trials were at a high risk of bias.	Yes: The risk of bias in individual studies was accounted for several times when interpreting and discussing the results.	No: The risk of bias was not assessed.
14.	No: Heterogeneity was not addressed.	No: Though it was planned to measure heterogeneity, reviewers did not provide the explanation for heterogeneity in the results, as meta-analysis was not conducted.	Yes: As stated on page 390.e5: "With regard to the materials used, the studies involved could be considered non-homogenous. The adhesives can all be described as containing fluoride, but they essentially have different chemical properties".
15.	Meta-analysis was not performed.	Meta-analysis was not performed.	Meta-analysis was not performed.
16.	Yes: As stated on page 376: "The authors report no commercial, proprietary or financial interest in the products or companies described in this article".	Yes: As stated on page 34: "No interests to declare".	Yes: As stated on page 390.e1: "The authors of this article report no commercial, proprietary or financial interest in the products or companies described in this article".

Continued Supplementary Table 3

	Chadwick 2005[19]	Derks 2004[14]
1.	No: The PICO components were not all included when addressing the inclusion criteria (comparison was not stated).	No: The PICO components were not all included when addressing the inclusion criteria.
2.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including all of the following: RCTs, clinical trials, and prospective observational studies with concurrent or historical comparison groups.	No: Authors did not provide the explanation for including only RCTs.
4.	No: – Authors searched 6 databases. – Trial registries and grey literature were not searched. – Key words were not provided. – No restrictions were applied on the language, publication year or status.	Partial Yes: – Authors searched 2 databases. – Trial registries, grey literature and bibliographies were not searched. – Key words and the search strategy were provided in Fig. 1. – Restrictions were applied on the language (only articles written in English).
5.	Yes: As stated on page 602: "For each stage, 2 independent reviewers were used. If their opinions differed, a third reviewer independently reviewed the article and decisions, and compared the results".	Yes: As stated on page 3: "Two observers (JE and AD) independently carried out the screening of publications based on the abstracts of the retrieved publications".
6.	Yes: As stated on page 602: "Finally, all the included studies were double-extracted onto data extraction sheets, which were compared. If there was disagreement, a third team member reviewed the article to resolve the disagreement".	No: The review did not contain an explicit statement that authors performed data extraction in duplicate.
7.	No: The list of the excluded studies and the reasons for exclusion were not provided.	Yes: The excluded studies and the reasons for exclusion were provided in Table 2.
8.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described, but not in details. Moreover, the authors' names, the study setting and follow-up were not addressed.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described, but not in details. Moreover, the study setting and follow-up were not addressed.
9.	No: The risk of bias was not assessed.	No: The risk of bias was not assessed.
10.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.
11.	Meta-analysis was not performed.	No: Authors did not justify combining the data in meta-analysis and did not investigate the causes of any heterogeneity.
12.	Meta-analysis was not performed.	No: The risk of bias was not assessed.
13.	No: The risk of bias was not assessed.	No: The risk of bias was not assessed.
14.	No: Heterogeneity was not addressed.	No: Heterogeneity was not addressed.
15.	Meta-analysis was not performed.	No: Publication bias was not assessed.
16.	No: Though authors mentioned their funding sources: "Funded by the Wales Office of Research and Development Health and Social Care grant No. R00/2/006", they did not explain how they managed the potential conflict of interest.	No: Neither funding nor conflicting interests were stated in the review.

PROSPERO – International Prospective Register of Systematic Reviews; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; DOAJ – Directory of Open Access Journals; PQDT – ProQuest Dissertations and Theses; CCT – controlled clinical trial; ROBINS-I – Risk Of Bias In Non-randomized Studies-of Intervention; NRSI – non-randomized studies of intervention; GRADE – Grading of Recommendations Assessment, Development and Evaluation; APF – acidulated phosphate fluoride; EWLS – enamel white spot lesions; ICTRP – International Clinical Trials Registry Platform; CONSORT – Consolidated Standards of Reporting Trials; NIH – National Institutes of Health; SIGLE – System for Information on Grey Literature in Europe; ISI – Institute for Scientific Information.

Supplementary Table 4. Detailed comparison of the reviews assessing topical fluoride application according to the Jadad decision algorithm

Are the included reviews addressing the same question?		
No.	Review	Question
1	Tasios 2019[15]	Are topical fluorides effective in the management of OIWSLs?
2	Sardana 2019[16]	Are topical fluorides effective in the management of OIWSLs?
3	Sardana 2019[4]	Are topical fluorides effective in the management of OIWSLs?
4	Nascimento 2016[13]	Are topical fluorides effective in the management of OIWSLs?
5	Lapenaite 2016[17]	Are topical fluorides effective in the management of OIWSLs?
6	Sonesson 2016[6]	Are topical fluorides effective in the management of OIWSLs?
7	Chen 2013[18]	Are topical fluorides effective in the management of OIWSLs?
8	Benson 2013[8]	Are topical fluorides effective in the management of OIWSLs?
9	Chadwick 2005[19]	Are topical fluorides effective in the management of OIWSLs?
10	Derks 2004[14]	Are topical fluorides effective in the management of OIWSLs?

Continued Supplementary Table 4

Given that the included reviews were addressing the same question, did the reviews include the same trials?		
No.	Review	Studies included
1	Tasios 2019[15]	1 – Kumar Jena 2015; 2 – Øgaard 1997; 2001; 3 – Stecksén-Blicks et al. 2007; 4 – Vivaldi-Rodrigues et al. 2006
2	Sardana 2019[16]	1 – Sonesson et al. 2014; 2 – van der Kaaij et al. 2015; 3 – Willmot 2004
3	Sardana 2019[4]	1 – Stecksén-Blicks et al. 2007; 2 – Jiang et al. 2013; 3 – Hutto Fretty 2014; 4 – Kirschneck et al. 2016; 5 – Du et al. 2012; 6 – Huang et al. 2013; 7 – He et al. 2016; 8 – Restrepo et al. 2016; 9 – Singh et al. 2016; 10 – Bock et al. 2017; 11 – Ebrahimi et al. 2017
4	Nascimento 2016[13]	1 – Vivaldi-Rodrigues et al. 2006; 2 – Stecksén-Blicks et al. 2007
5	Lapenaite 2016[17]	1 – Farhadian et al. 2008; 2 – Huang et al. 2013; 3 – Richter et al. 2011; 4 – Al Mulla et al. 2010; 5 – Du et al. 2012; 6 – Enaia et al. 2011; 7 – Baeshen et al. 2011
6	Sonesson 2016[6]	1 – Agarwal et al. 2013; 2 – Akin et al. 2012; 3 – Du et al. 2012; 4 – Huang et al. 2013
7	Chen 2013[18]	1 – Willmot 2004; 2 – Du et al. 2012; 3 – Baeshen et al. 2011; 4 – Andersson et al. 2007
8	Benson 2013[8]	1 – Luther 200; 2 – Stecksén-Blicks et al. 2007; 3 – Øgaard 2006
9	Chadwick 2005[19]	1 – Hirschfield 1978; 2 – Boyd 1992; 3 – Boyd 1993; 4 – D'Agostino et al. 1988; 5 – Denes 1991; 6 – Alexander 2000
10	Derks 2004[14]	1 – D'Agostino et al. 1988; 2 – Alexander and Ripa 2000

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Studies included
1	Tasios 2019[15]	**Population:** Human patients of any age, sex, ethnicity, or malocclusion. **Intervention:** Any intervention administered at the beginning of treatment with the aim to prevent the development of OIWSLs. **Control:** A control/placebo group or other intervention. **Outcome:** The incidence and severity of OIWSLs. **Study design:** Randomized or quasi-randomized prospective controlled trials, including both parallel and within-person randomized trials. **Limitations:** No limitations concerning the language, publication year or status were applied.
2	Sardana 2019[16]	**Population:** Patients undergoing multi-bracketed fixed orthodontic treatment or patients who had OIWSLs at the end of multi-bracketed fixed orthodontic treatment. **Intervention:** Self-applied topical fluorides in the form of fluoridated dentifrices, mouth rinses or home-applied gels used by patients. **Control:** Standard treatment, placebo control or no intervention control. Standard treatment (or routine treatment) was pre-defined as the use of any fluoride dentifrice containing 1000 / 1055 / 1100 / 1250 ppm of fluoride, as these are the most common concentrations in over-the-counter available dentifrices which have been found to effectively prevent caries in children and adolescents. **Outcome:** Studies that evaluated the prevention of OIWSLs during multi-bracketed fixed orthodontic treatment or the reversal of OIWSLs were included. For studies assessing the prevention of OIWSLs, changes in the incidence of OIWSLs during multi-bracketed fixed orthodontic treatment was the primary outcome, and for studies assessing the reversal of OIWSLs after multi-bracketed fixed orthodontic treatment, a reduction in the size of OIWSLs or mean fluorescence values or the prevalence of OIWSLs were the primary outcomes. **Study design:** Randomized or quasi-randomized prospective controlled trials. **Limitations:** Only articles written in English were included, with no limitations concerning the publication year or status.
3	Sardana 2019[4]	**Population:** Patients undergoing multi-bracketed fixed orthodontic therapy, or patients having 1 or more OIWSLs after the completion of multi-bracketed fixed orthodontic therapy. **Intervention:** Professionally applied topical fluorides in the form of gels, foams or varnishes. **Control:** Placebo control or no control. **Outcome:** Changes in the incidence, a decrease in the prevalence or changes in the size of OIWSLs. **Study design:** Randomized or quasi-randomized prospective controlled trials, including only parallel designs. **Limitations:** Only articles written in English were included, with no limitations concerning the publication year or status.
4	Nascimento 2016[13]	**Population:** Patients using fixed orthodontic appliances. **Intervention:** The use of fluoride-containing dental materials. **Control:** A control group not using these materials. **Outcome:** Only studies evaluating the risk of OIWSLs in terms of a binary outcome (the presence or absence of lesions) were included. **Study design:** RCTs, including both parallel and split-mouth designs. **Limitations:** No limitations concerning the language, publication year or status were applied.
5	Lapenaite 2016[17]	**Population:** Patients of any age undergoing treatment with fixed orthodontic appliances. **Intervention:** Fluoride-containing products or casein derivatives used throughout appliance therapy or immediately after debonding. **Control:** Not provided. **Outcome:** The prevention of OIWSLs. **Study design:** Randomized or quasi-randomized controlled clinical studies. **Limitations:** Only articles written in English and published between 2008 and 2013 were included.
6	Sonesson 2016[6]	**Population:** Adolescents and young adults (<30 years) with OIWSLs registered and scored within 3 months after the debonding of fixed orthodontic appliances. **Intervention:** Any intervention, except laminate veneers, with the aim to reverse OIWSLs or to improve their esthetic appearance. **Control:** No treatment, placebo or best clinical practice. **Outcome:** The extent, hardness or appearance of OIWSLs with a follow-up period of at least 8 weeks, as assessed with visual clinical scores, photographs, caries detection devices, or patient/therapist satisfaction. **Study design:** CCTs (randomized or non-randomized) on >20 subjects, including parallel and split-mouth designs. **Limitations:** Only articles written in English and published between 2011 and Oct 31, 2015 were included.

