Dental and Medical Problems

QUARTERLY ISSN 1644-387X (PRINT) ISSN 2300-9020 (ONLINE) www.dmp.umed.wroc.pl

2022, Vol. 59, No. 4 (October–December)

Ministry of Science and Higher Education – 70 pts
Index Copernicus (ICV) – 132.50

Wroclaw Medical University

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ISSN 1644-387X (PRINT) ISSN 2300-9020 (ONLINE) www.dmp.umed.wroc.pl

QUARTERLY
2022, Vol. 59, No. 4
(October–December)

"Dental and Medical Problems" is an international, peer-reviewed, open access journal covering all aspects of oral sciences and related fields of general medicine, published quarterly by Wroclaw Medical University.

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Wroclaw Medical University
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50-367 Wrocław, Poland

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Indexed in: PubMed/MEDLINE, Web of Science, Clarivate Journal Citation Report, Scopus, ICI Journals Master List, DOAJ, WorldCat, Embase, Polska Bibliografia Naukowa, EBSCO, Crossref, CLOCKSS

Typographic design: Monika Kolęda, Piotr Gil
Cover: Monika Kolęda
DTP: Adam Barg
Printing and binding: Drukarnia I-BiS Bierońscy Sp.k.

Dental
and Medical Problems

QUARTERLY 2022, Vol. 59, No. 4 (October–December)

ISSN 1644-387X (PRINT)
ISSN 2300-9020 (ONLINE)
www.dmp.umed.wroc.pl

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Acknowledgements

We would like to express our gratitude to all reviewers who devoted their time and expertise to evaluate manuscripts in "Dental and Medical Problems". We sincerely appreciate all your hard work and dedication. It is due to your contribution that we can achieve the standard of excellence.

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Original paper

Does childhood chemotherapy affect mandibular bone structures in a lifetime?

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

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):495–501

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on November 10, 2021
Reviewed on February 1, 2022
Accepted on February 16, 2022

Published online on December 2, 2022

Abstract

Background. Chemotherapy, one of the most important treatment modalities for treating childhood cancers, is a major cause of bone loss in patients and survivors.

Objectives. This study aimed to evaluate mandibular bone structures in childhood cancer survivors (CCSs) by means of fractal dimension (FD) analysis and the Klemetti index (KI), and to compare them with regard to the control group.

Material and methods. In this retrospective study, the panoramic radiographs of 49 CCSs were included as the study group and the panoramic radiographs of 49 cancer-free volunteers were included as the control group. Based on the panoramic radiographs, FD and KI were determined.

Results. No significant differences were observed between the study and control groups in terms of mean FD values for regions of interest (ROIs) ROI_1, ROI_2 and ROI_3 ($p = 0.750$, $p = 0.490$ and $p = 0.910$, respectively). The mean FD values for ROI_1 for the study and control groups were 1.08 ±0.18 and 1.07 ±0.14, respectively. The mean FD values for ROI_2 for the study and control groups were 1.11 ±0.13 and 1.09 ±0.13, respectively. The mean FD values for ROI_3 for the study and control groups were 1.15 ±0.14 and 1.15 ±0.15, respectively. Statistically significant differences between the study and control groups were noted only in the distribution of the KI categories ($p = 0.015$).

Conclusions. Childhood chemotherapy may affect mandibular bone structures during a lifetime. The Klemetti index should be considered a useful clinical diagnostic tool for the examination of mandibular bone structures.

Keywords: pediatric oncology, panoramic radiography, fractals, childhood chemotherapy

Cite as
Kış HC, Coşgunarslan A, Delikan E, Aksu S. Does childhood chemotherapy affect mandibular bone structures in a lifetime? *Dent Med Probl.* 2022;59(4):495–501. doi:10.17219/dmp/146752

DOI
10.17219/dmp/146752

Introduction

Cancer is associated with the abnormal and uncontrolled proliferation of cells.[1] Childhood cancers are all cancers that occur in children up to the age of 19 years. The treatment and follow-up of these patients are performed in pediatric oncology service facilities. Although certain etiological factors (genetic predisposition or fetal exposure to ionizing radiation) have been suggested, the etiology of most childhood cancers remains unknown.[2,3] Leukemia and lymphomas are the most common childhood cancers in the world. They are followed by brain tumors, peripheral nervous system tumors, retinoblastomas, kidney tissue tumors, liver tumors, malignant bone tumors, sarcomas, germ cell tumors, malignant epithelial neoplasms, malignant melanomas, and other neoplasms.[4,5]

The diagnosis of a childhood cancer can be made through blood work, a biopsy and a clinical examination. Different imaging methods can also be used, e.g., ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography/computed tomography (PET/CT).[6]

Treatment methods for childhood cancers include surgery, chemotherapy, radiotherapy, and stem cell transplant.[7] Oncologists and surgeons can choose one of these treatment options upon mutual consultations after diagnosis, or they can decide on a treatment strategy that combines 2 or more of the aforementioned modalities. Depending on the type of cancer, 60–70% of childhood cancer patients can achieve complete response if provided with appropriate treatment.[4] However, some studies have concluded that childhood cancer survivors (CCSs) struggle with chronic diseases for the rest of their lives.[8]

Unfortunately, cancer treatment has some undesirable effects. For example, in the surgical method, the tumor and the surrounding tissue are removed radically, which results in esthetic and functional handicaps. In chemotherapy, adjusting the drug doses can be a serious problem. Also, chemotherapeutic agents can cause destruction of varying extent in healthy tissues and organs throughout the body. Hair loss and nausea are among the most common side effects of chemotherapy, whereas fatigue, weakness, mouth sores, digestive system problems, bleeding, and febrile infections are less common.[9] Radiotherapy consists in the direct application of X-rays to the area where the tumor is located. This treatment method is used as little as possible in childhood cancers, as it can cause growth and developmental retardation, and create a secondary malignancy risk in immature organs and tissues.[10]

Childhood cancer treatment may cause a decrease in bone mineral density (BMD), bone quality impairments or other side effects in the bone tissue, such as avascular necrosis due to chemotherapy-induced osteoporosis. Moreover, low BMD and bone microarchitecture disorders may persist during adulthood, thereby increasing the risk of fractures. There are numerous studies that report on osteoporosis and low BMD, previously induced by childhood cancer chemotherapy, observed in long bones with the use of dual-energy X-ray absorptiometry (DXA).[11–13]

The trabecular bone structure is essential in determining BMD.[14] The degree of mineralization decreases with increasing trabecular porosity.[15] The term 'fractal' defines self-similar geometric shapes. Fractal dimension (FD) analysis is a quantitative method for evaluating complex self-similar structures, such as the trabecular bone, and can easily be performed on dental radiographs. The resultant FD value represents the complexity of the structures. It has been previously demonstrated that as bone complexity increases, the FD value similarly increases.[16,17] Fractal dimension analysis has been successfully used to evaluate the osteoporotic conditions of the craniofacial bones.[18–21]

The mandibular cortical index (MCI), also known as the Klemetti index (KI), is one of the most established techniques for the diagnosis and evaluation of osteoporotic bone changes on dental radiographs.[22] The determination of KI is based on the qualitative evaluation of the mandibular cortical bone appearance on panoramic radiographs. It has been previously demonstrated that there is a statistically significant relationship between the BMD values obtained with DXA and the KI classification. Thus, KI could be used as a diagnostic tool to identify the risk of bone mass loss.[23–25]

To the best of our knowledge, our research is the first clinical study that evaluates mandibular bone alterations in CCSs by means of FD analysis and KI. Our study aimed to evaluate mandibular bone structures in CCSs after chemotherapy by means of FD analysis and KI, and to compare the obtained results with those for a cancer-free control group.

Material and methods

Image data acquisition

This study was carried out with the permission of the institutional Ethics Committee at Mersin University, Turkey (decision No. 2018/209). The study group consisted of the panoramic images taken from 49 CSSs whose detailed anamneses were received and referred to the clinic at the Department of Pediatric Dentistry of Mersin University in the years 2018–2019. All 49 patients were included in the study group. The patients were referred to our clinic for dental check-ups; their pediatric oncological follow-up was performed at least 2 years after the oncological treatment was completed. The types of cancer the patients in the study group were treated for are presented

in Fig. 1. Treatment modalities for all patients in the study group included at least one of the following: dexamethasone; prednisolone; or methotrexate. None of the patients in the study group underwent cranial radiation therapy. Patients in the study group were divided into 2 categories – solid tumor patients or blood cancer patients, according to the kind of chemotherapy they received. The control group, on the other hand, consisted of the panoramic images of 49 patients who were referred to the Department of Pediatric Dentistry due to different dental complaints, without any systemic disease or drug use listed in their detailed medical history. The panoramic images of those who used drugs that might affect bone metabolism (other than chemotherapeutics), underwent cranial radiation therapy or had any other systemic disease were excluded from the study.

All panoramic radiographs were taken using the same CRANEX® Novus panoramic machine (Soredex, Tuusula, Finland) set at 70 kVp, 10 mA and 8 s of exposure time. All participants were positioned so that the Frankfurt horizontal plane was parallel to the floor and the sagittal plane was adjusted to the vertical line produced by the device. All digital panoramic radiographs were stored at a resolution of 5.5 LP/mm. The size of all stored digital panoramic radiographic images was 2,976 × 1,536 pixels.

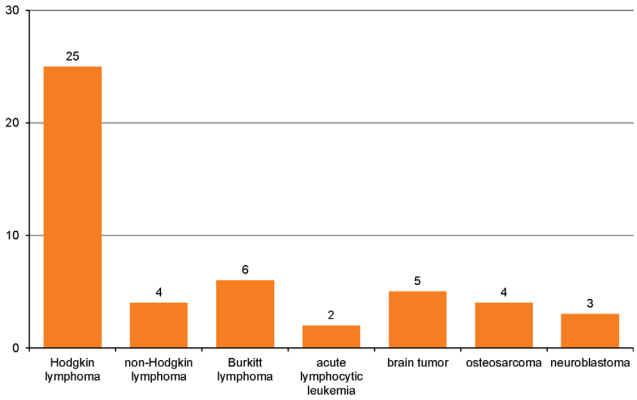

Fig. 1. Distribution of the types of cancer the patients in the study group were treated for

Evaluation of the images

Fractal dimension analysis

All digital panoramic radiographic images were exported in the JPEG (Joint Photographic Experts Group) file format at 1,600 × 887 pixels. The exported images were analyzed with the ImageJ software, v. 1.3 (National Institutes of Health, Bethesda, USA; https://imagej.nih.gov/ij/). Fractal dimension analysis was performed according to White and Rudolph's box-counting method.[18]

Three different regions of interest (ROIs) were determined. Each ROI on both the left and right sides was measured, and the obtained values were used for statistical analysis (Fig. 2):

– ROI_1 – a square of 30 × 30 pixels in the geometric center of the subcortical area in the mandibular condyle;
– ROI_2 – a square of 30 × 30 pixels in the supracortical area of the angulus mandibulae; and
– ROI_3 – a square of 30 × 30 pixels in the trabecular bone area, distal to the root of the first or second premolar, above the mandibular canal. This area was determined to detect the FD value in the mandibular corpus. To standardize the measurement in this area, as presented in Fig. 2, it was made from the premolar tooth which did not have any lesion in or around its apical part.

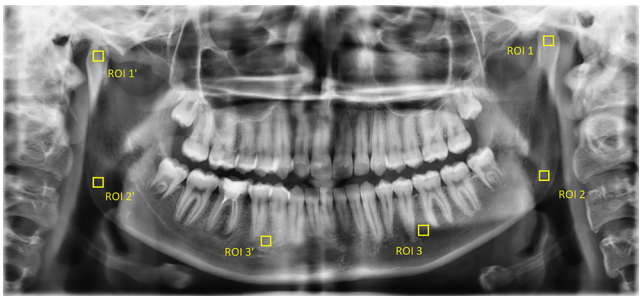

Fig. 2. Determined 6 regions of interest (ROIs), symmetrically on both the left and right sides

The chosen ROI was cropped and duplicated (Fig. 3A). The image was blurred with the Gaussian filter to remove the large-scale variations of brightness related to object thickness or the soft tissue (Fig. 3B). The overly blurred image was subtracted from the initial image (Fig. 3C). A gray value of 128 was added to each pixel location, resulting in an image with a mean pixel value of 128 (Fig. 3D). With this step, certain variations, such as trabeculae and bone marrow, become visible. The image was then made binary with the threshold function, resulting in an image of 2 values – black and white (Fig. 3E). White areas represented trabeculae, while black areas represented bone marrow. Then, the image was eroded and dilated, reducing the noise (Fig. 3F and 3G). The resultant image was inverted so that the areas representing trabeculae were set to black (Fig. 3H). The image was further eroded with the skeletonization function until the only centerline of the pixels was present (Fig. 3I). The FD value was calculated with the box-counting function. The image was covered with squares of 2-, 3-, 4-, 6-, 8-, 12-, 16-, 32-, and 64-pixel-sized boxes. The number of boxes involving trabeculae and the total count of the boxes were calculated for each box size. The FD value was measured from the slope of the line in the logarithmic scale graph of the obtained values.

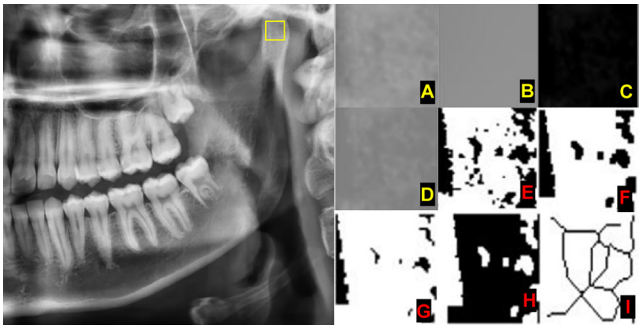

Fig. 3. Fractal dimension (FD) analysis of the selected region of interest (ROI) ROI_1

A – cropped and duplicated version of ROI_1; B – addition of the Gaussian filter; C – subtraction; D – addition of 128 pixels; E – binarized version; F – eroded version; G – dilated version; H – inverted version; I – skeletonization.

Klemetti index

The appearance of the mandibular cortical bone, distal to the mental foramen, was evaluated bilaterally to make a classification. The classification was made according to KI and described as[22]:

- C1 – the endosteal margin of the cortex is homogenous, even and sharp (bilaterally);
- C2 – the endosteal margin of the cortex displays semi-lunar defects (lacunar resorption) or endosteal cortical residues (unilaterally or bilaterally); and
- C3 – the cortical layer is porous and displays endosteal cortical residues (Fig. 4).

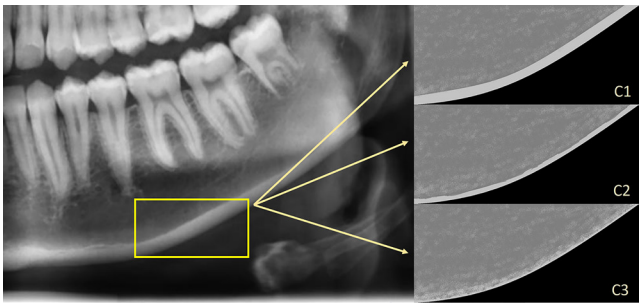

Fig. 4. Klemetti index (KI)

C1 – the endosteal margin of the cortex is sharp, even and homogenous (bilaterally); C2 – the endosteal margin shows semi-lunar defects (lacunar resorption) or endosteal cortical residues (unilaterally or bilaterally); C3 – the endosteal margin consists of a porous cortex and displays dense residues.

The measurements were performed by 2 oral radiologists with 4 years of experience. The observers re-evaluated a randomly chosen 20% of all patients 2 months after the completion of the first measurements to assess for intra-observer reliability and repeatability.

Statistical analysis

The analysis of the data was performed with the TURCOSA cloud software and the R programming language. Descriptive statistics was applied. The Shapiro–Wilk test was performed to test the normality of data distribution. As the values were normally distributed, parametric tests were used for all statistical analyses. Student's t test was performed to compare the study and control groups with regard to ROI_1, ROI_2 and ROI_3. The χ^2 test and Fisher's exact test were performed to compare the categorical variables between the study and control groups. All tests were judged statistically significant at 5% ($p < 0.05$).

Results

The mean age of patients in the study and control groups was 14.5 ±4.4 years and 14.6 ±4.8 years, respectively. Both study and control groups were comprised of 32 males and 17 females. The summary of demographic variables is presented in Table 1. The distribution of all numerical variables conformed to a normal pattern. There were no statistically significant differences between the variances of the numerical variables. The study and control groups were similar in terms of age and gender ($p > 0.5$). The mean FD values for ROI_1, ROI_2 and ROI_3 were not significantly different in the study and control groups ($p = 0.750$, $p = 0.490$ and $p = 0.910$, respectively). The mean FD values for ROI_1 for the study and control groups were 1.08 ±0.18 and 1.07 ±0.14, respectively. The mean FD values for ROI_2 for the study and control groups were 1.11 ±0.13 and 1.09 ±0.13, respectively. The mean FD values for ROI_3 for the study and control groups were 1.15 ±0.14 and 1.15 ±0.15, respectively. The mean (M), standard deviation (SD), minimum (min), and maximum (max) FD values are shown in Table 2. There was a statistically significant difference in the mean FD values for ROI_3 between the solid tumor and blood cancer groups; the values for the latter group were found to be higher (Table 3).

Statistically significant differences were noted only in the distribution of the MCI (KI) categories. In the chemotherapy group, C2 and C3 bones together occurred more frequently than C1 bones (Table 4). There was no statistically significant association between the cancer type and the KI category (Table 5).

Table 1. Summary of demographic data

Group	Age [years]		Gender	
	M ±*SD*	min–max	M *n* (%)	F *n* (%)
Chemotherapy (study) group	14.5 ±4.4	6–21	17 (34.7)	32 (65.3)
Control group	14.6 ±4.8	6–23	17 (34.7)	32 (65.3)
p-value	0.920		1.000	

M – mean; *SD* – standard deviation; min – minimum; max – maximum; M – male; F – female.

Table 2. Fractal dimension (FD) values for particular regions of interest (ROIs) according to the study and control groups

Group	ROI_1		ROI_2		ROI_3	
	M ±*SD*	min–max	*M* ±*SD*	min–max	*M* ±*SD*	min–max
Chemotherapy (study) group	1.08 ±0.18	0.60–1.36	1.11 ±0.13	0.83–1.34	1.15 ±0.14	0.80–1.39
Control group	1.07 ±0.14	0.75–1.38	1.09 ±0.13	0.86–1.30	1.15 ±0.15	0.68–1.38
p-value	0.750		0.490		0.910	

Table 3. Fractal dimension (FD) values for particular regions of interest (ROIs) according to the solid tumor and blood cancer groups

Cancer type group (*n*)	ROI_1		ROI_2		ROI_3	
	M ±*SD*	min–max	*M* ±*SD*	min–max	*M* ±*SD*	min–max
Solid tumor group (22)	1.07 ±0.18	0.64–1.34	1.12 ±0.12	0.85–1.30	1.08 ±0.14	0.82–1.38
Blood cancer group (27)	1.09 ±0.19	0.60–1.36	1.11 ±0.14	0.83–1.34	1.20 ±0.13	0.80–1.39
p-value	0.720		0.710		0.004*	

* statistically significant.

Table 4. Distribution of the Klemetti index (KI) categories according to the study and control groups

KI category	Chemotherapy (study) group	Control group
C1	21 (42.3)	33 (67.3)
C2	24 (49.0)	16 (32.7)
C3	4 (8.7)	0 (0.0)

Data presented as number (percentage) (*n* (%)).
* statistically significant; $p = 0.015$* (in the chemotherapy group, C2 and C3 bones together occurred more frequently than C1 bones).

Table 5. Distribution of the Klemetti index (KI) categories according to the solid tumor and blood cancer groups

KI category	Solid tumor group	Blood cancer group
C1	7 (31.8)	14 (51.9)
C2	13 (59.1)	11 (40.7)
C3	2 (9.1)	2 (7.4)

Data presented as *n* (%); $p = 0.370$.

The results of the post-hoc power analysis for the *t* test and the χ^2 test used in the intergroup comparisons of ROI_1, ROI_2, ROI_3, and the KI variables are presented in Table 6. The inter-observer agreement for ROI_1, ROI_2, ROI_3, and KI measurements and analysis was 0.79, 0.77, 0.79, and 0.72, respectively. The intra-observer agreement for observer 1 was 0.92, 0.96, 0.92, and 0.89, while the intra-observer agreement for observer 2 was 0.90, 0.92, 0.87, and 0.80 for ROI_1, ROI_2, ROI_3, and KI, respectively.