Continued Supplementary Table 4

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Studies included
7	Chen 2013[18]	**Population:** Participants who completed fixed orthodontic treatment and had at least 1 clinically visible lesion on the labial enamel surface upon the removal of fixed orthodontic appliances. **Intervention:** Remineralizing agents for the treatment of OIWSLs (i.e., any fluoride- or CPP-ACP-based system). **Control:** Patients subjected to different agents or not subjected to any intervention (placebo or no intervention). **Outcome:** Studies in which the primary outcome was a change in the severity of OIWSLs between the experimental and control groups, and the severity was expressed macroscopically in terms of the area over the whiteness of the lesion or microscopically as the amount of mineral loss or the lesion depth. **Study design:** RCTs. **Limitations:** No limitations concerning the language, publication year or status were applied.
8	Benson 2013[8]	**Population:** Participants of any age undergoing orthodontic treatment with fixed braces in cases when DWLs were assessed on the teeth remaining in the mouth at the end of orthodontic treatment (at debonding, immediately after the active fixed brace was removed). **Intervention:** Topical fluorides in the form of toothpastes, mouth rinses, gels, varnishes, or dietary sources at any dose, frequency, duration, or method of administration, and with any of the following active agents/ingredients: NaF, SMFP, SnF_2, APF, and AmF. **Control:** Individuals not subjected to the fluoride intervention, but instead treated with a placebo, such as a non-fluoride toothpaste and mouth rinse, or given no intervention. Studies involving a control group subjected to an alternative fluoride intervention were also included. **Outcome:** The presence or absence of new lesions by participant, differences in the size and severity of OIWSLs between the experimental and control groups, any quantitative assessment of enamel mineral loss, such as fluorescent light techniques or microradiography, used with in situ caries models, any participant-assessed outcomes, such as the perception of the lesions and oral health-related quality of life data, or adverse effects. **Study design:** RCTs, including only parallel designs. **Limitations:** No limitations concerning the language, publication year or status were applied.
9	Chadwick 2005[19]	**Population:** Human subjects undergoing orthodontic treatment with fixed appliances. **Intervention:** Topical fluorides used throughout appliance therapy. **Control:** Not provided. **Outcome:** The outcome measure had to be clearly described and reproducible, i.e., the severity of WSLs or DMFS. **Study design:** RCTs, clinical trials, and prospective observational studies with concurrent or historical comparison groups. **Limitations:** No limitations concerning the language, publication year or status were applied.
10	Derks 2004[14]	**Population:** Orthodontic patients in whom demineralization-inhibiting measures were applied during orthodontic treatment. **Intervention:** Topical fluorides used throughout appliance therapy. **Control:** Not provided. **Outcome:** The preventive measure was used from the beginning of orthodontic treatment with bonded fixed appliances until debonding. **Study design:** RCTs. **Limitations:** Only articles written in English were included, with no limitations concerning the publication year or status.

Given that different selection criteria were used, the Jadad algorithm would suggest assessing and comparing the publication status of primary studies, their methodological quality, language restrictions, and the analysis of data on individual patients.					
No.	Review	Publication status	Quality and quantity of primary studies	Language restrictions	Analysis of data on individual patients
1	Tasios 2019[15]	2019	4 trials: 1 – medium risk; 3 – high risk	no restrictions	aggregate data
2	Sardana 2019[16]	2019	3 trials: 1 – low risk; 2 – high risk	English-written only	systematic review
3	Sardana 2019[4]	Epub 2018	11 trials: 5 – low risk; 4 – medium risk; 2 – high risk	English-written only	aggregate data
4	Nascimento 2016[13]	2016	2 trials: all trials – high risk	no restrictions	aggregate data
5	Lapenaite 2016[17]	2016	7 trials quality not assessed	English-written only	systematic review
6	Sonesson 2016[6]	2016	4 trials: 1 – low risk; 3 – high risk	English-written only	systematic review
7	Chen 2013[18]	2013	4 trials: 1 – medium risk; 3 – high risk	no restrictions	systematic review
8	Benson 2013[8]	2013	3 trials: 1 – low risk, 1 – medium risk; 1 – high risk	no restrictions	systematic review
9	Chadwick 2005[19]	2005	6 trials quality not assessed	no restrictions	systematic review
10	Derks 2004[14]	2004	2 trials quality not assessed	English-written only	aggregate data
Accordingly, the study by Sardana et al.[4] (Epub 2018), which included 11 trials, assessed the risk of bias appropriately, including 5 trials at a low risk of bias and 4 trials at a medium risk of bias, was chosen to be the best available evidence regarding the effectiveness of topical fluorides in the management of OIWSLs.					

OIWSL – orthodontically induced white spot lesion; DWL – deep white lesion; SMFP – sodium monofluorophosphate; AmF – amine fluoride; WSL – white spot lesion; DMFS – decayed, missing, and filled teeth or surfaces.

Effect of casein phosphopeptide-amorphous calcium phosphate or other casein derivatives in the management of OIWSLs

Four systematic reviews appraised the outcomes from CPP-ACP application: Pithon et al. 2019,[20] Lapenaite et al. 2016,[17] Sonesson et al. 2016,[6] and Chen et al. 2013.[18] Two out of the 4 reviews found a lack of reliable evidence supporting the effectiveness of CPP-ACP.[6,18] Considering that these reviews were addressing the same question, using different trials and different selection criteria, the Jadad tool would once again suggest that the best available review be selected according to the superiority in its publication status, the methodological quality of its primary studies, language restrictions, and the analysis of data on individual patients. As a result, Pithon et al. 2019[20] was selected (Fig. 4). The detailed steps of the Jadad decision algorithm are provided in Supplementary Table 5.

Pithon et al. 2019[20] included 11 primary trials (9 RCTs and 2 CCTs) published between 2007 and 2016. The studies used either a parallel or cross-over design. The results indicated that CPP-ACP-containing products were effective in both preventing and reversing OIWSLs.

Effect of fluoride-releasing bonding materials in the management of OIWSLs

This outcome was addressed by 4 reviews: Tasios et al. 2019,[15] Nascimento et al. 2016,[13] Rogers et al. 2010,[21] and Derks et al. 2004.[14] The results of these reviews were inconsistent, indicating respectively that fluoride-releasing materials were not effective in the management of OIWSL; fluoride-releasing materials reduced the risk of lesion development; it was impossible to make recommendations on the use of fluoride-containing orthodontic adhesives; and the effect of fluoride-containing bonding materials was not statistically significant.

As in the previous situations, these reviews addressed the same question, but included different trials and utilized different selection criteria. Therefore, the best available review would be selected according to the superiority in its publication status, the methodological quality of its primary studies, language restrictions, and the analysis of data on individual patients. Accordingly, Tasios et al. 2019[15] was selected (Fig. 4). The detailed steps of the Jadad decision algorithm applied from the beginning until the final decision are provided in Supplementary Table 6.

Tasios et al. 2019[15] included 10 studies assessing the effectiveness of fluoride-containing bonding materials in the management of OIWSLs. All the studies had a split-mouth design. Data synthesis revealed that fluoride-releasing adhesives and glass-ionomer bracket adhesives showed no statistically significant differences in comparison with conventional and resin adhesives.

Effect of laser therapy in the management of OIWSLs

Only 1 systematic review was conducted to evaluate this outcome – Raghis et al. 2018,[3] including 8 trials (5 RCTs and 3 CCTs) published between 2000 and 2015. Different laser types were utilized in an attempt to manage OIWSLs, including CO_2, neodymium-doped yttrium aluminum garnet (Nd:YAG), argon, and Optodan® lasers. All primary studies indicated that laser irradiation was effective in the management of OIWSLs, with the exception of an argon laser with parameters of 250 mW, 12 J/cm^2, a beam diameter of 5 mm, and a duration of 10 s. An argon laser within these particular parameters demonstrated a positive effect in a study by Blankenau et al.,[22] whilst no effect was noticed in a study by Elaut and Wehrbein 2004.[23]

Effect of resin infiltration and micro-abrasion in the management of OIWSLs

The only systematic review to be included which addressed the effect of resin infiltration and micro-abrasion on OIWSLs was by Sonesson et al. 2016.[6] This review included 2 primary studies[24,25] that evaluated the efficacy of resin infiltration and 1 primary study[26] that evaluated the efficacy of micro-abrasion. Although these studies revealed both strategies to be effective, the results of this review indicated a lack of reliable scientific evidence to support camouflaging strategies in managing OIWSLs due to the limited number of available studies.

Discussion

To the best of our knowledge, this review of reviews represents the first state-of-the-art appraisal of the efficacy of different adjunctive interventions in the management of OIWSLs. The adjunctive interventions in question were topical fluorides, the CPP-ACP products, fluoride-releasing adhesives, laser therapy, resin infiltration, and micro-abrasion. The best available evidence regarding these interventions was derived from 5 separate reviews.

Regarding topical fluoride application, 10 of the systematic reviews made an assessment, 3 of which found a lack of reliable evidence in support of fluoride. Indeed, discordant conclusions are likely due to the conflicting results of primary studies. Therefore, it is worth highlighting 2 gaps in the evidence base in order to interpret these results. Firstly, though many relevant reviews and original studies have been conducted, the best clinical fluoride concentration in the management of OIWSLs was deemed to be unclear; in other words, most primary studies used different fluoride concentrations with different forms of application. A study by Bailey et al. raised warnings against high concentrations of fluoride, which may arrest the remineralization of deeper layers through superficial hypermineralization, thus jeopardizing the esthetic treatment result.[27]

Supplementary Table 5. Detailed comparison of the reviews assessing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) or other casein derivatives according to the Jadad decision algorithm

Are the included reviews addressing the same question?		
No.	Review	Question
1	Pithon 2019[20]	Is CPP-ACP application effective in the management of OIWSLs?
2	Lapenaite 2016[17]	Is CPP-ACP application effective in the management of OIWSLs?
3	Sonesson 2016[6]	Is CPP-ACP application effective in the management of OIWSLs?
4	Chen 2013[18]	Is CPP-ACP application effective in the management of OIWSLs?

Given that the included reviews were addressing the same question, did the reviews include the same trials?		
No.	Review	Studies included
1	Pithon 2019[20]	1 – Akin and Basciftci 2012; 2 – Andersson et al. 2007; 3 – Bailey et al. 2009; 4 – Beerens et al. 2010; 5 – Bröchner et al. 2011; 6 – Heshmat et al. 2014; 7 – Huang et al. 2013; 8 – Robertson et al. 2011; 9 – Singh et al. 2016; 10 – Uysal et al. 2010; 11 – Wang et al. 2012
2	Lapenaite 2016[17]	1 – Huang et al. 2013; 2 – Robertson et al. 2011; 3 – Bailey et al. 2009; 4 – Beerens et al. 2010; 5 – Bröchner et al. 2011
3	Sonesson 2016[6]	1 – Akin and Basciftci 2012; 2 – Huang et al. 2013; 3 – Vashisht 2013
4	Chen 2013[18]	1 – Andersson et al. 2007; 2 – Bröchner et al. 2011; 3 – Bailey et al. 2009; 4 – Beerens et al. 2010

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Selection criteria
1	Pithon 2019[20]	**Population:** Orthodontic patients with labial fixed appliances. **Intervention:** The use of CPP-ACP-containing products. **Control:** Other oral agents or placebos. **Outcome:** The prevention or treatment of OIWSLs around orthodontic braces. **Study design:** CCTs (randomized or non- randomized). **Limitations:** No limitations concerning the language, publication year or status were applied.
2	Lapenaite 2016[17]	**Population:** Patients of any age undergoing treatment with fixed orthodontic appliances. **Intervention:** Fluoride-containing products or casein derivatives used throughout appliance therapy or immediately after debonding. **Control:** Not provided. **Outcome:** The prevention of OIWSLs. **Study design:** Randomized or quasi-randomized controlled clinical studies. **Limitations:** Only articles written in English and published between 2008 and 2013 were included.
3	Sonesson 2016[6]	**Population:** Adolescents and young adults (<30 years) with OIWSLs registered and scored within 3 months after the debonding of fixed orthodontic appliances. **Intervention:** Any intervention, except laminate veneers, with the aim to reverse OIWSLs or to improve their esthetic appearance. **Control:** No treatment, placebo or best clinical practice. **Outcome:** The extent, hardness or appearance of OIWSLs with a follow-up period of at least 8 weeks, as assessed with visual clinical scores, photographs, caries detection devices, or patient/therapist satisfaction. **Study design:** CCTs (randomized or non-randomized) on >20 subjects, including parallel and split-mouth designs. **Limitations:** Only articles written in English and published between 2011 and Oct. 31, 2015 were included.
4	Chen 2013[18]	**Population:** Participants who completed fixed orthodontic treatment and had at least 1 clinically visible lesion on the labial enamel surface upon the removal of fixed orthodontic appliances. **Intervention:** Remineralizing agents for the treatment of OIWSLs (i.e., any fluoride- or CPP-ACP-based system). **Control:** Patients subjected to different agents or not subjected to any intervention (placebo or no intervention). **Outcome:** Studies in which the primary outcome was a change in the severity of OIWSLs between the experimental and control groups, and the severity was expressed macroscopically in terms of the area over the whiteness of the lesion or microscopically as the amount of mineral loss or the lesion depth. **Study design:** RCTs. **Limitations:** No limitations concerning the language, publication year or status were applied.