Discussion

Cancer is a major cause of death in children worldwide and the recorded incidence is increasing with time. With the help of advanced multimodality treatment, the 5-year survival of children diagnosed with cancer has improved considerably.[4] However, CSSs have to cope with serious medical and psychosocial late side effects.[8] Furthermore, CSSs are at risk for cardiomyopathy, cognitive impairment, chronic musculoskeletal diseases, renal failure, secondary malignant neoplasms, and early mortality. These late effects can often be attributed to cancer treatment-related risk factors.[9] Skeletal damage (osteopenia, osteoporosis or avascular necrosis) may be caused by glucocorticoids and methotrexate, cranial radiation, direct radiation to the bone, and cyclophosphamide/ifosfamide, which can also cause gonadal damage.[26–28] Glucocorticoids increase bone resorption, and inhibit bone formation as well as the gonadotropic and somatotropic axes. They also reduce the absorption of Ca^{+2} from the intestine, and change vitamin D metabolism and plasma parathyroid hormone (PTH) level, causing hypercalcemia.[29] Methotrexate induces chondrocyte apoptosis, suppresses chondrocyte proliferation, triggers osteocyte apoptosis, suppresses the proliferation of secondary spongious bone, and reduces the total thickness of the growth plate and collagen-II mRNA expression. A reduction in the total thickness of the growth plate

Table 6. Results of the post-hoc power analysis for the *t* test and the χ^2 test used in the intergroup comparisons of the study and control groups

Variable	Power	n1	n2	Effect size	α	β	Test
ROI_1	0.06	49	49	0.06	0.05	0.94	
ROI_2	0.11	49	49	0.14	0.05	0.90	*t* test
ROI_3	0.05	49	49	0.02	0.05	0.95	
KI	0.73	98		0.29	0.05	0.27	χ^2 test

leads to reduced primary spongious bone production, and consequently, secondary spongious bone volume decreases. According to a study on rats, the cellular effects of short-term methotrexate treatment on the growth plate and the trabecular bone as well as on the histological parameters subsided by day 14 or 21.[30] In the present study, all patients in the study group had different chemotherapeutic agents involved in their treatment, but all of them received cures that contained at least one of the following drugs: dexamethasone; prednisolone; or methotrexate. However, none of the patients in the present study underwent cranial radiation therapy. In addition to the late side effects of chemotherapy on the development of the permanent teeth, such as hypodontia, the cessation of root development, microdontia, taurodontism, and enamel hypoplasia were reported in previous studies.[31–35]

While investigating methotrexate-induced BMD loss in bone sarcoma survivors with DXA measurements, Pirker-Frühauf et al. found that the effects of childhood chemotherapy on bone loss were underestimated.[11] According to that study, vitamin D deficiency, calcium malnutrition and lactose intolerance might potentiate the negative effects of chemotherapy, and should be taken into consideration in long-term patient management. In cancer survivors, chemotherapy-induced osteoporosis causes late side effects. However, the abovementioned study focused only on the analysis of long bones.[11] In the present study, mandibular cortical and trabecular bone structures were examined for the first time in cancer survivors, and it was concluded that the mandibular cortical bone thickness in CSSs was affected in terms of KI as compared to the control group. However, no differences in mandibular trabecular structures were observed between the chemotherapy and control groups.

Marcucci et al., in a review of CCS bone health management, stated that there was a higher risk of low BMD and bone fracture after the treatment of some cancers, i.e., acute lymphoblastic leukemia, Hodgkin and non-Hodgkin lymphomas, osteosarcoma, Ewing's sarcoma, chondrosarcoma, brain tumors, and neuroblastoma.[7] In the current study, CSSs from the study group were treated for some of these types of cancer (Fig. 1).

Fractal dimension analysis and KI have been used for the evaluation of the changes in craniofacial bone structures, related to osteopenic diseases or pharmacological treatment. Numerous studies reported that the FD values for mandibular bone areas, calculated on panoramic radiographs, were fair surrogate calculations of skeletal BMD.[18–21,36] Apolinário et al. investigated the FD measurements in children with osteogenesis imperfecta under pamidronate treatment and concluded that the FD values were higher after the therapy.[20] Gupta et al. evaluated the effect of selective serotonin reuptake inhibitors by using morphometric analysis on panoramic radiographs.[37] They stated that KI was the strongest predictor of drug-related osteoporotic alterations.[37] On the other hand, in a study by Allen et al., in which the researchers evaluated the compatibility of the BMD values for the mandible with KI by using quantitative computed tomography (QCT) and panoramic radiography, it was observed that KI was not compatible with the mineral density of the bone.[38] On the contrary, in the current study, the C2 index frequency was higher in the study group.

To the best of our knowledge, the present study is the first to analyze mandibular bone structures in CSSs with the help of FD analysis and KI on panoramic radiographs. Overall, with regard to the effects of childhood cancer therapy on the mandibular bone FD, the study is inconclusive. As stated in the results of this study, there were no differences in mandibular bone structures between CSSs and the control group in terms of FD. Since the limitation of this study is the small size of the study group, there was a lack of adequate power to detect a statistically significant change. In this study, only the KI frequencies differed between the study and control groups. The C2 index frequency was higher in the study group, whereas the C1 index frequency was higher in the control group. One of the key findings of the present study is that KI is one of the precise indices for examining alterations in the mandibular cortical bone. These findings reinforce the general belief that childhood cancer therapy affects mandibular bone density.

Conclusions

Childhood chemotherapy may affect mandibular bone structures. The Klemetti index may be a useful clinical diagnostic tool for the examination of mandibular bone structures on dental panoramic radiographs. Since this study included a limited number of participants, more experimental and clinical studies are needed to investigate the potential effects of childhood chemotherapy on mandibular bone structures.

Ethics approval and consent to participate

This study was carried out with the permission of the institutional Ethics Committee at Mersin University, Turkey (decision No. 2018/209).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Oral health-related quality of life of preschool-aged Turkish children with congenital heart disease

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):503–508

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Funding sources
This research project was supported by the Scientific Research Projects Coordination Office of Selçuk University, Konya, Turkey (project No. 18102016).

Conflict of interest
None declared

Acknowledgements
None declared

Received on August 31, 2021
Reviewed on October 30, 2021
Accepted on November 4, 2021

Published online on October 27, 2022

Abstract

Background. Dental caries and poor oral hygiene can affect the quality of life (QoL) of patients with congenital heart disease (CHD). Information about the oral health-related quality of life (OHRQoL) of Turkish preschool children with CHD is scarce.

Objectives. The aim of the present study was to assess the OHRQoL, and the presence of caries, plaque and gingivitis in Turkish preschool children with CHD as compared to children without CHD (control group).

Material and methods. Children aged 3–6 years with CHD ($n = 75$) and a control group ($n = 75$) were included in the study. Examinations were conducted using the plaque index (PI), the gingival index (GI) and the World Health Organization (WHO) caries diagnostic criteria. The Early Childhood Oral Health Impact Scale (ECOHIS) questionnaire was completed by the children's families.

Results. The amount of caries and plaque, as well as the number of missing teeth were higher in children with CHD. The OHRQoL was lower in children with CHD. However, the differences between the 2 groups were not statistically significant ($p > 0.05$). The number of filled teeth was significantly higher in the control group ($p < 0.05$).

Conclusions. According to the findings of the present study, the high amount of caries and plaque in both groups demonstrates that caries continues to be a major public health problem. Although there was no significant difference in terms of QoL scale scores between the 2 groups, the study showed that OHRQoL was lower in children with CHD.

Keywords: dental caries, congenital heart disease, ECOHIS, oral health-related quality of life

Cite as
Yavsan ZS, Tosun G, Sert A. Oral health-related quality of life of preschool-aged Turkish children with congenital heart disease. *Dent Med Probl.* 2022;59(4):503–508. doi:10.17219/dmp/143581

DOI
10.17219/dmp/143581

Introduction

Congenital heart disease (CHD) is caused by congenital structural or functional anomalies in the cardiovascular system. Advances in diagnostics, neonatal care and surgical management have increased the survival rates in children with CHD.[1] With this increase in survival comes an increased burden of complexity when managing these children's oral health and disease. The maintenance of optimal oral health in children with CHD is of utmost importance.[2]

Oral and dental health is one of the most important factors affecting the quality of life (QoL) of preschool-aged children.[3] Untreated dental caries results in diminished QoL.[4] Previous studies have found that the prevalence of caries, including untreated caries, is higher in children with CHD than in healthy children.[5–8] Conversely, there are also studies indicating that the prevalence of dental caries is not higher in children with CHD.[9,10] Other studies have found that children with CHD also more often present with severe gingival disease and have more accumulated plaque.[5,11] It is known that dental caries, especially when untreated, results in nutritional difficulties, an insufficient chewing function, speech disorders, and esthetic problems. These factors can lead to numerous physical and psychosocial issues in children, such as pain, infection, the loss of self-confidence, the loss of concentration, learning difficulties, and school absenteeism.[12] Dental caries and its consequences can affect the QoL of children with CHD.[13]

The oral health surveys conducted in Turkey have determined that caries is a serious public health problem in preschool-aged children. In those studies, the clinical and microbiological aspects of caries have been investigated.[14–16] To the best of our knowledge, the psychosocial effects of caries on children with CHD have not been studied. In the present study, we evaluated the oral health-related quality of life (OHRQoL) of children with CHD aged 3–6 years as compared to healthy control children in Turkey.

Material and methods

Study design and sampling

The study protocol was approved by the institutional Ethics Committee at the Faculty of Dentistry of Selcuk University, Konya, Turkey (approval No. 2018/03). The study enrolled 75 children aged 3–6 years, diagnosed with CHD in the Department of Pediatric Cardiology of Selcuk University Hospital, Turkey, and 75 healthy children (control group without CHD) of similar age who reported to the Department of Pediatric Dentistry of Selcuk University Hospital. The dental examinations of both groups were performed in the Department of Pediatric Dentistry. The study was conducted over a period of 4 months, from April 2018 to July 2018. The power value for 150 individuals was determined to be 99.817%, using the G*Power program, v. 3.1.9.7 (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower). Informed consent forms were signed by the parents of all children. The inclusion criteria were as follows: children aged 3–6 years; complete primary dentition; and no other systemic diseases, syndromes or mental illnesses.

Oral examinations

Data collection was based on the clinical examinations of the teeth and gingiva. The detailed oral examinations of the children included in the study were conducted with a dental mirror and a dental probe. The examination results were recorded in accordance with the dmft index. The dmft/DMFT index (for primary and permanent dentition, respectively) provides information about tooth decay. The total number of decayed (d), missing due to caries (m) and filled (f) teeth in the examined individuals was divided by the total number of the examined individuals, and the dmft value for the group was obtained.