Given that different selection criteria were used, the Jadad algorithm would suggest assessing and comparing the publication status of primary studies, their methodological quality, language restrictions, and the analysis of data on individual patients.					
No.	Review	Publication status	Quality and quantity of primary studies	Language restrictions	Analysis of data on individual patients
1	Pithon 2019[20]	2019	11 trials: 9 – low risk; 2 – medium risk	no restrictions	systematic review
2	Lapenaite 2016[17]	2016	5 trials quality not assessed	English-written only	systematic review
3	Sonesson 2016[6]	2016	3 trials: 1 – low risk; 2 – high risk	English-written only	systematic review
4	Chen 2013[18]	2013	4 trials: all trials – high risk	no restrictions	systematic review
Accordingly, the study by Pithon et al.[20] (2019), which included 11 trials, where 9 trials were at a low risk of bias and 2 trials at a medium risk of bias, was chosen to be the best available evidence regarding the effectiveness of CPP-ACP-containing products in the management of OIWSLs.					

Supplementary Table 6. Detailed comparison of the reviews assessing fluoride-containing bonding materials according to the Jadad decision algorithm

Are the included reviews addressing the same question?		
No.	Review	Question
1	Tasios 2019[15]	Are fluoride-containing materials effective in the management of OIWSLs?
2	Nascimento 2016[13]	Are fluoride-containing materials effective in the management of OIWSLs?
3	Rogers 2010[21]	Are fluoride-containing materials effective in the management of OIWSLs?
4	Derks 2004[14]	Are fluoride-containing materials effective in the management of OIWSLs?

Given that the included reviews were addressing the same question, did the reviews include the same trials?		
No.	Review	Studies included
1	Tasios 2019[15]	1 – Allabdullah 2017; 2 – Banks et al. 1997; 3 – Gaworski 1999; 4 – Marcusson et al. 1997; 5 – Millett et al. 1999; 6 – Mitchell 1992; 7 – Trimpeneers and Dermaut 1996; 8 – Turner 1993; 9 – Adriaens 1990; 10 – van der Linden 1998
2	Nascimento 2016[13]	1 – Sonis and Snell 1989; 2 – Trimpeneers and Dermaut 1996; 3 – Marcusson et al. 1997; 4 – Millett et al. 2000
3	Rogers 2010[21]	1 – Sonis and Snell 1989; 2 – Marcusson et al. 1997; 3 – Millett et al. 1999; 4 – Gaworski 1999; 5 – Turner 1993; 6 – Banks et al. 1997; 7 – Mitchell 1992; 8 – Trimpeneers and Dermaut 1996; 9 – Millet et al. 2000; 10 – Gillgrass 2001
4	Derks 2004[14]	1 – Mitchell 1992; 2 – Turner 1993; 3 – Trimpeneers and Dermaut 1996; 4 – Marcusson et al. 1997; 5 – Banks et al. 1997; 6 – Millet et al. 1999; 7 – Millet et al. 2000

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Selection criteria
1	Tasios 2019[15]	**Population:** Human patients of any age, sex, ethnicity, or malocclusion. **Intervention:** Any intervention administered at the beginning of treatment with the aim to prevent the development of OIWSLs. **Control:** A control/placebo group or other intervention. **Outcome:** The incidence and severity of OIWSLs. **Study design:** Randomized or quasi-randomized prospective controlled trials, including both parallel and within-person randomized trials. **Limitations:** No limitations concerning the language, publication year or status were applied.
2	Nascimento 2016[13]	**Population:** Patients using fixed orthodontic appliances. **Intervention:** The use of fluoride-containing dental materials. **Control:** A control group not using these materials. **Outcome:** Only studies evaluating the risk of OIWSLs in terms of a binary outcome (the presence or absence of lesions) were included. **Study design:** RCTs, including both parallel and split-mouth designs. **Limitations:** No limitations concerning the language, publication year or status were applied.
3	Rogers 2010[21]	**Population:** Patients who completed a full course of fixed orthodontic treatment. **Intervention:** Fluoride-containing adhesives. **Control:** Not provided. **Outcome:** Decalcification at the baseline and the end point of the study. When possible, the total number of OIWSLs, decalcifications as well as DMFT were recorded for the start and finish of the trial for both the subjects and the teeth. **Study design:** RCTs, clinical trials, and prospective observational studies with concurrent or historic comparison groups. **Limitations:** No limitations concerning the language, publication year or status were applied.
4	Derks 2004[14]	**Population:** Orthodontic patients in whom demineralization-inhibiting measures were applied during orthodontic treatment. **Intervention:** Topical fluorides used throughout appliance therapy. **Control:** Not provided. **Outcome:** The preventive measure was used from the beginning of orthodontic treatment with bonded fixed appliances until debonding. **Study design:** RCTs. **Limitations:** Only articles written in English were included, with no limitations concerning the publication year or status.

Given that different selection criteria were used, the Jadad algorithm would suggest assessing and comparing the publication status of primary studies, their methodological quality, language restrictions, and the analysis of data on individual patients.					
No.	Review	Publication status	Quality and quantity of primary studies	Language restrictions	Analysis of data on individual patients
1	Tasios 2019[15]	2019	10 trials: 3 – medium risk; 7 – high risk	no restrictions	aggregate data
2	Nascimento 2016[13]	2016	4 trials: all trials – high risk	no restrictions; however, only 1 database searched	aggregate data
3	Rogers 2010[21]	2010	10 trials quality not assessed	no restrictions	systematic review
4	Derks 2004[14]	2004	7 trials quality not assessed	English-written only	aggregate data
Accordingly, the study by Tasios et al.[15] (2019), which included 10 trials, assessing fluoride-containing adhesives, was chosen to be the best available evidence regarding the effectiveness of fluoride-containing bonding materials in the management of OIWSLs.					

DMFT – decayed, missing and filled teeth.

On the other hand, a study by Sonesson et al. indicated that high concentrations of fluoride could significantly manage OIWSLs.[28] Secondly, the inappropriate split-mouth design which was used by some primary studies might manipulate the outcomes, as fluorides could be distributed throughout the mouth by saliva and a carry-over or cross-contamination effect would be possible. Consequently, more robust, randomized, parallel-designed CCTs are still required.

As far as CPP-ACP-containing products are concerned, 2 out of 4 reviews found a lack of reliable evidence to support the effectiveness of CPP-ACP. Conflicts could be attributed to the application protocols, which differed with regard to application duration and frequency.[27,29] The best current evidence, according to the Jadad decision algorithm, indicated that the release of phosphate and calcium ions from the CPP-ACP products led to the saturation of the medium and the re-establishment of oral pH, thereby achieving a remineralization effect.[20]

Concerning the efficacy of fluoride-emitting adhesives, the best available evidence proposed that no statistically significant differences were found between conventional and fluoride-releasing adhesives[15]; however, these results have to be treated with considerable caution, because the primary studies included in all the reviews followed a split-mouth design, which also might result in a cross-contamination effect and incorrect data.

Regarding laser application, the only systematic review which was concerned in this intervention was from Raghis et al. 2018.[3] Their results proposed that laser therapy was effective in preventing OIWSLs by assuming that laser application would lead to a higher enamel microhardness than in the case of the non-irradiated enamel.[3]

Resin infiltration and micro-abrasion have been recently proposed for camouflaging OIWSLs. Contemporary studies on etching and the development of a material with a high penetration coefficient, called an infiltrant, have expanded the use of the resin infiltration technique.[30] Regarding technical concerns, the application of resin infiltration must be repeated several times, while the micro-abrasion technique is normally administered at a single appointment.[6] Although primary studies in the review by Sonesson et al. 2016[6] revealed both techniques to be effective, a definite conclusion could not be drawn due to the limited number of studies. Perhaps more importantly, the long-term success rate of both techniques is still unknown; therefore, these methods should be used selectively on challenging cases.

Limitations

As with all reviews, this review has strengths and limitations. With regard to strengths, we followed the PRISMA checklist, applied an extensive electronic search, used the AMSTAR-2 tool in order to assess the quality of the selected reviews, and chose the best current evidence from among multiple reviews handling multiple methods of OIWSL management.

The review-of-reviews approach relies on 'second-hand' information, so it is potentially vulnerable to the interpretive biases of the previous reviewers. We attempted to control this using an objective method to choose the best available evidence, i.e., the Jadad decision algorithm. Additionally, all the included reviews ranged in quality between critically low to moderate and some results were ultimately drawn based on critically-low-quality reviews. The heterogeneity of the topical fluoride concentrations used in primary studies, the various CPP-ACP application protocols used and the inappropriate split-mouth design of many of primary studies assessing fluoride-releasing adhesives are considered to be the limitations of this review. Finally, as in all reviews of reviews, the most recent primary trials may not be covered.

Conclusions

Based on the currently available information and the Jadad decision algorithm criteria, topical fluorides yielded a 25–30% prevention of OIWSLs; however, their effect on reversing OIWSLs is unclear. The CPP-ACP products are effective in preventing and reversing OIWSLs. Fluoride-releasing adhesives offer no significant differences in comparison with conventional adhesives. Laser irradiation is effective in preventing OIWSLs, with some concerns regarding argon lasers. Finally, there is a lack of a reliable evidence to support resin infiltration and micro-abrasion due to the limited number of available studies.

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Osteopetrosis complicated by osteomyelitis of the maxilla: A rare case report and review of the literature

Osteopetroza powikłana zapaleniem szpiku szczęki – opis rzadkiego przypadku i przegląd piśmiennictwa

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Abstract

Osteopetrosis is a rare hereditary bone disorder that results in an increase in bone density due to gene mutations and osteoclastic dysfunction. This may lead to cranial nerve compression, bone fractures and osteomyelitis. Osteomyelitis of the maxilla is rare even in osteopetrosis patients.

We report on a case of a 25-year-old male who presented with multiple episodes of osteomyelitis of the maxilla following dental extractions. The patient was initially managed with the incision and drainage of an acute infection, and intravenous amoxicillin-clavulanic acid. This was followed by the debridement of necrotic bony margins and packing with bismuth iodoform paraffin paste (BIPP) as well as long-term clindamycin. Once osteomyelitis was clear, the primary closure was achieved with a buccal advancement flap and supported by an acrylic obturator. Challenges in the management are highlighted, including preparing for a surgical intervention a patient with chronic low hemoglobin levels and a lack of healthy bony margins in the maxilla. The literature is also reviewed for similar cases.