The plaque index (PI) and gingival index (GI) measurements used in the evaluation of periodontal health were taken from the mesial, distal, buccal, and palatal surfaces of each primary tooth, and were recorded accordingly.

The plaque index, developed by Silness and Löe,[acc.17] was used to determine the amount of supragingival microbial dental plaque. The teeth were isolated with cotton pads and air-dried. Microbial dental plaque on the 4 surfaces, in the region near the edge of the gingiva, was examined visually and with a periodontal probe. The PI values between 0 and 3 were obtained for each surface.

The GI values were obtained after evaluating the gums around all primary teeth in the mouth according to color, consistency, edema, and bleeding during probing. In the GI calculation, each of the 4 gingival regions was scored from 0 to 3 according to the GI criteria.

The PI and GI values with regard to the circumference of each tooth were calculated by dividing the obtained score by 4. To obtain the PI and GI values for each individual, the values calculated for each tooth were added and the sum was divided by the number of teeth scored.[17]

Quality of life (QoL) questionnaire

The assessment of the QoL of each child was carried out using the Early Childhood Oral Health Impact Scale (ECOHIS), the validity and reliability of which has been proven. The ECOHIS questionnaire was completed by the children's parents. This scale consists of a questionnaire section with 13 questions and 6 answer options for each question presented to the parents of the children.

The first 9 questions constitute the Child Impact Section (CIS), which evaluates the direct effects of dental problems and dental treatment on the child's daily activities, such as eating, drinking and communicating. The 2nd part (4 questions) is the Family Impact Section (FIS), which determines to what extent the child's dental problems and dental treatment affect their family members.[3]

There are 4 areas evaluated in the 9-question section that refer to the impact on the child. One question covers the child's symptoms, 4 questions cover the child's functioning, 2 questions cover the child's psychology, and 2 questions cover the child's self-confidence and social interaction. In the section consisting of 4 questions that refer to the impact on the child's family, 2 areas are evaluated. Two questions cover the family's distress and anxiety, and 2 questions cover the functioning of the family. Answer options are presented according to a Likert scale: 'never' = 0; 'rarely' = 1; 'sometimes' = 2; 'often' = 3; 'very often' = 4; and 'don't know' = 5. The question scores are added to determine the total score of the section. The higher the score, the more dental health problems occur and the worse OHRQoL is observed.[3]

Statistical analysis

The data was expressed as mean (*M*) and standard deviation (*SD*). The Kolmogorov–Smirnov normality test and Levene's test were used to examine the homogeneity of variances. While examining the differences between the 2 groups, the independent samples *t* test or the Mann–Whitney *U* test was used. The bivariate associations of continuous variables were assessed using Pearson's correlation coefficient. The results were considered significant at $p < 0.05$. Statistical analysis was performed using the IBM SPSS Statistics for Windows software, v. 21.0 (IBM Corp., Armonk, USA).

Results

The average age of children with CHD was 4.4 ±1.2 years, while the average age of children in the control group was 4.2 ±0.9 years. The 2 groups were similar with respect to age and gender ($p > 0.05$).

Comparison of the dmft values

The mean dmft values for both study groups are presented in Table 1. The number of decayed, missing due to caries and filled teeth was counted for all participants. The mean number of decayed teeth in children with CHD was 4.93, which was similar to 4.53 in the control group ($p > 0.05$). The mean number of missing teeth was 0.32 in the CHD group, whereas it was 0.19 in the control group. The mean number of filled teeth in children with CHD was 0.20, while it was 0.64 in the control group. There were no statistically significant differences between the 2 groups with regard to the number of carious and missing teeth. However, the number of filled teeth was significantly higher in the control group as compared to the CHD group.

Table 1. Comparison of the number of decayed (d), missing due to caries (m) and filled (f) teeth, and the total dmft values between children with congenital heart disease (CHD) and the control group

Variable	CHD group $n = 75$	Control group $n = 75$	*p*-value
d	4.933 ±4.303	4.533 ±3.116	0.515
m	0.320 ±1.198	0.186 ±0.537	0.384
f	0.200 ±0.753	0.640 ±1.530	0.031*
dmft	5.453 ±4.366	5.360 ±3.182	0.881

Data presented as mean ± standard deviation (*M* ±*SD*).
* statistically significant ($p < 0.05$).

Comparison of the PI and GI values

While the mean PI value was found to be 1.15 in children with CHD, it was 1.14 in the control group. With regard to the mean GI value, it was 0.98 and 1.05 in the CHD and control groups, respectively. When the 2 groups were compared in terms of PI and GI values, although the mean PI value was higher in children with CHD than in the control group, the differences in both indices were not statistically significant ($p > 0.05$) (Table 2).

Description of ECOHIS

The ECOHIS subscores and general scores depicting QoL are shown in Table 3.

The child subdimension overall score represents the total score for the answers given to the first 9 questions in the questionnaire. When children with CHD and the control group were compared in terms of child subdimension overall scores, although the score was higher in children with CHD, the difference was not statistically significant ($p > 0.05$). Quality of life was negatively affected to a greater extent in children with CHD than in the control group, but the difference was not statistically significant ($p > 0.05$).

The 2 groups were also compared in terms of family distress and anxiety, as well as family functioning. The family concern subscore type was represented by the total score for the answers given to questions 10 and 11 on the scale.

Table 2. Comparison of the plaque index (PI) and gingival index (GI) values between children with congenital heart disease (CHD) and the control group

Variable	CHD group $n = 75$	Control group $n = 75$	*p*-value
PI	1.152 ±0.384	1.139 ±0.259	0.625
GI	0.979 ±0.323	1.048 ±0.303	0.185

Data presented as *M* ±*SD*.

Table 3. Comparison of the Early Childhood Oral Health Impact Scale (ECOHIS) subscores and general scores in children with congenital heart disease (CHD) and in the control group

Scale subdimension	Evaluated area	Scale scores		*p*-value
		CHD group *n* = 75	control group *n* = 75	
Child subdimension	the child's symptoms	1.040 ±1.190	1.040 ±0.921	0.569
	the child's functioning	2.253 ±2.515	1.813 ±1.821	0.712
	the child's psychology	1.226 ±1.681	1.053 ±1.261	0.989
	the child's self-image	0.480 ±1.004	0.400 ±0.788	0.877
	overall score	4.999 ±5.499	4.306 ±3.701	0.866
Family subdimension	parental distress and anxiety	1.680 ±2.411	1.746 ±1.717	0.127
	family functioning	0.786 ±1.535	0.973 ±1.173	0.027*
	overall score	2.466 ±3.584	2.719 ±2.322	0.033*
Total score		7.465 ±8.558	7.025 ±5.104	0.275

Data presented as *M* ±*SD*. * statistically significant ($p < 0.05$).

The score was higher in the control group, but this difference was not statistically significant ($p > 0.05$). The family functioning subscore type was represented by the total score for the answers given to questions 12 and 13 on the scale. The score was significantly higher in the control group ($p = 0.027$). The family subdimension overall score was represented by the total score for the answers given to the last 4 questions in the questionnaire. The family subdimension overall score was significantly higher in the control group ($p = 0.033$). The families of the control group individuals were more concerned about their children's oral health; therefore, their QoL was reduced.

Finally, children with CHD and the control group were compared in terms of general scores for the whole scale.

Table 4. Correlation between the scale scores and the dmft, plaque index (PI) and gingival index (GI) values in children with congenital heart disease (CHD)

Variable	Correlation	Child subdimension overall score	Family subdimension overall score	Total score
dmft	correlation coefficient	0.671	0.695	0.723
	p-value	<0.0001*	<0.0001*	<0.0001*
PI	correlation coefficient	0.221	0.376	0.300
	p-value	0.056	0.001*	0.009*
GI	correlation coefficient	0.239	0.440	0.338
	p-value	0.039*	<0.0001*	0.003*

* statistically significant ($p < 0.05$).

The scale total score was represented by the total score for the answers given to all questions. The scale total score was higher in children with CHD than in the control group, but the difference was not statistically significant ($p > 0.05$). Although OHRQoL was lower in children with CHD, the difference was not statistically significant ($p > 0.05$). There was a significant correlation between the scale total score for children with CHD and their dmft, PI and GI values (Table 4).

Discussion

Congenital heart disease is one of the most common developmental anomalies in children. The disease is serious, as it can cause infective endocarditis in children. The keys to protecting these patients from infective endocarditis are proper oral health education and effective preventive strategies.[8]

Some studies have shown that even in European countries, with better access to dental health services, children with CHD present with a higher rate of caries, despite great preventive efforts.[18,19] Conversely, numerous other studies have found that there is no statistically significant difference in the dmft values between children with CHD and the control group.[9,10,13,20] Da Fonseca et al. did not find any statistically significant difference between the 2 groups.[13] They attributed this to some limitations of their study. One limitation was that radiographs were not used to diagnose caries. Another limitation was that the results might have been different if the sample size had been increased.[13] Talebi et al. showed that although there was no difference between the 2 groups in terms of dmft values, dental health was poor in both groups.[21] This finding underscores the importance of developing preventive strategies in children with CHD in the first years of their lives.

In this study, there was a high rate of caries observed in both groups, but there was no statistically significant difference between the 2 groups, which is similar to the findings of Da Fonseca et al.[13] and Talebi et al.[21] The reason why no statistically significant difference between the 2 groups was found and why the dmft values were higher than in other studies conducted across the country might be the small sample size.[14–16] Thus, the sample size is one of the limitations of the present study. If the sample size had been larger, the results might have been statistically significant.

According to the results of the QoL questionnaire, the family distress and anxiety subscores were lower in the CHD group. This study demonstrated that families did not have enough information about oral and dental health. We think that the dmft values may have been higher in children whose families had insufficient information. However, the level of knowledge on oral and dental health, as well as the socioeconomic status of the families were not evaluated in the present study.

One study reported that the parents of children with CHD did not take much care over dental treatment, and even avoided treatment due to the underlying medical problem.[10] This finding is supported by another study, which reported that 19% of children with CHD had never visited a dentist.[9] In our study, the number of filled teeth in the control group was significantly higher than in children with CHD. This suggests that the families of children with CHD may have avoided dental treatment, since they focused on the underlying medical problem. This study also confirms the high rate of tooth extraction in children with CHD. In previous studies, children with CHD had a higher amount of caries than the control group.[5–8] On the other hand, a few studies found that the difference between the groups was not statistically significant.[9,10] When all these studies were evaluated, the common and consistent result was the excessive amount of untreated caries in children with CHD. This result was also revealed in our study, which is consistent with the literature.[7–10,19]

The reason why PI is significantly higher during the period of primary dentition is probably the poor tooth brushing ability noted in children under the age of 8.[22] Therefore, it is important to reduce the amount of plaque and improve oral health in this age group. It is also critical to raise the awareness of families about the importance of teaching children the habit of tooth brushing by providing children with oral hygiene education. In this study, while the PI values in children with CHD were higher than in the control group, the difference was not statistically significant. Our findings are consistent with those reported by Hallett et al.[7] and Franco et al.[9] In previous studies, the higher PI and GI values demonstrated that oral hygiene and gum health were poor.[7,23] In our study, there was no statistically significant difference between the 2 groups in terms of GI values; however, the mean GI value was found to be slightly lower in children with CHD. The reduced GI value in children with CHD as compared to the control group suggests that the examiner may have examined the teeth and gums gently in an unconscious attempt to avoid causing any gingival bleeding in children with CHD.

This study demonstrated that the OHRQoL of children with CHD was poorer when compared to the control group, but this difference was not statistically significant. This result is different from other studies. Da Fonseca et al.[13] and Amirabad et al.[18] found that the QoL of children with CHD was significantly lower as compared to the control group. In our study, children with CHD had lower OHRQoL in specific areas, such as functioning, psychology, and self-confidence and social interaction. The child functioning subdimension referred to the child's difficulty with drinking hot and cold liquids, eating certain foods, and speaking due to caries, as well as their poor kindergarten attendance due to caries. In the child's psychology subdimension, the extent of the child's frustration or anxiety, and the child's difficulty with sleeping were scored. The self-confidence and social interaction subdimension referred to how often the child was afraid to smile, laugh and speak. In our study, we observed that the family concern and family functioning subdimension scores in the CHD group were lower than those of the control group. The family distress and anxiety section scored to what extent the family members were disturbed by the child's caries and how guilty they felt. Low family distress and anxiety subscale scores might be due to the families not caring about dental problems and dental treatment, as they were focused on CHD.

When the scale scores were evaluated in this study, in general, we found that children with CHD were affected by the consequences of caries. However, as the families did not have sufficient information about the importance of oral and dental health, we think that the children and their families were not concerned about dental problems, and consequently the children were not brought to dental treatment and follow-ups. In the families of the children from the control group, the family subdimension scores were higher as compared to the CHD group. Therefore, the families of the control group were more concerned about dental problems and dental treatment. The higher number of filled teeth in the control group supports this finding. Da Fonseca et al.[13] found that the parents of children with CHD felt more guilty about their children's oral health than the parents whose children were in the control group.[13] Such results were not reflected in our study. We think that the parents of children with CHD in the Turkish community do not know much about oral hygiene and its relationship to heart health, and thus they are not concerned about these problems. During consultations with parents and other family members, both pediatric cardiologists and dentists should work together to provide more detailed information in order to raise awareness. Another limitation of our study might be the absence of a system that would measure whether the families understood the survey questions correctly. Responses from the parents of young children might have skewed the data due to the children's inability to communicate certain aspects of OHRQoL.

Our study revealed that the high amount of caries, the excessive number of extracted teeth and the high dmft value negatively affected the OHRQoL of children with CHD. There were statistically significant relationships between the dmft and GI values and the child subdimension score. Our findings are consistent with a study by Amirabad et al.[18] These researchers also stated that high dmft values negatively affected QoL. The presence of untreated caries can impact children's social lives, as well as their mental and physical development, by causing pain, infection and swelling.[18] Again, in our study, a statistically significant positive correlation was found between the amount of caries, the dmft, PI and GI values and the total scale score in children with CHD. This indicates that an increased amount of caries and decreased oral hygiene in children with CHD negatively affect their OHRQoL.

Conclusions

The findings of this study clearly demonstrate that the amount of caries and plaque was high in both healthy children and children with CHD. This can be especially dangerous for children with CHD. The high dmft values in both groups show that caries continues to be a major public health problem. The number of filled teeth was significantly higher in the control group. Although there was no significant difference in terms of QoL scale scores between the 2 groups, we found that OHRQoL was lower in children with CHD. Our findings provide important baseline data that pediatric dentists can use to plan appropriate preventive dental strategies for children with CHD. This study may raise awareness among pediatric dentists and other health professionals.

Ethics approval and consent to participate

The study protocol was approved by the institutional Ethics Committee at the Faculty of Dentistry of Selcuk University, Konya, Turkey (approval No. 2018/03). Informed consent forms were signed by the parents of all the children participating in the study.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Prevalence of Simonart's band in cleft children at a cleft center in Indonesia: A nine-year retrospective study

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):509–515

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on October 6, 2021
Reviewed on November 15, 2021
Accepted on December 17, 2021

Published online on December 19, 2022

Abstract

Background. Simonart's band is a soft tissue band that connects the cleft gap of the base of the nostril or the margin of the alveolus. While research on the prevalence of Simonart's band in cleft lip and palate cases has been carried out in various countries, research on Simonart's band in Indonesia has yet to be conducted.

Objectives. This study aimed to determine the prevalence of different types of Simonart's band at a cleft center in Indonesia.

Material and methods. The data of cleft patients were reviewed retrospectively over a 9-year period at the Cleft Lip and Palate Center Center, Harapan Kita Women and Children Hospital, Jakarta, Indonesia. The patients were divided based on the type of cleft and the type of Simonart's band. The results were analyzed by means of descriptive statistics.

Results. Out of 638 cleft patients from the period 2008–2016, 77 patients had Simonart's band. The lip-to-lip band was most commonly found (52 cases, 67.5%). The lip-to-alveolus band was found in 20 cases (26.0%) and the alveolus-to-alveolus band had the lowest prevalence of 5 cases (6.5%). Associations between the cleft type (unilateral cleft lip and palate (UCLP), unilateral cleft lip and alveolus (UCLA), and bilateral cleft lip and palate (BCLP)) and Simonart's band type were all significant ($p = 0.001$, according to Fisher's exact test), which indicates significant differences in the distribution of the bands with regard to different cleft types. There was a significant difference in the distribution of the bands between the UCLP and UCLA groups ($p = 0.000$). On the other hand, the distribution of the bands in the UCLP group did not differ much from that in the BCLP group ($p = 0.065$).

Conclusions. The prevalence of Simonart's band was significantly higher in the patients with the unilateral complete cleft of the primary and secondary palate than in the subjects with the cleft of the primary palate. In the UCLP group, most patients had the lip-to-lip band type. In the BCLP group, the majority also had the lip-to-lip band type. In contrast, in the UCLA group, the majority showed the lip-to-alveolus band type.

Keywords: cleft lip and palate, Simonart's band, soft-tissue band, cleft lip and alveolus

Cite as
Ariawan D, Vitria EE, Sulistyani LD, et al. Prevalence of Simonart's band in cleft children at a cleft center in Indonesia: A nine-year retrospective study. *Dent Med Probl.* 2022;59(4):509–515. doi:10.17219/dmp/145065

DOI
10.17219/dmp/145065

Introduction

Cleft lip with or without cleft palate is the most common orofacial birth defect, with a prevalence of 1:700.[1–5] Cleft lip and palate occurs in males twice as often as in females and is more commonly unilateral on the left side.[1,6] In children, the disorder involves impaired masticatory and speech functions, and middle ear problems.[5,7]

The etiology of cleft lip and palate is multifactorial, with genetic and environmental factors, including maternal exposure to tobacco smoke, nutrition and access to medical care.[1,2,8] Approximately 30% of cleft lip cases are associated with more than 275 syndromes and are usually diagnosed as additional syndromes.[2,9] The most common syndrome is Van der Woude syndrome, which is an autosomal dominant disorder that is characterized by cleft lip and palate. Van der Woude syndrome accounts for about 2% of all cases of cleft lip and palate.[2,9,10]

In some patients with complete cleft lip and palate, soft tissue bands may be found; they connect the cleft gap of the base of the nostril or the margin of the alveolus.[11] These soft tissue bands are commonly known as Simonart's bands. The term "Simonart's band" was at first associated with Dr. Gustav Simon (1824–1876), a German surgeon renowned for treating urogenital fistulas and bilateral lip adhesion surgery. The word "Simonart" itself probably comes from "Simonarzt", a combination of Simon and "Arzt" – a German word for doctor.[11–14] Meanwhile, a Belgian obstetrician Dr. Pierre-Joseph Cécilien Simonart (1816–1846) described congenital bands in children, although he did not specifically describe the congenital band in the lip.[11–13] Yet, Simonart's band is more commonly known worldwide to indicate a soft tissue band in cleft lip and palate.[11,15] Kitamura postulates that soft tissue bands are formed by the portion of the lip or the alveolar region which escaped the post-fusion rupture.[16] On the other hand, Semb and Shaw suggest that soft tissue bands occur due to disharmony in cell proliferation between the lateral and medial nasal processes, or the impaired apoptosis of cells within the epithelial surfaces.[17] Moreover, Vermeij-Keers et al. presented a theory that the formation of Simonart's band is caused by fusion or differentiation defects.[18]

The presence of Simonart's band in cleft lip and palate subjects might be associated with less hypoplastic embryological processes in the maxillary process.[19,20] This condition may lead to a lower prevalence of maxillary lateral incisor agenesis distally to the cleft area.[20] In a Brazilian study using the panoramic radiographs of a sample of 121 non-syndromic cleft lip and palate children with and without Simonart's band, the most common condition in children with Simonart's band was the maxillary lateral incisors located on the distal side of the cleft (48.3%). Agenesis of maxillary lateral incisors was found in 35% of the cleft children with the band, followed by the teeth on the mesial and distal sides (10%), and then the teeth on the mesial side of the cleft (6.7%).[20] Different conditions of maxillary lateral incisors were found in the cleft children without Simonart's band, with tooth agenesis being the most common (45.9%), followed by the teeth located on the distal side of the cleft (29.5%), the teeth located on the mesial and distal sides (13.1%), and the teeth located only on the mesial side of the cleft (11.5%). There were statistically significant differences between the groups in the prevalence of the maxillary lateral incisors located on the distal side of the cleft.[20] This result supported the previous theory that the maxillary process is less hypoplastic in patients with Simonart's band.