Key words: osteomyelitis, maxilla, osteopetrosis

Słowa kluczowe: zapalenie szpiku, szczęka, osteopetroza

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Introduction

Osteopetrosis is a rare hereditary bone disorder that results in an increase in bone density due to gene mutations and osteoclastic dysfunction. The disorder is classically divided into 3 types with variable clinical features. The dominant form of osteopetrosis is typically seen in adults with a late onset whereas the 2 recessive forms of osteopetrosis are typically observed in children with an early onset and a high mortality rate. As bone expansion occurs, marrow spaces become obliterated, which results in fractures, poor wound healing and an increased risk of infections, such as osteomyelitis. Osteomyelitis of the maxilla is relatively rare owing to rich collateral blood supply and thin cortical bone. The diagnosis is established with a thorough history, and physical and radiographic examinations, with the latter being the mainstay. Treatment principles involve managing the identified complications. In the case of osteomyelitis, conservative and preventative care principles play a significant role in the management of patients with osteopetrosis. It is vital that patients with osteopetrosis are made aware of good oral hygiene and dental care practices so as to avoid the need for further treatment. Carious teeth should thus initially be treated with restorations or the endodontic therapy with the aim of preventing tooth extractions and the subsequent surgical complications, such as osteomyelitis. If conservative and preventative measures are compromised, and patients with osteopetrosis develop osteomyelitis, the debridement of necrotic tissue with an adjunctive antibiotic therapy is mandated.[1]

Case report

A 25-year-old male patient was referred to the Department of Maxillofacial and Oral Surgery at the University of the Western Cape, Tygerberg Hospital in Cape Town, South Africa, with chronic infections and recurrent swelling. The patient reported that the infective process had started 6 months ago, after the extraction of the upper right molar, and had exacerbated 1 day prior to presentation at the clinic.

Past medical history revealed that the patient sustained multiple bone fractures throughout his life, such as forearm and ankle fractures. Upon proceeding with a detailed history, and physical and radiographic examinations, the diagnosis of osteopetrosis with underlying osteomyelitis was confirmed. The patient was not on any chronic medications and had not been on antiresorptive/antiangiogenic agents previously.

Clinically, the patient presented with soft, tender, right facial swelling associated with the right canine space region and the upper lip. Intraorally, the mandible appeared edentulous and pus discharge was found in the right maxillary region with a draining fistula associated with the right first molar area (Fig. 1). A radiographic examination demonstrated increased bone opacity, poorly pneumatized paranasal sinuses and multiple unerupted teeth (Fig. 2). Additionally, cone-beam computed tomography (CBCT) further illustrated increased bone opacity with poor differentiation between medullary and cortical bone (Fig. 3).

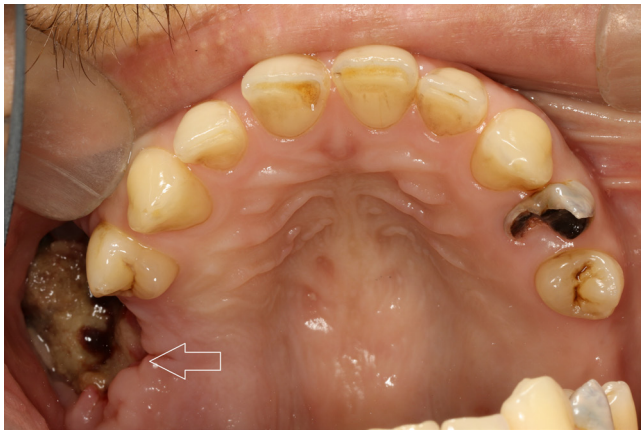

Fig. 1. Intraoral image showing the osteomyelitis of the right maxilla following a dental extraction

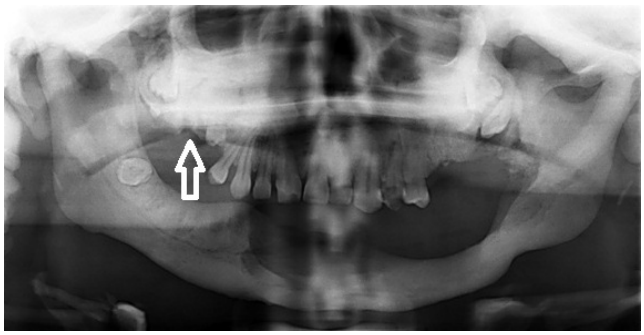

Fig. 2. Pantomograph of the patient showing opacity in the maxilla and multiple unerupted teeth (note the previous marginal resection of the left mandible)

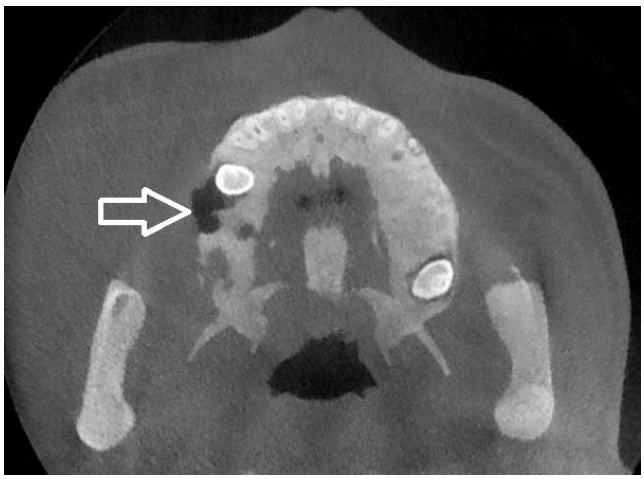

Fig. 3. Axial cone-beam computed tomography (CBCT) scan showing right-sided osteomyelitis in the maxilla

With regard to the management of the patient at this point, the retained root of a maxillary first molar was surgically removed, incision and drainage were performed, a pus swab was taken, and augmentin IV was administered for 7 days. Following this initial intervention, swelling decreased and the patient reported the alleviation of pain.

Three weeks following discharge, the patient returned, complaining of severe pain and tenderness associated with the same area. An intraoral examination revealed pus discharge from a non-healing maxillary first molar socket with areas of exposed bone. The region was then debrided and packed with bismuth iodoform paraffin paste (BIPP) gauze, the canine space was explored and irrigated, and biopsy was performed. Thereafter, the patient was admitted for 7 days for monitoring and irrigation, with an adjunctive antibiotic therapy in the form of 1.2 g of augmentin, administered intravenously (i.v.) every 8 h pending microscopy, culture and sensitivity testing. At day 3 of admission, the patient was switched to 600 mg of clindamycin i.v. every 6 h, as the cultured bacteria were resistant to penicillin. Hematological studies revealed reductions in the red blood cell count (2.78×10^{12}/L), hemoglobin (6.8 g/dL) and platelet count (146×10^{9}/L) with the C-reactive protein level markedly elevated (83 mg/L). Additionally, the iron level was at the lower limit of the normal range, requiring the prescription of ferric sulfate. The histological examination of the obtained biopsy showed strips of acanthotic, stratified squamous oral mucosa with dense submucosal chronic inflammation (Fig. 4). Fragments of non-vital bone with the surrounding cellular debris, hemorrhage and basophilic bacterial colonization were noted, which was indicative of a sequestrum.

Following that, the patient required 2 additional debridements under general anesthesia with blood transfusions due to chronic low hemoglobin. The patient was also prescribed pentoxifylline and tocopherol orally to aid in bone healing. The wound was then closed, primarily with a buccal advancement flap, and an acrylic obturator was used to support the wound.

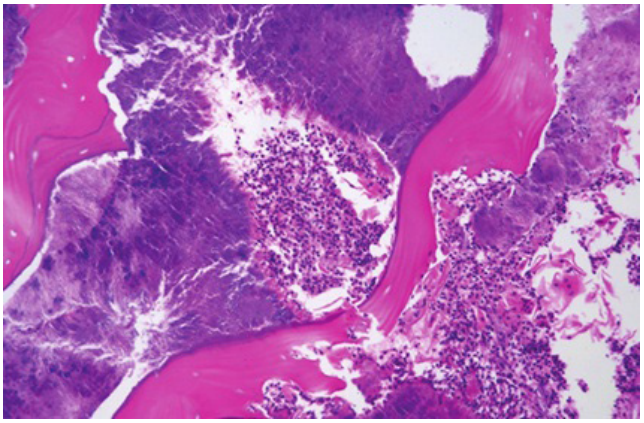

Fig. 4. Hematoxylin and eosin (H&E)-stained slide showing the signs of suppurative osteomyelitis with inflammatory infiltrate and necrotic bone

Discussion

Multiple genetic mutations are responsible for the presentation of osteopetrosis.[2] The mutated genes of significance include *CLCN7* and *TGIRG1*, which results in the functional defects of the enzyme carbonic anhydrase II.[2] Osteoclasts ultimately cannot form ruffled borders, causing defective bone resorption with the subsequent accumulation of bone, thereby increasing bone density and the fracture risk.[2]

Osteopetrosis is classified into 3 clinical categories, namely benign autosomal dominant, severe malignant autosomal recessive and intermediate mild autosomal recessive. The dominant form of the disorder is more common in adults. In contrast, the rarer autosomal recessive types are typically associated with an early onset and poor prognosis.[2]

Bones in patients with osteopetrosis are poorly vascularized. This adversely affects the healing process and results in a marked increase in infection susceptibility.[3] As bone becomes denser, its marrow cavities and the pulpal chambers of the teeth become obliterated with the resultant constriction of the neurovascular bundles supplying the jaws and the teeth.[3] The extension of bone into the cranial nerve foramina and marrow cavities may compromise both hematologic and neurological functions.[4] Hematological compromises include frequent infections, profound anemia and hepatosplenomegaly,[4] as in the case of our patient. Neurological compromises may result in nerve palsies, deafness and blindness.[4] Additionally, dental caries and bone necrosis may also develop as a consequence of bone expansion, which ultimately results in osteomyelitis.[5] Osteomyelitis is thus a well-known complication associated with osteopetrosis due to its hypovascular nature.[1] This infection commonly presents in the mandible post-extraction or after the surgical exposure of bone, warranting adequate infection control practices before and after dental surgical procedures.[1]

In the dental setting, patients with osteopetrosis present with complications such as dental caries, premature tooth loss, delayed eruption of teeth, enamel hypoplasia, tooth crown and root malformations, and thickened lamina dura.[5]

The diagnosis of osteopetrosis is based on both clinical and radiographic findings, with the latter being the mainstay.[5] A radiographic examination reveals diffuse osteosclerosis, involving the spine, the skull, the pelvis, and appendicular bones. Additionally, cortical thickening with the resultant medullary encroachment can be visualised.[6] Differential diagnoses that are to be considered include metaphyseal dysplasia, pyknodysostosis, diaphyseal sclerosis, osteopathia striata, osteopoikilosis, melorheostosis, Camurati–Engelmann disease, and infantile cortical sclerosis.[5]

Table 1. Summary of 24 reported cases of osteomyelitis of the maxilla in patients with osteopetrosis