Naidoo and Bütow classified soft tissue bands into 3 categories: type 1 – a band that connects both sides of the lip (lip-to-lip); type 2 – a band that connects the lip with the alveolar process (lip-to-alveolus); and type 3 – a band that connects the medial and lateral alveolar processes (alveolus-to-alveolus) (Fig. 1).[21] The clinical appearance of these soft tissue bands has 2 variations: a band covered by the skin; or a band that consists only of mucosal tissue, known as the subclinical variant.[11,15]

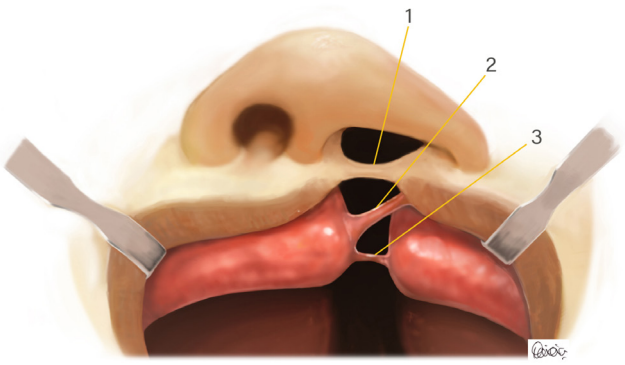

Fig. 1. Simonart's band types
1 – lip-to-lip; 2 – lip-to-alveolus; 3 – alveolus-to-alveolus.

Simonart's band has a favorable effect on the orofacial outcome after a cleft lip and palate repair. In addition, patients with Simonart's band usually require fewer secondary nose and lip repairs. Simonart's band affects the morphology of the maxillary dental arch and directs the anterior end of the non-cleft segment closer to the cleft segment. The condition may require a less traumatic lip and palate repair procedure.[15,17] As a summary of various studies regarding the influence of Simonart's band on the orofacial region, the following points can be mentioned: (1) Simonart's band does not interfere with the anatomical arrangement of the orbicularis oris muscle, which is separated at the cleft area; (2) Simonart's band has a minor positive effect on the final facial pattern in unilateral cleft lip and palate (UCLP) subjects; (3) Simonart's band could reduce the need for a secondary nose and lip repair; (4) Simonart's band has a long-term effect on the

morphology of the maxillary dental arch in unoperated unilateral cleft patients; and (5) patients with Simonart's band have a greater cranial base angle and a slightly better maxillomandibular relationship.[5,15,22]

Research on the prevalence of Simonart's band in cleft lip and palate cases has been carried out in various countries. Semb and Shaw reported that from among 257 UCLP subjects in Norway, 80 (31.1%) had Simonart's band.[17] In these 80 subjects, 68 patients (85.0%) had Simonart's band located at the base of the nostrils and covered by the skin, while in the rest of patients, Simonart's band was composed of the mucosa only and was located at the alveolar process.[17] Silva Filho et al. revealed that from among 2,014 Brazilian Caucasian UCLP patients, 394 (19.6%) had Simonart's band, regardless of the cleft side and the patient's gender.[11] Most of the 394 patients had Simonart's band that was covered by the skin (94.9%). The remaining 5.1% of Simonart's bands were considered a subclinical variant due to a smaller size and not being covered by the skin.[11] In another study, which examined 407 complete cleft lip and alveolus and complete cleft lip and palate patients, Simonart's band was found in 127 patients (31.2%).[15] This soft-tissue bridge occurred slightly more commonly in unilateral cleft patients (92 (31.7%) out of 290) than in bilateral cleft subjects (35 (29.9%) out of 117). The prevalence was higher in the primary palate cleft subjects with unilateral cleft lip and alveolus (UCLA) (48 (64.8%)) and bilateral cleft lip and alveolus (BCLA) (5 (45.5%)) than in the UCLP subjects (44 (20.3%)) and bilateral cleft lip and palate (BCLP) subjects (30 (28.3%)).[15] On the other hand, Acharya et al. reported that among 260 Indian UCLP patients, there were 90 patients (34.6%) with Simonart's band.[22]

Having the abovementioned research in mind, an investigation on Simonart's band in Indonesia has yet to be conducted. Thus, the objective of this study was to determine the prevalence of different types of Simonart's band in unoperated Indonesian cleft lip and palate patients. The research was conducted at the Cleft Lip and Palate Center, Harapan Kita Women and Children Hospital, Jakarta, Indonesia.

Material and methods

The present research was approved by the Dental Research Ethics Committee at the Faculty of Dentistry of the University of Indonesia, Jakarta, Indonesia (No. 36/Ethical Approval/FKGUI/IX/2020). This retrospective study was conducted based on the medical records from January 2008 to December 2016 obtained from the Cleft Lip and Palate Center. The type of cleft, the type of Simonart's band and the variations of Simonart's band were evaluated, taking into account the medical records as well as the standardized extraoral and intraoral preoperative photographs of the subjects. The inclusion criterion was the complete clinical preoperative photograph of the subject. The research subjects were divided into 4 groups as follows: UCLP; UCLA; BCLP; and BCLA. All clinical photographs were reviewed and re-evaluated by the cleft surgeon who operated on all cleft patients and has more than 20 years of clinical experience (MSH). Syndromic patients were excluded from the study. The data was analyzed with the χ^2 test and Fisher's exact test, with the level of significance set at 5% ($p < 0.05$).

Results

Over the 9-year period from January 2008 to December 2016, a total of 638 cleft patients attended the Cleft Lip and Palate Center. Out of the 638 cases, UCLP was the type of cleft with the highest prevalence of 411 cases (64.4%), followed by BCLP with 130 cases (20.4%), UCLA with 90 cases (14.1%), and finally BCLA with 7 cases (1.1%). In the unilateral cleft cases, more cleft cases were found on the left side than on the right side. In the UCLP cleft type there were 263 cleft cases on the left side (41.2%) and 148 cleft cases on the right side (23.2%). In the UCLA cleft type there were 62 cleft cases on the left side (9.7%) and 28 cleft cases on the right side (4.4%) (Table 1).

Table 1. Distribution of the cleft patients over the 9-year period according to the type of cleft

Type of cleft		*n* (%)	Total *n* (%)
UCLP	left	263 (41.2)	411 (64.4)
	right	148 (23.2)	
UCLA	left	62 (9.7)	90 (14.1)
	right	28 (4.4)	
BCLP		130 (20.4)	
BCLA		7 (1.1)	
Total *n* (%)		638 (100)	

UCLP – unilateral cleft lip and palate; UCLA – unilateral cleft lip and alveolus; BCLP – bilateral cleft lip and palate; BCLA – bilateral cleft lip and alveolus.

The present study showed that out of 638 cleft lip and palate patients, 77 had Simonart's band. The most common was the lip-to-lip band type (Fig. 2), with 52 cases (67.5%) – 26 cases were on the left side, 23 cases were on the right side and 3 cases were on both sides (i.e., BCLP). The lip-to-alveolus band type (Fig. 3) was found in 20 cases (26.0%) –12 cases were on the left side, 7 on the right side and 1 on both sides (i.e., BCLP). The alveolus-to-alveolus band type (Fig. 4) had the lowest prevalence of 5 cases (6.5%) – 4 cases on the left side and 1 case on the right side (Table 2). Regarding the gender of the subjects, Simonart's band was found more frequently in males than in females, but this difference failed to meet our statistical threshold (Table 3).

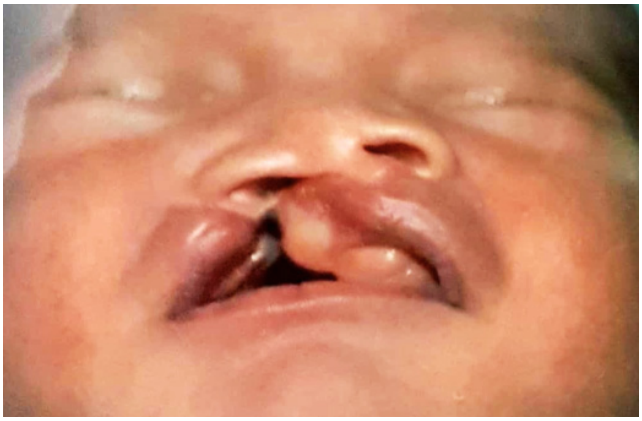

Fig. 2. Complete unilateral cleft lip and palate patient with a lip-to-lip band on the right side

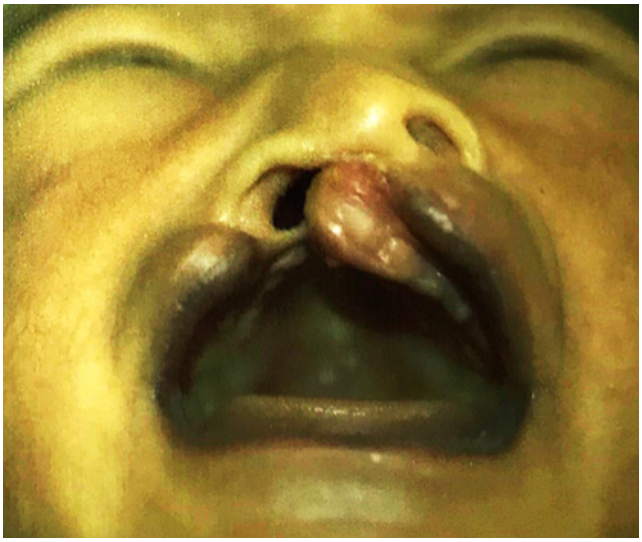

Fig. 3. Complete unilateral cleft lip and palate patient with a lip-to-alveolus band on the right side

In terms of Simonart's band variations, the skin-covered band was more frequent than the subclinical variant (the mucosal-only band) in both unilateral and bilateral clefts (Table 4). The skin-covered variant was observed in 51 (82.3%) out of 62 unilateral cleft patients with the band, while the mucosal-only band was observed in 11 (17.7%) unilateral cleft patients. In bilateral cleft subjects, the skin-covered band was observed in 12 patients (80.0%) and the mucosal-only band only in 3 patients (20.0%).