Study	Patient's age	Patient's gender	Clinical signs	Radiographic signs	Management
Celakil et al. 2016[3]	48	male	purulent discharge from the maxilla	extensive bone defects of the maxilla and the mandible	– dental extractions – sequestrectomy – use of a denture as an obturator
de Azambuja Carvalho et al. 2018[9]	40	male	pain and swelling of the left buccal, periorbital and temporal regions, a fistula in the left maxillary region	CT scan showing temporoparietal and maxillary swelling	surgical management: – incision and drainage – sequestrectomy – partial resection of the left maxilla and the zygomatic bone – treatment with hyperbaric oxygen post-operative antibiotics: – ciprofloxacin for 6 months – clindamycin for 6 months
Pavan et al. 2018[10]	13	male	diffuse, erythematous, tender swelling of the right maxillary and zygomatic regions, a slight mobility of the right maxillary molars with a discharging sinus	increased bone density, the obliteration of the frontal and maxillary sinuses	The extractions of necessary teeth and the sinus tract excision were recommended, but the patient's parents refused surgical interventions. The patient was managed with systemic antibiotics and blood transfusions due to the resultant anemia.
Kulyapina et al. 2016[11]	66	male	oroantral fistula, a non-healing socket of a third molar with areas of exposed bone, hearing impairment	area of bone destruction and sequestrum formation in the right maxilla	initial management: – systemic antibiotics for 1 month surgical management: – closure of the oroantral fistula – sequestrectomy
Mikami et al. 2016[12]	54	male	pain and swelling of the right facial region, trismus	radiolucent areas associated with the maxillary and mandibular molars	– dental extractions – sequestrectomy – cephazolin – clindamycin
de Carvalhosa et al. 2016[13]	6	female	avulsion of 2 maxillary central incisors, resulting in a non-healing wound, exposed necrotic bone in the anterior maxilla	intense opacity of the cortical bone of the maxilla and the periorbital region	– extractions of unerupted maxillary teeth – sequestrectomy
Infante-Cossio et al. 2014[14]	40	female	cutaneous fistula with purulent discharge from the bilateral submandibular and right infraorbital regions, exposed necrotic bone, blindness due to optic nerve compression	diffuse opacity of the maxillary and mandibular bone, multiple impacted teeth	initial management: – amoxicillin/clavulanic acid for 1 month surgical management: – local debridement
Adachi et al. 2013[15]	44	female	fistula with purulent discharge in the left maxillary buccal region	generalized sclerosis of the maxilla and the mandible, the obliteration of the maxillary sinuses	initial management: – cefazolin for 7 days. surgical management: – sequestrectomy
Arunkumar et al. 2011[16]	54	male	chronic discharge, swelling and an ulcer over the left cheek, a discharging sinus tract inferior to the left outer canthus, oroantral fistula	destruction of the alveolar process in the 2nd quadrant and the left zygomatic arch	– ofloxacin – extractions of involved teeth – excision of the fistula – sequestrectomy
Balan et al. 2011[17]	8	male	painful left-sided facial swelling with purulent discharge from a carious primary molar	increased bone density, diffuse sclerosis, multiple unerupted teeth	– systemic antibiotics – local debridement of the maxilla
Khademi et al. 2011[18]	15	male	bilateral facial pain and swelling with infraorbital sinus tract drainage, vision and hearing problems	obliteration of the maxillary sinuses, sequestration of the maxilla and the zygomatic bone	initial management: – clindamycin surgical management: – curettage – sequestrectomy – sinus tract excision
Ambika et al. 2010[19]	28	male	non-healing extraction socket with exposed necrotic bone in the right molar region associated with painful, extraorally draining facial swelling	increased bone density, erosion of the buccal cortices of the right maxilla, the zygomatic bone, the lateral orbital wall, and the maxillary sinus	– ciprofloxacin – local debridement – sequestrectomy Partial maxillectomy was planned, but the patient refused treatment.
Oğütcen-Toller et al. 2010[20]	18	female	purulent discharge from the infraorbital and left maxillary molar regions, partial edentulism with multiple malformed teeth, blindness	diffuse hyperdensity of the maxilla and the mandible, sequestrum formation, multiple impacted teeth	initial management: – amoxicillin for 7 days surgical management: – extractions of all partially impacted and malformed teeth – sequestrectomy post-operative antibiotics: – sultamicillin and ornidazole for 5 weeks – treatment was altered to clindamycin for 1 week, sultamicillin and ornidazole for 3 weeks followed by cefuroxime axetil for 4 weeks

Continued Table 1

Study	Patient's age	Patient's gender	Clinical signs	Radiographic signs	Management
Krithika et al. 2009[21]	18	male	purulent discharge bilaterally from buccal mucosa, yellow-white exposed bone appearing bilaterally in the maxilla at non-healing molar extraction sites, vision and hearing impairment	increased bone density with the diffuse sclerosis of the maxillary and zygomatic bones	initial management: – blood transfusion to address anemia – augmentin surgical management: – corticotomy
Krithika et al. 2009[21]	16	male	infraorbital, cutaneous pus-draining sinus following a dental extraction, generalized enamel hypoplasia, multiple missing permanent teeth	generalized sclerosis of bones with an increase in bone density, the obliteration of the maxillary and paranasal sinuses	initial management: – blood transfusion to address anemia – levofloxacin for 1 week surgical management: – sequestrectomy
Trivellato et al. 2009[22]	25	male	recent extraction socket with right maxillary and mandibular bone exposure with associated cutaneous draining fistulas	increased bone density, multiple edentulous areas	initial management: – clindamycin surgical management: – marginal resection of the right maxilla and mandible – partial resection of the mandible after recurrence
Vázquez et al. 2009[23]	23	female	infection of the right posterior maxilla and anterior mandible with an associated fistula	marked increase in bone opacity, periapical radiolucency associated with the mandibular teeth	– dental extractions – curettage of sockets – penicillin IV for 3 weeks
Barry et al. 2007[24]	28	female	oroantral fistula, poorly healed extraction socket with areas of visible sequestration, mucopurulent discharge from middle meati	osteosclerosis, moth-eaten appearance, the bone destruction of the maxillary sinus, the hard palate and the left nasal cavity	conservative management: – metranidazole – cefuroxime – 0.1% betamethasone sodium phosphate nasal drops
Barry et al. 2007[24]	27	female	severe halitosis with chronic nasal discharge, oroantral fistula with purulent discharge	increased bone density	– amoxicillin/clavulanic acid – local debridement – antral wash – closure of the oroantral fistula with a buccal advancement flap
Junquera et al. 2005[25]	60	female	poorly healed extraction sockets with sequestrum formation in the 2nd quadrant	bone destruction with visible sequestration	initial management: – amoxicillin/clavulanic acid for 1 month surgical management: – sequestrectomy
Fernandez et al. 2003[26]	9	female	painful, erythematous swelling of the left maxillary region with purulent discharge from the cutaneous sinus tract, unerupted maxillary teeth, vision problems	increased bone density, radiolucency associated with first and second molars, multiple unerupted and malformed permanent teeth	initial management: – clindamycin – blood transfusion to address anemia surgical management: – curettage – local debridement
Long et al. 2001[27]	54	male	palatal swelling, an oroantral fistula, multiple draining fistulas of the maxilla	reduced marrow spaces, areas of necrotic maxillary bone	– systemic antibiotics – extractions of remaining maxillary teeth – local debridement – sequestrectomy
Crockett et al. 1986[28]	24	female	diffuse swelling of the left middle and lower thirds of the face with a draining sinus tract, soft green-colored exposed bone in the 2nd quadrant	increased bone density, generalized sclerosis of bone, bone destruction of the left maxilla, the antrum and the zygomatic bone	initial management: – cefoxitin IV surgical management: – removal of polypoid nasal tissue – sequestrectomy – left partial maxillectomy rehabilitation: – upper denture with an obturator to close the surgical defect
Sofferman et al. 1971[29]	27	female	exposed necrotic anterior maxillary alveolar bone with halitosis and purulent nasal discharge following the extractions of the maxillary teeth, total blindness of the right eye	obliteration of the maxillary sinuses, sequestration of the left maxilla	– local debridement – sequestrectomy – drains placed from the maxillary sinuses through nasal antrostomies – construction of a maxillary prosthesis

CT – computed tomography.

If patients start exhibiting such symptoms as fractures, sepsis, or hematological or neurological abnormalities, medical consultation and management may be necessary.[7] Management principles aim to modulate and stimulate osteoclastic activity.[5] Attempts at stimulating osteoclastic activity have been made previously, all with variable success rates, such as utilizing the calcitriol therapy, the regulation of calcium, steroids, and parathyroid hormone.[5] Palliative treatment involves the debridement of grossly necrotic bone and nerve decompression.[5] Hemopoietic stem cell transplantation has been proven to be a useful modality to improve the survival rate of patients with the autosomal recessive variants of osteopetrosis.[7]

Treatment modalities that are utilized for osteomyelitis in the jaws secondary to osteopetrosis include incision and drainage, dental extractions, an antibiotic therapy, sequestrectomy, saucerization, decortication, jaw resections, and hyperbaric oxygen.[8] Obturators are ideally used to close defects; free bone grafts are not recommended due to the compromised blood supply to the graft bed.[8]

No definitive treatment protocol currently exists for osteopetrosis, as shown in Table 1.[3,9–29]

In conclusion, from our experience in the management of this patient and the reviewed literature, patients with osteopetrosis complicated by osteomyelitis of the maxilla should be treated with a long-term antibiotic therapy (amoxicillin/clavulanic acid and/or clindamycin), accompanied with the surgical debridement/sequestrectomy and packing the site with a medicament (BIPP or Whitehead's varnish) to aid in healing and to prevent further infections. Regular long-term follow-up is vital to assess healing and prevent the dissemination of the disease process.

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Simple bone cyst of the hyoid: A radiological diagnosis and follow-up

Torbiel samotna kości gnykowej – rozpoznanie radiologiczne i badanie kontrolne

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Abstract

Simple bone cyst (SBC), also known as unicameral bone cyst, is a benign, fluid-filled cystic lesion that mainly appears in the long bones of young patients. Simple bone cysts are considered dysplastic or reactive lesions of bone. The most common locations for SBCs are the proximal humerus and femur. Lesions may occasionally be found in the jawbones. Simple bone cysts often have no clinical impact and are usually detected during routine radiographic examinations unless a gross pathologic fracture occurs. When symptoms develop, they may include mild pain, local tenderness and swelling. Computed tomography (CT) scans demonstrate a central, well-defined, mildly expansile or non-expansile, thin-walled lytic lesion, with little or no marginal sclerosis. Magnetic resonance imaging (MRI) usually confirms the cystic nature of the lesion by showing its fluid content. Cystic masses in the hyoid bone are very rare. Here we report an asymptomatic SBC in the hyoid bone, incidentally discovered in a cone-beam computed tomography (CBCT) examination, which appears to be the 2nd reported case.

Key words: simple bone cyst, aneurysmal bone cyst, hyoid bone, thyroglossal cyst

Słowa kluczowe: samotna torbiel kostna, torbiel tętniakowa kości, kość gnykowa, torbiel przewodu tarczowo-językowego

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Introduction

Simple bone cyst (SBC) is a benign, fluid-filled cystic lesion, which constitutes approx. 3% of all bone tumors, and mainly appears in the long bones of predominantly male children and adolescents.[1] Simple bone cysts lack an epithelial lining; therefore, they do not represent true cysts. Several names have been used as synonyms for SBC, including idiopathic bone cavity, unicameral bone cyst (UBC), traumatic bone cyst, hemorrhagic bone cyst, solitary bone cyst, and extravasation cyst.[2] The etiology and pathogenesis of SBC are not completely understood, as can be seen from the wide variety of synonyms. The proposed causative mechanisms include trauma, obstruction in the venous flow in bone marrow sinusoids, and a growth defect in the epiphyseal plate.[1]

Simple bone cysts have been largely found in the metaphyseal areas of long bones, with the majority in 2 locations – the proximal humerus and femur.[1] The occurrence of SBC elsewhere is uncommon. Lesions may occasionally be found in the jawbones.[3]

On imaging, SBCs usually present as well-defined, unilocular radiolucency, but they may also have multilocular or separated appearance.[2,4] These lesions are usually asymptomatic and found incidentally. Pain and swelling may be the reasons for presentation, and a pathological fracture may also occur.[5]

Histologically, a cyst cavity is lined with a thin fibrous membrane, which may contain reactive bone, hemorrhage, inflammatory granulation tissue, and bone fragments.[6]

Treatment methods for SBCs include observation, steroid injection, autologous bone marrow injection, decompression, and open curettage with a bone graft.[7]

The cystic lesions of the hyoid bone are rare and have been seldom reported in the literature. Here we report an incidentally discovered SBC in the hyoid bone, which might be interesting, as it is extremely rare and has been reported only once before.[8]

Case report

An 18-year-old male patient was referred to the Department of Dentomaxillofacial Radiology at Hacettepe University in Ankara, Turkey, for cone-beam computed tomography (CBCT) in order to evaluate the maxillofacial region prior to orthodontic treatment. Scans were obtained with the i-CAT™ Next Generation device (Imaging Sciences International, Hatfield, USA), using a field-of-view of 160 × 100 mm (tube voltage: 120 kVp; tube current: 5 mA; exposure time: 7 s; voxel: 0.2 mm). During the evaluation of CBCT images, a solitary, circumscribed, osteolytic, well-defined lesion involving the body of the mid-hyoid bone was found (Fig. 1). The lesion had dimensions of approx. 5.6 mm × 4.8 mm and showed corticated margins. Slight cortical expansion, erosion and thinning were noted. The patient had no history of pain, dysphagia, previous neck surgery or trauma. No associated cervical lymphadenopathy was present and the rest of the physical examination was unremarkable.