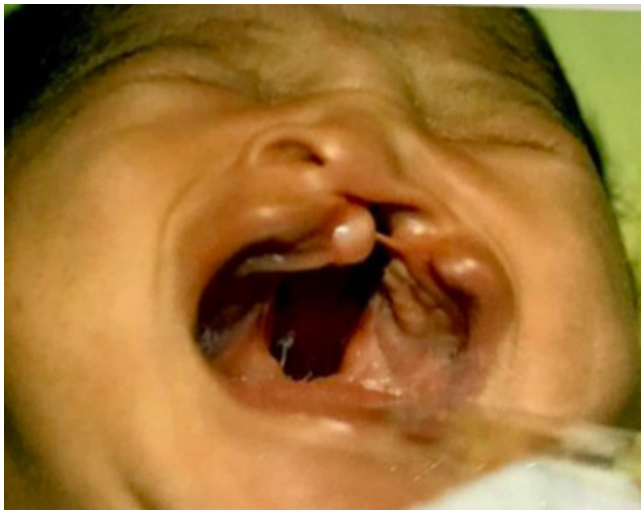

Fig. 4. Complete unilateral cleft lip and palate patient with an alveolus-to-alveolus band on the left side

Table 3. Presence of Simonart's band according to gender

Gender	With Simonart's band *n* (%)	Without Simonart's band *n* (%)	Total
Male	49 (12.7)	338 (87.3)	387
Female	28 (11.2)	223 (88.8)	251
Total	77	561	638

χ^2 test ($p = 0.620$; $p > 0.05$).

Table 4. Distribution of Simonart's band variations according to unilateral or bilateral clefts

Cleft	Skin-covered band	Mucosal-only band	Total *n* (%)
Unilateral	51	11	62 (80.5)
Bilateral	12	3	15 (19.5)
Total *n* (%)	63 (81.8)	14 (18.2)	77 (100)

χ^2 test ($p = 1.000$; $p > 0.05$).

Associations between the cleft type (UCLP, UCLA and BCLP) and Simonart's band type (lip-to-lip, lip-to-alveolus and alveolus-to-alveolus) were also investigated. of the 52 patients who had Simonart's band in the UCLP group, 80.8% had a lip-to-lip band, 13.5%

Table 2. Distribution of Simonart's band types in the cleft patients according to the cleft type

Cleft type	Simonart's band type									*n* (%)
	lip-to-lip			lip-to-alveolus			alveous-to-alveous			
	left	right	bilateral	left	right	bilateral	left	right	bilateral	
UCLP	24	18	–	4	3	–	3	0	–	52 (67.5)
UCLA	0	2	–	5	2	–	1	0	–	10 (13.0)
BCLP	2	3	3	3	2	1	0	1	0	15 (19.5)
BCLA	0	0	0	0	0	0	0	0	0	0 (0)
Total	26	23	3	12	7	1	4	1	0	77 (100)

had a lip-to-alveolus band and 5.8% had an alveolus-to-alveolus band. of the 10 patients who had Simonart's band in the UCLA group, 20.0% had a lip-to-lip band, 70.0% had a lip-to-alveolus band and 10.0% had an alveolus-to-alveolus band. Moreover, from among the 15 patients who had Simonart's band in the BCLP group, 53.3% had a lip-to-lip band, 40.0% had a lip-to-alveolus band and 6.7% had an alveolus-to-alveolus band.

There were significant differences in the distribution of the bands with regard to different cleft types (p = 0.001) (Table 5). Furthermore, to investigate significant differences between the groups, Fisher's exact test was performed for each of the 2 groups of a particular cleft type. There was a significant difference in the distribution of the bands between the UCLP and UCLA groups, with p = 0.000 (Table 6), whereas the UCLP and BCLP groups did not differ significantly in terms of distribution of the bands (p = 0.065) (Table 7).

Associations between the cleft type (UCLP, UCLA and BCLP) and Simonart's band variations (skin-covered band or mucosal-only band) were investigated as well. In all cleft types, the majority had skin bands (86.5% in UCLP, 60.0% in UCLA and 80.0% in BCLP), and the p-value of Fisher's exact test was p = 0.143 (Table 8).

Table 5. Distribution of Simonart's band types according to the cleft type

Cleft type	Simonart's band type			Total
	lip-to-lip	lip-to-alveolus	alveolus-to-alveolus	
UCLP	42 (80.8)	7 (13.5)	3 (5.8)	52 (67.5)
UCLA	2 (20.0)	7 (70.0)	1 (10.0)	10 (13.0)
BCLP	8 (53.3)	6 (40.0)	1 (6.7)	15 (19.5)
Total	52 (67.5)	20 (26.0)	5 (6.5)	77 (100)

Data presented as number (percentage) (n (%)). Fisher's exact test (p = 0.001; p < 0.05).

Table 6. Distribution of Simonart's band types in the UCLP and UCLA groups

Cleft type group	Simonart's band type			Total
	lip-to-lip	lip-to-alveolus	alveolus-to-alveolus	
UCLP	42 (80.8)	7 (13.5)	3 (5.8)	52 (83.9)
UCLA	2 (20.0)	7 (70.0)	1 (10.0)	10 (16.1)
Total	44 (71.0)	14 (22.6)	4 (6.5)	62 (100)

Data presented as n (%). Fisher's exact test (p = 0.000; p < 0.05).

Table 7. Distribution of Simonart's band types in the UCLP and BCLP groups

Cleft type group	Simonart's band type			Total
	lip-to-lip	lip-to-alveolus	alveolus-to-alveolus	
UCLP	42 (80.8)	7 (13.5)	3 (5.8)	52 (77.6)
UCLA	8 (53.3)	6 (40.0)	1 (6.7)	10 (22.4)
Total	50 (74.6)	13 (19.4)	4 (6.0)	67 (100)

Data presented as n (%). Fisher's exact test (p = 0.065; p > 0.05).

Table 8. Distribution of Simonart's band variations according to the cleft type

Cleft type	Simonart's band type		Total
	skin-covered band	mucosal-only band	
UCLP	45 (86.5)	7 (13.5)	52 (67.5)
UCLA	6 (60.0)	4 (40.0)	10 (13.0)
BCLP	12 (80.0)	3 (20.0)	15 (19.5)
Total	63 (81.8)	14 (18.2)	77 (100)

Data presented as n (%). Fisher's exact test (p = 0.143; p > 0.05).

Discussion

There are still differences of opinion among cleft surgeons regarding the type of cleft and the presence of Simonart's band, and whether it is incomplete or complete cleft lip. Naran et al. conducted a survey on 373 respondents who were members of the American Cleft Palate-Craniofacial Association (ACPA).[12] As many as 87.1% of them agreed that the presence of Simonart's band was a condition that existed in cases of complete cleft lip. The authors suggested that if the soft-tissue band is at or above the line from the alar-facial groove to the columellar-philtral junction, the condition is classified as complete cleft lip, whereas if the soft-tissue band is below the abovementioned line, the condition is classified as incomplete cleft lip.[12] In this regard, several articles that classify cleft lip cases with a soft-tissue band as complete cleft lip have been published. Among them, there are studies by Carvalho Carrara et al.,[23] Elsherbiny and Mazeed,[24] and Reddy et al.[25] Other studies, i.a., those conducted by Nollet et al.,[26] Jorge et al.,[27] Akarsu-Guven et al.,[28] and Vandersluis et al.,[29] excluded cases of complete cleft lip in the presence of Simonart's band, since it affected the maxillary arch.

The prevalence of Simonart's band in cleft patients varies among different populations. The present study aimed to determine the prevalence of different types of Simonart's band in cleft lip and palate children at the Cleft Lip and Palate Center, Harapan Kita Women and Children Hospital, Jakarta, Indonesia. This study has several limitations, including the incompleteness of the patients' medical records. Some clinical data was incomplete, including incomplete clinical photographs.

Out of the 638 cleft lip and palate patients from the 9-year period (2008–2016), there were 411 UCLP patients, with 52 (12.7%) having Simonart's band. This number was lower than those presented in previous studies. A study conducted in Stockholm, Sweden, reported that out of a total of 85 UCLP patients, there were 19 patients (22.4%) with Simonart's band.[30] A Brazilian study reported 394 such patients (19.6%) out of a total of 2014,[11] and another study with 72 UCLP subjects from Oslo, Norway, and Bristol, UK, reported a percentage of 22.2%.[31] Furthermore, our study also found fewer UCLP subjects with Simonart's band than a study conducted in Norway, which reported 80 patients with Simonart's band (31.1%) out of a total of 257 UCLP subjects.[17] A study conducted

in Bhubaneswar, India, also reported a higher incidence than that observed in our study.[22]

We found 15 subjects with Simonart's band (11.5%) out of 130 BCLP patients. This result was similar to that found in a previous study conducted in Stockholm, Sweden, where the number of individuals with BCLP and Simonart's band was 2 out of 19 subjects (10.5%).[30] Regarding gender, 49 (12.7%) male cleft patients had Simonart's band out of a total of 387 subjects, whereas in females, the proportion was 28 (11.2%) cleft patients with the band out of 251 female subjects. These results were lower than those previously reported in a Brazilian study (20.2% in males and 18.5% in females, respectively).[11]

In our study, the prevalence of Simonart's band was significantly higher in the patients with the unilateral complete cleft of the primary and secondary palate than in the subjects with the cleft of the primary palate. These results are in disagreement with previous results from a study conducted in Brazil, which revealed that the prevalence of Simonart's band in the unilateral clefts of the primary palate was higher than in the complete unilateral clefts of the primary and secondary palate.[15] In the UCLP cleft type, most individuals had the lip-to-lip band type. In the BCLP group, the majority also had the lip-to-lip band type. In contrast, in the UCLA group, the majority had the lip-to-alveolus band type. There was a significant difference in the distribution of different types of bands between the UCLP and UCLA groups. Differences in the type of Simonart's band may be explained by the theory of fusion or differentiation defects in early embryonic development. The skin-covered band is formed by the fusion of the medial and lateral nasal processes, and is categorized as a differentiation defect. The mucosal-only band is considered a submucous cleft of the alveolar processes caused by the insufficient outgrowth of the premaxilla and maxilla bone centers. The condition can be categorized as a differentiation defect of the alveolus combined with a fusion defect of the lip.[18,31,32]

Conclusions

This study found that the prevalence of Simonart's band was significantly higher in the patients with the unilateral complete cleft of the primary and secondary palate than in the subjects with the cleft of the primary palate. In the UCLP group, most patients had the lip-to-lip band type. In the BCLP group, the majority also had the lip-to-lip band type. In contrast, in the UCLA group, the majority showed the lip-to-alveolus band type.

Ethics approval and consent to participate

The present research was approved by the Dental Research Ethics Committee at the Faculty of Dentistry of the University of Indonesia, Jakarta, Indonesia (No. 36/Ethical Approval/FKGUI/IX/2020).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Can sleeping habits be associated with sleep bruxism, temporomandibular disorders and dental caries among children?