The patient returned to the Department 3 years later with no symptoms, and then he was referred for magnetic resonance imaging (MRI). An MRI examination was performed with a 3.0T scanner (SIGNA™ Architect; GE Healthcare, Milwaukee, USA) by using a standard neck coil. The standard neck protocol included fat-saturated (fat-sat) T2-weighted imaging, T1-weighted imaging, pre- and post-contrast with and without fat-sat T1-weighted imaging, and diffusion-weighted imaging (DWI) (b = 600). The intravenous administration of a contrast agent with gadolinium was performed at a dose of 0.1 mmol/kg. Axial three-dimensional (3D) constructive interference in steady-state (CISS) imaging was added to the protocol due to the small size of the lesion. Magnetic resonance imaging revealed a T1 hypointense and T2 hyperintense cystic lesion in the hyoid bone without any solid or soft tissue component (Fig. 2,3). The lesion showed no contrast enhancement or diffusion restriction. There were no internal septation or fluid-fluid levels. The radiographic examinations were suggestive of SBC in the diagnosis. Then, clinical and radiographic follow-up was planned.

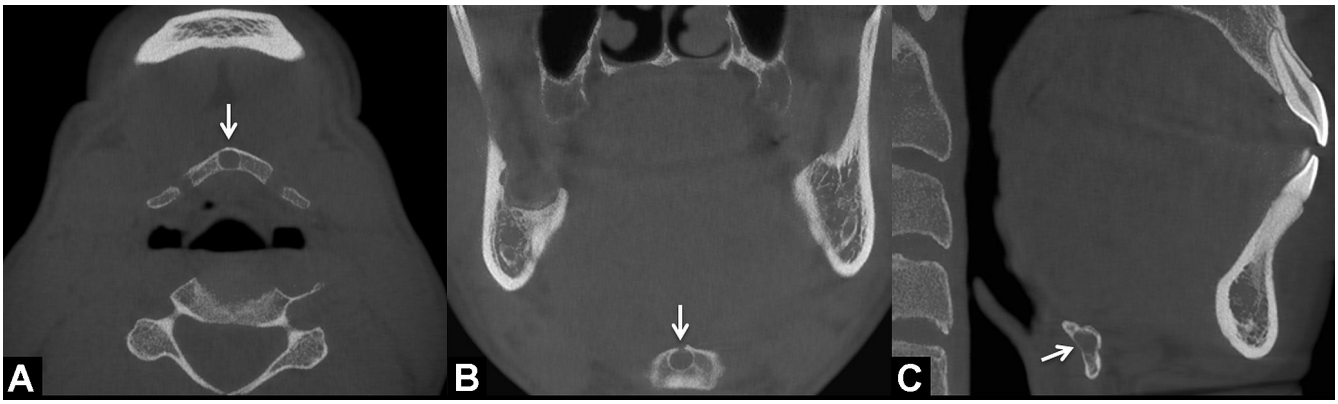

Fig. 1. Cone-beam computed tomography (CBCT) images showing a well-defined osteolytic lesion (arrow) involving the body of the mid-hyoid bone
A – axial view; B – coronal view; C – sagittal view.

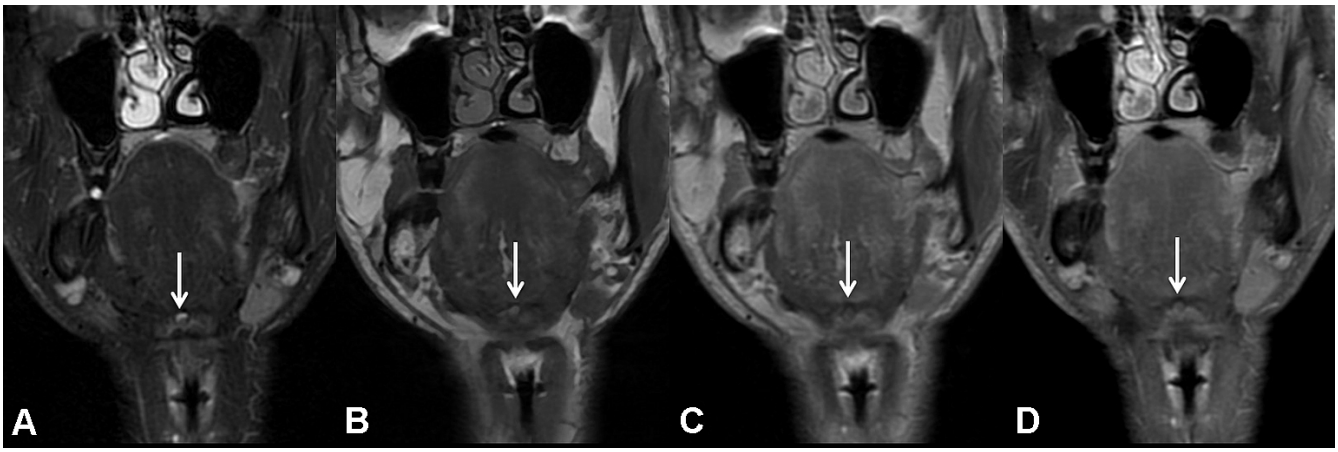

Fig. 2. Coronal magnetic resonance imaging (MRI) sections of the head show that the lesion (arrow) in the hyoid bone appears hyperintense on fat-saturated (fat-sat) T2-weighted images (A) and hypointense on T1-weighted images (B); after contrast administration, the lesion demonstrates no enhancement on T1-weighted images (C) and fat-sat T1-weighted images (D)

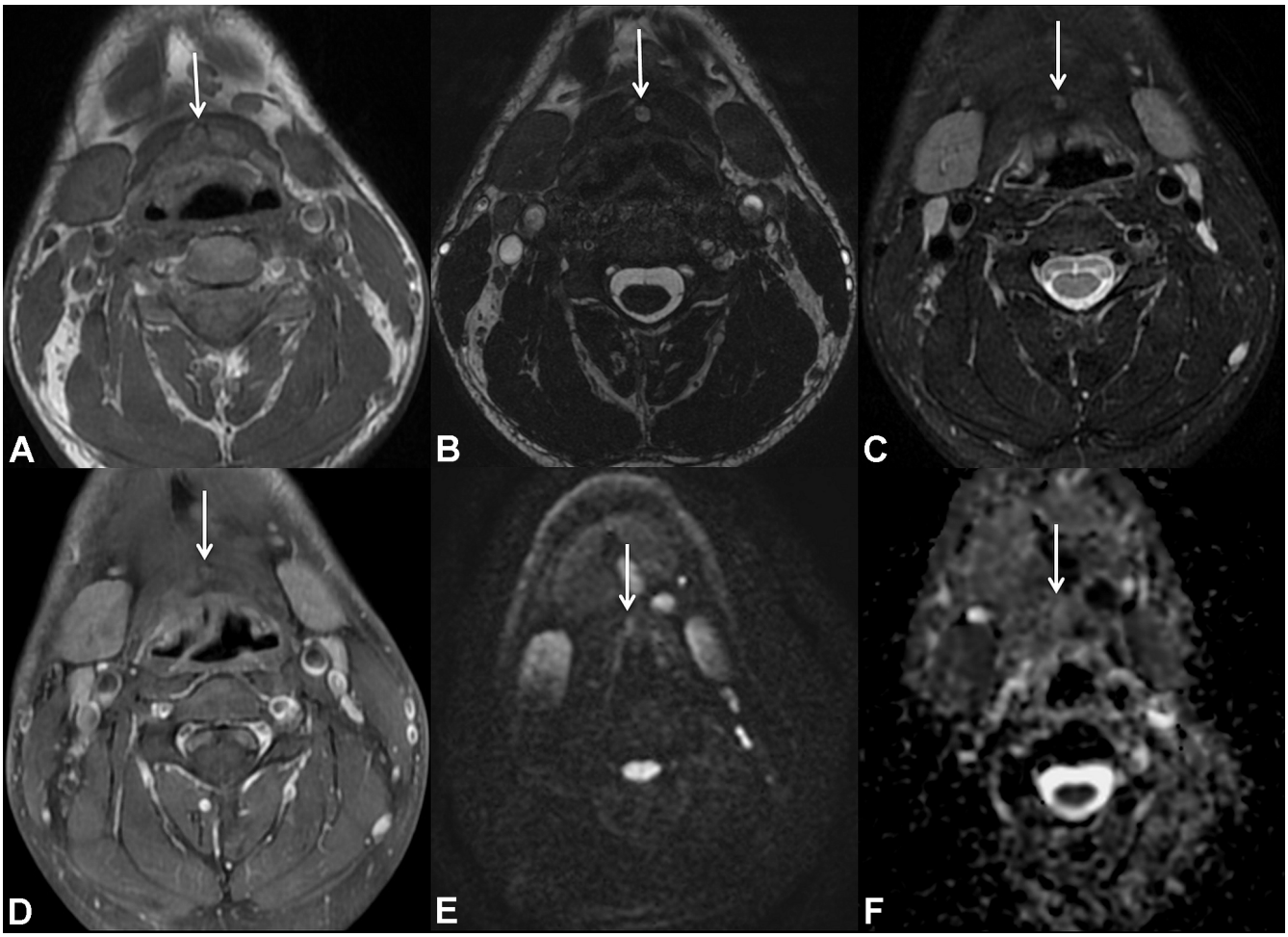

Fig. 3. Axial magnetic resonance imaging (MRI) sections of the head show that the hyoid lesion (arrow) appears hypointense on T1-weighted images (A) and hyperintense on T2-weighted three-dimensional (3D) constructive interference in steady-state (CISS) imaging (B) and fat-saturated (fat-sat) (C) images; after gadolinium administration, the lesion demonstrates no contrast enhancement on fat-sat T1-weighted images (D); the lesion shows no restricted diffusion on diffusion-weighted imaging (DWI) (E) and on the apparent diffusion coefficient (ADC) map (F)

Discussion

Cystic masses in the hyoid bone are quite rare and there have been 6 cases reported in the literature to date, including 4 thyroglossal duct cysts (TDCs),[9–12] 1 aneurysmal bone cyst (ABC),[13] and 1 UBC or SBC.[8] Cases of TDC penetrating the hyoid bone have also been reported.[14,15]

Thyroglossal duct cyst is typically located in the midline and is the most common congenital neck mass that occurs due to the incomplete obliteration of the thyroglossal duct.

Histologically, cyst walls contain an epithelial lining. Thyroglossal duct cysts can occur anywhere along the course of the thyroglossal duct, with the majority being associated with the hyoid region.[16] The most frequent location for TDCs is in the infrahyoid muscles, below the hyoid bone. The diagnosis of TDC can be made clinically, as it typically presents as a mobile midline structure, which increases in size over time and moves cranially with swallowing and the protrusion of the tongue because of its close relationship with the hyoid bone and the foramen cecum. On computed tomography (CT) imaging, TDCs appear as well-circumscribed masses with mucoid attenuation. On MRI, TDCs show low signal intensity with T1-weighted imaging, high signal intensity with T2-weighted imaging and do not demonstrate restricted diffusion.[17] In the presence of infection, peripheral rim enhancement and wall thickening can be observed in TDCs on both CT and magnetic resonance (MR) images after the intravenous injection of contrast material.[18]

Aneurysmal bone cysts are benign, expansile, tumor-like lesions consisting of blood-filled spaces contoured by fibrous septa that especially involve long bones, the spine and the pelvis in young patients. The lesion is classified as primary ABC if no underlying lesion is present, and as secondary if the lesion occurs in association with other tumors.[3] The exact etiology is unknown, but the proposed mechanism in secondary ABC includes intraosseous or subperiosteal hemorrhage, and osteolysis due to trauma. Although ABCs are relatively rare in the head-neck region and the mandible is the most common site of occurrence, a case of ABC has been described in the hyoid bone. The plain radiographic features of ABC include soap-bubble, honeycomb or multilocular cystic appearance, which may cause the expansion or destruction of cortical bone.[19] The found multiple internal septa with fluid-fluid levels caused by the separation of the hemorrhagic components, which is better observed on MRI, is pathognomonic in many cases. On an MRI scan, the lesion shows low to intermediate signal intensity with T1-weighted imaging and high signal intensity with T2-weighted imaging.[3]

Simple bone cysts are solitary cavities that are considered dysplastic or reactive lesions of bone.[3] The exact etiopathology remains unclear. Trauma has been postulated in the etiology, as it may cause an intramedullary hematoma, which eventually invokes bone resorption.[20] However, the incidence of a traumatic injury in patients with SBCs is not higher as compared to that of the general population.[21] Moreover, it appears that in many cases of SBC, there has been no history of a traumatic injury.[4]

Since the lesions predominantly occur in young patients, during the period of active bone growth, the theory of localized disturbance in bone metabolism or bone growth has also been considered in the pathogenesis of SBCs.[22,23]

Simple bone cysts often have no clinical impact and the lesions are usually detected during routine radiographic examinations unless a gross pathologic fracture occurs. When symptoms develop, they may include mild pain, local tenderness and swelling.[5]

The typical radiographic appearance of the lesion is unilocular radiolucency with well-circumscribed borders.[2] A CT scan demonstrates a central, well-defined, mildly expansile or nonexpansile, thin-walled lytic lesion, with little or no marginal sclerosis.[1] There can be partial septa or a pseudo-septum in the cystic cavity.[3] Magnetic resonance imaging usually confirms the cystic nature of the lesion by showing its fluid content. Fluid-fluid levels are rarely seen. However, fractured SBCs may contain blood products and fluid-fluid levels. On MRI, the lesion shows low signal intensity on T1-weighted images, and high signal intensity on T2-weighted or Short Tau Inversion Recovery (STIR) images.[5]

Simple bone cysts are considered to be self-limiting benign lesions that heal spontaneously after skeletal maturity.[24] Moreover, several studies have described the spontaneous resolution of the lesions over time.[24–28] Thus, it has been suggested that non-interventional treatment (observation) could be chosen as an alternative to surgical approaches in cases when a radiologic diagnosis is possible, particularly in young patients with asymptomatic cysts.[24,27,29]

In the present case, the clinical and radiographic features of the solitary lesion in the hyoid bone were strongly indicative of SBC. No surgical pathologic examination was performed, as the patient was asymptomatic for at least 3 years, and there was no sign of fracture of the cyst or an increase in the size of the lesion over time. For these reasons, the periodic observation of the patient was decided.

In conclusion, although cystic lesions rarely occur in the hyoid bone, SBC should be considered in the diagnosis of a well-circumscribed, radiolucent lesion in the hyoid bone of a young patient.

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Foundations of fluoride prophylaxis in Poland and the prosthetic rehabilitation of the masticatory organ in arthropathies and malocclusion: Scientific achievements of Professor Noemi Wigdorowicz-Makowerowa

Podwaliny profilaktyki fluorkowej w Polsce oraz rehabilitacji protetycznej narządu żucia w artropatiach i w wadach zgryzu – dorobek naukowy Profesor Noemi Wigdorowicz-Makowerowej

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Abstract

Professor Noemi Wigdorowicz-Makowerowa was born in Warsaw to a Polish Jewish family on November 24, 1912. She graduated from the Medical University of Warsaw in 1937 and from the Academy of Dentistry in 1939. In early 1940, she was forcibly relocated to the Warsaw Ghetto, from which she escaped in January 1943. Shortly after the Second World War, in 1946, she started working at Wroclaw University. She conducted multiple studies there on the fluoride prophylaxis of caries, and on temporomandibular joint arthropathy and its etiology. She proved the efficiency of tap water fluoridation in caries prevention through a comparative study on children from schools in Wroclaw and Malbork, where the fluoride concentrations were 0.1 mg/L and 3.2 mg/L, respectively. The incidence of deep caries and the rate of tooth mortality were significantly lower in Malbork. Her long-term studies on the fluoride prophylaxis of caries prompted Professor Wigdorowicz-Makowerowa to found the Scientific and Technical Team for Fluoride Prophylaxis, based at the Department of Dental Prosthetics in the Institute of Dentistry of Wroclaw Medical University, which led to the creation of 35 fluoride water treatment plants in Poland by 1980. Moreover, she emphasized that malocclusion caused by dental caries and tooth loss, bruxism, higher susceptibility to stress, and increased muscle tone may constitute reasons for masticatory organ disorders. In her long career of over 30 years, she published 68 articles about fluorine and its use in dentistry, and 50 articles about temporomandibular joint arthropathy and other masticatory organ disorders.

Key words: caries, fluoride prophylaxis, temporomandibular joint disorders

Słowa kluczowe: próchnica, profilaktyka fluorkowa, zaburzenia stawu skroniowo-żuchwowego

Introduction

In the etiology of dental caries, 4 factors are considered to be significant: the presence of dental plaque with bacteria, the supply of substrates for bacteria – mainly sucrose – the susceptibility of the tooth surface to acids, and the time in which all these factors work together.[1,2] In order to prevent tooth decay, it is enough to remove just one of these factors. This can be accomplished, for example, by frequent tooth brushing and regular plaque removal, eliminating sucrose from the diet, reducing bacterial metabolism, or reducing tooth susceptibility by strengthening its structure with fluoride compounds. The discovery that fluorine inhibits tooth decay is one of the greatest achievements in caries prevention. Fluorine itself acts endogenously at the stage of enamel formation and strengthens its structure from the very beginning; it also works exogenously, enhancing the remineralization of enamel and weakening carbohydrate metabolism by caries-forming bacteria.[3] The progression of caries without proper treatment leads to tooth loss, which affects not only the condition of the masticatory organ, facial esthetics and the development of disorders in the temporomandibular joints, but also the well-being of the individual and the health of their whole body.[4,5]

The aim of the article is to present the biography and the most important achievements of an outstanding Polish doctor and dentist, Professor Noemi Wigdorowicz-Makowerowa, who devoted her scientific career to the subject of fluoride prophylaxis in dental caries, the prosthetic rehabilitation of the masticatory organ in temporomandibular joint disorders (TMD) and malocclusion, and the education of the Polish society in the field of oral hygiene.

Methodology

We searched for articles which mention all the achievements of Professor Noemi Wigdorowicz-Makowerowa.[6] We included articles that were in Polish or English and concerned fluorine and arthropathy. We found 68 articles about fluorine and 50 about temporomandibular joint arthropathy. Six of these 118 articles were excluded, because they were written in German or French. From the remaining 112 articles written in Polish or English, we excluded 84 articles, because they covered the same research, they were the same articles published in Polish or English, the topic was not crucial, or they were post-conference materials or articles about the achievements of employees. We then searched Jagiellonian University Library for the articles, of which 23 were available. Only 1 out of 8 monographs was available.

Biography

Professor Noemi Wigdorowicz-Makowerowa was born in Warsaw to a Polish Jewish family on November 24, 1912. In 1930, she graduated from the Zofia Kalecka gymnasium and – following family tradition – she began studies at the Department of Medicine of the Józef Piłsudski Medical University in Warsaw in 1931. After 6 years, on June 22, 1937, she obtained her medical degree. Shortly afterward, she started studying at the Academy of Dentistry, also in Warsaw, and graduated in 1939. That same year, on January 28, she registered at the Warsaw-Bialystok Medical Chamber and accepted a job at the Warsaw Academy of Dentistry.[7,8]

Shortly after the outbreak of World War II – at the beginning of 1940 – in accordance with the ordinance of the General Governor, she was forcibly relocated to the Warsaw Ghetto. There, she started working at the Department of Surgery in the Orthodox Jewish Hospital in Czyste under the supervision of Dr. Alexander Wertheim. In addition, she was responsible for running a dental clinic in an outpatient department for the Jewish community. In the summer of 1942, during *Grossaktion Warschau* – the operation which liquidated the ghetto – she married Dr. Henryk Makower (1904–1964), with whom she escaped from the ghetto in January 1943. Then, for over a year, the couple hid in the family home of Janusz Tadeusz Urzykowski in Nowa Miłosna, near Warsaw.[9,10] In August 1944, she and her husband joined the Polish Army in Lublin, where she worked in the Evacuation Hospital as a dental consultant and assistant at the Surgical Department.[8,11]

In 1946, she was dismissed from military service and at the invitation of Prof. Ludwik Hirszfeld, MD, PhD (1884–1954), dean of the Faculty of Medicine at Wroclaw University, she took up the post of senior assistant there. Initially, she worked at the Clinic of Dental Surgery under the supervision of Professor Tadeusz Szczęsny Owiński (1904–1995), later moving to the Clinic of Conservative Dentistry, which was headed by Professor Ignacy Pietrzycki (1885–1964). After 2 years, on September 2, 1948, she started working as a senior assistant at the Department of Prosthodontics of Dental Division under the leadership of Professor Henryk Gorczyński. On December 28, 1948, based on a dissertation entitled "Infectious Gingivitis and Oral Mucositis with Particular Emphasis on Fusospirochetosis and its Treatment Applying the Author's Own Method", supervised by Professor Witold Grabowski (1902–1963), she earned the degree of PhD in Medicine.[8]

From May 1959 to August 1960, she volunteered at École Dentaire in Geneva, Switzerland. There, she had an opportunity to observe and train alongside prominent dentists, such as professors Arthur-Jean Held, Louis Joseph Baume and Francois Ackermann.[8]

Her scientific achievements and undertaking a series of studies on dental prophylaxis using fluorine enabled her to start a post-doctoral habilitation procedure at the Faculty of Medicine of the Medical University of Lodz. On January 12, 1963, based on her habilitation dissertation, "The Development and Fluoride Prophylaxis of Tooth Decay in Children", Noemi Wigdorowicz-Makowerowa, PhD was awarded the academic degree of assistant professor.[7]

On April 1, 1964, she was appointed full-time assistant professor at the Department of Prosthodontics of Wroclaw Medical University by Jerzy Sztachelski, PhD, the then Minister of Health and Social Care. On December 1, she obtained the title of associate professor of Wroclaw Medical University. On May 1, 1965, she assumed the position of Head of the Department of Prosthodontics at Wroclaw Medical University, which she held until she retired on September 30, 1983. Professor Noemi Wigdorowicz-Makowerowa died on February 7, 2015 in Stockholm.

Fluoride prophylaxis introduced by Prof. Noemi Wigdorowicz-Makowerowa

Fluorine, like any other element, exerts a dose-dependent influence, which is why it can be stated to have both beneficial and harmful effects on human health. The first laboratory tests on the use of fluorine in the prophylaxis of oral contagious diseases were conducted by Gerald J. Cox, who proved that small doses of fluoride, applied to drinking water given to rats, significantly improved oral health.[12] Grand Rapids, Michigan, USA, became the first city in the world to introduce fluoride water treatment on January 25, 1945. The aforementioned study was initiated by Henry T. Dean and Francis A. Arnold Jr., who also jointly investigated the optimal dose of fluorine in drinking water. After carrying out a number of prospective studies, they proposed a safe dose of 1 mg/L fluorine in water.[13] Ten years after the implementation of water fluoridation in Grand Rapids, F.A. Arnold Jr. conducted a comprehensive analysis of dentition among children aged 4–16 years, which proved that the prevalence of caries was reduced by 60–65% in comparison with the baseline data.[14]

As early in 1948, Professor Wigdorowicz-Makowerowa took up the subject of applying fluorine in the prophylaxis of caries. In her publications on arthropathy and myoarthropathy, she repeatedly emphasized the impact of tooth decay and tooth loss on the development of these disorders.[15] In her article "Problem of fluorine in stomatology", Professor described the methods of caries prevention that were in use at the time, consisting of oral hygiene, the reduction of carbohydrate intake in the diet, and the early treatment of dental caries.[16] She considered all of these activities to be definitely insufficient in relation to the entire population, both Polish and global. Professor Wigdorowicz-Makowerowa advocated more decisive steps to combat tooth decay. She was in favor of fluoridating tap water, drinking water and kitchen salt, and of applying topical fluoride salts to the teeth. She believed that only a combination of these 2 methods and their application to the entire population could contribute to improved dental health in society.[16,17]

In 1946, the Polish Ministry of Health commissioned the National Institute of Hygiene in Warsaw to conduct tests of fluorine concentration in tap water all over the country. An accurate fluorine map was prepared, which showed that the level of fluorine exceeded 1 mg/L in only 8 cities, and that in 6 cities, the level varied between 0.5–1 mg/L.[18] The aforementioned studies revealed that the concentration of fluorine in tap water was very low in Poland. Professor Wigdorowicz-Makowerowa decided to compare the teeth of schoolchildren from Malbork (where the natural level of fluorine in water was 3.2 mg/L) with ones from Wroclaw (0.1 mg/L).[19] The condition of their teeth was determined using the indicator DMF (D – decayed, M – missing, F – filled) and a modified version, DMF-N, which is an indicator of superficial caries that does not require treatment. In the years 1955 and 1956, 5,864 schoolchildren aged 7–13 years were examined in Wroclaw. These children constituted a random sample selected from the entire population of children at this age living in Wroclaw. In 1958, 1,417 children aged 7–13 years who were born and attended schools in Malbork were examined. The percentage of children with caries, determined by the DMF index, increased with age – in Wroclaw, from 73% at the age of 7 to 97% at the age of 13, and in Malbork from 49% to 90%, respectively. Also, the percentage of children with superficial caries, as determined by the DMF-N index, increased with age: in Wroclaw, from 49% at the age of 7 to 94% at the age of 13, and in Malbork from 19% to 74%, respectively. In addition, the average tooth mortality rate in all age groups in Wroclaw was significantly higher than in Malbork. The corresponding average values in Wroclaw ranged from 0.33 at the age of 10 to 0.90 at the age of 13. In Malbork, tooth mortality also increased with age, although in the first 12 years of life it constituted only a small fraction and at the age of 13 it represented an average of 0.16. In the conclusion of the study, Professor Wigdorowicz-Makowerowa stated that the results clearly proved the protective effect of fluorine in preventing tooth decay in healthy teeth and the inhibiting effect of fluorine on the further development of existing caries. She indicated that the results pointed to the urgent need for mass fluoride treatment in Poland.[19]

In September 1957, the World Health Organization (WHO) issued a resolution in which it recommended the widest possible introduction of artificial water fluoridation as a preventive measure for dental caries.[20]

On July 23, 1969 at its 22nd session in Boston, USA, WHO adopted a proposal prepared and presented by a delegation of 37 countries, including Poland, which obliged Member States to fluoridate drinking water where appropriate.[21]

Professor Noemi Wigdorowicz-Makowerowa founded the Scientific and Technical Team for Fluoride Prophylaxis, based at the Department of Dental Prosthetics in the Institute of Dentistry of Wroclaw Medical University, which she later headed. This team launched the first fluoride water treatment plant in Wroclaw in 1967. Professor Wigdorowicz-Makowerowa promoted the introduction of fluoride water treatment plants throughout Poland. Her efforts met great societal resistance, from people reluctant to introduce a new form of prevention and from media, reporting on on the harmful effects of fluorine on humans. Professor repeatedly presented the results of her original research and of studies conducted in Western countries, which showed that fluorine at a dose of 1 mg/L prophylactically prevents caries.[22] In 1972, 4 years after the introduction of water treatment in Wroclaw, she carried out a controlled trial, which she presented in 1973. Tooth decay was significantly lower than in 1967. The DMF index decreased by 60.6% in 3-year-old children, by 46.4% in 4-year-old children, by 50% in 7-year-old children, by 31.5% in 8-year-old children, and by 14.2% in 12-year-old children. These studies suggested that the older the child, the less difference in caries reduction can be expected after 4 years of consuming fluoridated water; this finding may have resulted from the fact that older children had begun consuming fluoridated water after partial tooth formation and may have had tooth decay before.[23,24]

Due to the efforts of Professor Wigdorowicz-Makowerowa, in 1977 the Polish Sejm adopted a resolution requiring fluoridation of tap water with sodium fluorosilicate when fluorine content in water is lower than 0.5 mg/L. The many years of work of the Scientific and Technical Team under the leadership of Professor Wigdorowicz-Makowerowa led to the creation of 35 fluoride water treatment plants, serving 2.5 million people in Poland by 1980.[25]

Studies on the rehabilitation of patients with myoarthropathy

Professor Wigodorowicz-Makowerowa explained myoarthropathy (from Greek: *μυς mys* – muscle, *ἄρθρον árthron* – joint, and *πάθος páthos* – suffering) as a dysfunction of the masticatory organ – either painless or painful – caused by the contact of premature teeth and malocclusion.[26] She described bruxism (from Greek: *βρυγμός brygmós*– teeth grinding) as fixed, abnormal jaw movements involving the unconscious grinding and clenching of the teeth.[27] In today's terminology, myoarthropathy is diagnosed as TMD.

One of the main areas of interest of Professor Noemi Wigodorowicz-Makowerowa was the rehabilitation of patients with temporomandibular joint arthropathy and myoarthropathy. Her first publications on this subject appeared in 1968 and concerned toothless patients using complete dentures, those with partially missing teeth and those with occlusal problems.[28–31] More detailed research on the incidence of temporomandibular joint arthropathy was published 5 years later.[32] These were population-based studies, which also covered the etiopathogenesis of arthropathy. In 1974, she published a study involving a group of 1,000 soldiers on the relationship between temporomandibular joint arthropathy and bruxism.[33] In subsequent years, she continued to explore the topic of myoarthropathy and wrote papers on the types of pain in temporomandibular joint myoarthropathy as well as treatment methods, on functional disorders in children and adolescents, and also presented a modern view on the etiology of this arthropathy.[15,34–41] Professor Wigodorowicz-Makowerowa published 2 monographs and 50 articles, and supervised 7 doctoral students and 2 post-doctoral students, all works revolving around the subject of temporomandibular arthropathy and masticatory disorders. The last article by Professor Wigodorowicz-Makowerowa on the subject of myoarthropathy was published in 1984.[6]

Studies on the etiology of myoarthropathy

According to the research of Professor Wigodorowicz-Makowerowa, 50% of the middle-aged population had functional disorders of the masticatory organ at that time.[15,27] They were more often observed in people with malocclusion, and in such cases, functional disorders were particularly frequently manifested as arthropathy.[27] In her articles, Professor Wigodorowicz-Makowerowa emphasized that the problem of myoarthropathy had a complex etiology, and originated from increased muscle tone and bruxism, among other things. She listed the main risk factors in the following order: malocclusion, bruxism, and increased sensitivity to stress. She proved that bruxism and malocclusion increased the risk of disorders 1.4–2 times and that excessive neuromuscular excitability doubled the risk, while tooth wear reduced the frequency unless it occurred along with malocclusion.[15,27] She pointed out in numerous publications that increased stress in society was one of the causes of bruxism and of the functional disorders of the masticatory organ, which were being observed more and more frequently.[15,27,28,37] She stated that the temporomandibular joints were extremely resistant to cancer and infectious agents, but were susceptible to occlusal microtraumas and took a very active part in showing emotions, especially negative ones (fear, anger

or fury) through the clenching of the teeth. In addition, they were somewhat overloaded in people with abnormal masticatory function. This problem was most often the result of a lack of compensation for stress related to the environment (biting pencils, lips or cheeks). Professor Wigodorowicz-Makowerowa also pointed out the important role of a properly conducted interview in determining the cause of the disease and proposed that the best specialist to help patients with the problem was a prosthodontist. An imperative issue which she drew attention to was the need to combine a physical examination directly with an interview in order to determine the individual's susceptibility to stress. She repeatedly emphasized that in the etiology of problems with joints, the impact of the environment and stress were more important than age, for example. In the prevention of functional disorders, she proved that fluoride prophylaxis was vital in preventing tooth decay as well as tooth loss and occlusal disorders.[15,28,32] Based on her research, Professor invented the concept of 'traumatic occlusion'.

Treatment of myoarthropathy

Other aspects of TMD which Professor Wigdorowicz-Makowerowa focused on were the types of pain in myoarthropathy and the treatment methods thereof as well as the relationship with bruxism.[34–38] In her articles, she reported other authors' results of causal treatment as being positive in 50–90% of research participants, while in her own research in Wroclaw it was 85%. The method of treatment depended on whether the case was acute or chronic. For the former, she recommended a soft diet, biting on the problematic side, compresses, painkillers, muscle relaxers, and leveling the occlusal surface, but advised against immobilization, which she said was indicated only in cases of fractures. In situations of chronic arthropathy, she maintained that the most appropriate method was causal treatment, i.e., the alignment of the occlusal surface, the elimination of bruxism and prosthetic rehabilitation; as the muscles stop working synchronously, which is necessary for the proper functioning of the masticatory organ, the treatment should consist in practicing opening the mouth without lateral deviations, exercises also with the excessive mobility of the mandible (helping to stabilize the joint) to increase suprahyoid muscle tone, and – in exceptional cases – injections of adrenal gland hormone.[28] Professor Wigdorowicz-Makowerowa emphasized the need for periodic monitoring, causal treatment and good contact with the patient, as these are factors which determine the success of treatment. She regarded bruxism and bad emotional condition as causes of relapses. In her opinion, patients with emotional disorders, and numerous somatic symptoms of stress in particular, did not have a good prognosis for the treatment.[37]

Conclusions

The scientific achievements of Professor Wigodorowicz-Makowerowa are clearly part of modern dentistry in Poland. She published 68 articles on fluorine and its use in dentistry, and analyzed its mechanism of action in caries prophylaxis and the most effective methods for applying it in Poland. Based on many years of research, she came to the conclusion that the best method of prevention should be the fluoridation of tap water and the topical application of the solutions of fluoride salts to the teeth. In Poland, there are currently no fluoride water treatment plants, and caries prophylaxis relies on the daily use of fluoridated toothpaste. Although more than half a century has passed since Professor's research, it is still valid in many matters. Then and today, problems with joints are mainly dealt with by prosthodontists, often in cooperation with physical therapists and psychologists, which can be interpreted as following the path of Professor, because these specialists help relax muscles and reduce stress.[42] Until the 1980s, she used the term 'arthropathies', but later realized that temporomandibular joint problems are not only caused by occlusal problems, but also problems with the muscles. The first time she used the term 'myoarthropathies' was in 1978.[25] It is important to point out that she considered that problem before the currently used Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) were invented in 1992. Currently in medical practice, there is a biaxial approach to functional disorders, i.e., including a physical examination of the patient as well as a medical interview and the determination of the stress level – RDC/TMD and the latest Diagnostic Criteria/Temporomadibular Disorders (DC/TMD).[43,44] Another issue that remains controversial these days is malocclusion in the etiology of functional disorders and their impact on the outcome of treatment.[45–47]

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