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):517–522

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on March 27, 2022
Reviewed on May 24, 2022
Accepted on June 2, 2022

Published online on December 21, 2022

Abstract

Background. Sleeping problems are common in the pediatric population. Their potential relationship with oral manifestations is in the scope of researchers' interest.

Objectives. The aim of the present study was to evaluate the possible associations between sleeping habits and sleep bruxism, temporomandibular disorders (TMD) and dental caries among children by using Children's Sleep Habits Questionnaire (CSHQ).

Material and methods. A cross-sectional study was carried out at the Faculty of Dentistry of Istanbul Aydin University, Turkey, with a representative sample of 100 children aged 6–13 years. The CSHQ was completed by their parents. In addition, an intraoral examination was carried out in a clinical setting and sleep bruxism was recorded. The temporomandibular joints (TMJ) were examined and TMD were rated according to the Helkimo anamnestic and clinical dysfunction index. Data was analyzed with Fisher's exact test and the χ^2 test.

Results. Among sleeping habits, bedtime resistance was found to be significantly associated with sleep bruxism and TMD symptoms in children. Sleep behavior problems were also found to be related to TMD. Untreated dental caries was significantly associated with sleep fragmentation.

Conclusions. Sleep bruxism, TMD and untreated dental caries might have a negative impact on children's sleeping habits and characteristics. Pediatricians and pedodontists should collaborate to identify the causes and clinical features of sleeping habits and disorders in order to avoid adverse effects on the child's stomatognathic system.

Keywords: dental caries, temporomandibular disorders, sleep bruxism, sleeping habits, Children's Sleep Habits Questionnaire (CSHQ)

Cite as
Topaloglu-Ak A, Kurtulmus H, Basa S, Sabuncuoglu O. Can sleeping habits be associated with sleep bruxism, temporomandibular disorders and dental caries among children? *Dent Med Probl.* 2022;59(4):517–522. doi:10.17219/dmp/150615

DOI
10.17219/dmp/150615

Introduction

It is well-known that sleep has an essential effect on the growth and development of a child. Nevertheless, sleep disorders are common in children from infancy through adolescence.[1–3] Parents and pediatricians should prudently detect sleeping habits and patterns to avoid possible adverse effects on the child's general health.[4] Sleeping habits may vary from bedtime resistance, through the delayed and fragmented sleep, to inability to sleep alone. These are all associated with sociocultural, physical, emotional, and neurological development.[5,6]

To identify the child's sleeping habits, many techniques, instruments and questionnaires are available. The Children's Sleep Habits Questionnaire (CSHQ) is a valid and reliable parent-proxy instrument for the investigation of the child's sleep-related difficulties.[7]

According to the International Classification of Sleep Disorders (ICSD), sleeping disorders can be categorized as insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep–wake disorders, sleep-related movement disorders, and parasomnia.[8] According to the new consensus on the definition of bruxism, it is a repetitive masticatory muscle activity characterized by the clenching or grinding of the teeth and/or the bracing or thrusting of the mandible, and it can be specified as either sleep bruxism or awake bruxism.[9]

Among the abovementioned, one of the sleep-related movement disorders – sleep bruxism – is frequently reported by parents or partners. A recent systematic review and meta-analysis showed that the prevalence of sleep bruxism in children was 31.16%.[10] The risk factors related to bruxism include male gender, genetic predisposition, anxiety, poor sleep quality, object biting, exposure to second-hand smoke, headaches, peer problems, emotional symptoms, and mental health problems.[11–13]

Exacerbated sleep bruxism may lead to an imbalance in the stomatognathic system. This may cause heterogeneous musculoskeletal disorders, involving the temporomandibular joints (TMJ) and related structures in the long term.[14–17] Furthermore, the resulting discomfort leads to dysfunction.[18–20] Yet, it is still questionable whether sleep bruxism is related to the clinical findings of temporomandibular disorders (TMD).[21,22]

Notably, individuals with sleep bruxism are reported to present with the fragmented sleep, which adversely affects the quality of sleep and the quality of life in general.[23,24] Hence, the early diagnosis of sleep bruxism and TMD as well as follow-up reports are crucial.[25–27]

Another factor affecting sleeping patterns is dental caries, which can also lead to awakening from sleep at night. A cohort study revealed that late bedtime was associated with the incidence of dental caries.[28] Like in a chain reaction, poor sleep quality impacts the level of attention and motor skills, which might increase the incidence of dental trauma.[29,30]

Considering that sleep problems are common in the pediatric population, their potential relationship with oral manifestations is of interest to many researchers.[14]

Thus, the present study is innovative in searching for the possible associations between sleeping habits and sleep bruxism, TMD and dental caries while underlining the importance of collaboration between pediatricians and pediatric dentists.

The present study aimed to evaluate the possible associations between sleeping habits and sleep bruxism, TMD and dental caries among children aged 6–13 years by using CSHQ.

Material and methods

The study protocol was approved by the Human Research Ethics Committee of Istanbul Aydin University, Turkey (2020/169). Furthermore, the study was fully compliant with the World Medical Association Declaration of Helsinki.

This cross-sectional study involved 100 children who were referred to the Department of Pediatric Dentistry at the Faculty of Dentistry of Istanbul Aydin University for routine control or dental treatment during the period from March 2, 2020, to May 29, 2020. All cooperative children aged 6–13 years were included. The exclusion criteria were as follows: systemic diseases; fixed/removable intraoral/extraoral appliances; and previously diagnosed sleep disorders. Finally, informed written consent was obtained from the children's parents.

The data on sleeping habits was collected through parent-proxy reports with regard to CSHQ, which contains 33 questions. This questionnaire is segmented into 4 main topics: bedtime resistance; sleep behavior problems; sleep fragmentation; and daytime sleepiness. Each item has 3 response options regarding how often these conditions occurred the previous week. Frequencies are coded as: 'usually' if the specified behavior occurred more than 4 times per week; 'sometimes' for 2–4 times per week; and 'rarely' for 0–1 time per week. The presence of sleep bruxism was reported based on the answers to CSHQ.

One experienced dentist conducted intraoral examinations in a clinical setting to avoid inter-examiner bias. Carious lesions were recorded using the World Health Organization (WHO) criteria.[31] The examiner recorded a surface as decayed only if it presented with a detectably softened floor, undermined enamel or a softened wall. According to this criterion, all stages that precede cavitation and other conditions, like the early stages of a carious lesion, were considered sound.

The TMJ examination was conducted by an experienced prosthodontist, and TMD were rated according to the Helkimo anamnestic and clinical dysfunction index.[32] The lack of symptoms was encoded as 'grade 0', mild symptoms (the feeling of fatigue in the muscles, muscle stiffness and pain, and masticatory muscle disorders) were encoded as 'grade 1', and serious symptoms (not being able to open the mouth widely, jaw locking or dislocation, jaw pain, and limitation in mandibular movements, pain in the area of TMJ and/or masticatory muscles, and condyle–disc irregularities in TMJ) were encoded as 'grade 2'.

Statistical analysis

The statistical analysis was conducted using the IBM SPSS Statistics for Windows software, v. 25 (IBM Corp., Armonk, USA). Data was analyzed with Fisher's exact test and the χ^2 test. In cases where the expected frequencies were less than 20%, the evaluation was made by means of the Monte Carlo simulation method so that these frequencies could be included in the analysis. For the significance level of the tests, *p*-values <0.05 and <0.01 were set as thresholds.

Results

One hundred patients within the age range of 6–13 years (45 males and 55 females) met the inclusion criteria, and both the patients and their parents were included in this study. Mothers (76%) comprised the majority of these parents, followed by fathers (21%) and other relatives (3%).

Sixty percent of parents reported that their children had sleep bruxism. Gender was not found to be significantly associated with the presence of sleep bruxism. The prevalence of TMD symptoms was 9%. A significant association was found among children between sleep bruxism and TMD symptoms ($p = 0.015$).

Sleep bruxism and TMD both showed significant associations with bedtime resistance. The presence of sleep bruxism was significantly higher in children with bedtime difficulties ($p = 0.024$) (Table 1). A statistically significant association was observed among children between TMD symptoms and bedtime resistance ($p = 0.020$), and between TMD symptoms and sleep behavior problems ($p = 0.041$) (Table 2). The prevalence of untreated dental caries was 98%. The presence of caries was also found to be significantly associated with awakening from sleep at night and sleep fragmentation ($p = 0.001$) (Table 3).

Table 1. Association between sleeping habits and sleep bruxism

Sleeping habits		Sleep bruxism		Total	*p*-value
		presence	absence		
Bedtime resistance	yes	15 (44.1)	19 (55.9)	34 (100)	0.020*
	no	45 (68.2)	21 (31.8)	66 (100)	
Sleep behavior problems	yes	0 (0)	2 (100)	2 (100)	0.080
	no	60 (61.2)	38 (38.8)	98 (100)	
Waking up at night/sleep fragmentation	yes	2 (66.7)	1 (33.3)	3 (100)	0.811
	no	58 (59.8)	39 (40.2)	97 (100)	
Inability to wake up/daytime sleepiness	yes	6 (40.0)	9 (60.0)	15 (100)	0.086
	no	54 (63.5)	31 (36.5)	85 (100)	
Total		60 (60.0)	40 (40.0)	100 (100)	–

Data presented as number (percentage) (*n* (%)). * statistically significant ($p < 0.05$).

Table 2. Association between sleeping habits and temporomandibular disorders (TMD)

Sleeping habits		TMD		Total	*p*-value
		presence	absence		
Bedtime resistance	yes	0 (0)	34 (100)	34 (100)	0.024*
	no	9 (13.6)	57 (86.4)	66 (100)	
Sleep behavior problems	yes	1 (50.0)	1 (50.0)	2 (100)	0.041*
	no	8 (8.2)	90 (91.8)	98 (100)	
Waking up at night/sleep fragmentation	yes	0 (0)	3 (100)	3 (100)	0.580
	no	9 (9.3)	88 (90.7)	97 (100)	
Inability to wake up/daytime sleepiness	yes	1 (6.7)	14 (93.3)	15 (100)	0.732
	no	8 (9.4)	77 (90.6)	85 (100)	
Total		9 (9.0)	91 (91.0)	100 (100)	–

Data presented as *n* (%). * statistically significant ($p < 0.05$).

Table 3. Association between sleeping habits and dental caries

Sleeping habits		Dental caries		Total	*p*-value
		presence	absence		
Bedtime resistance	yes	33 (97.1)	1 (2.9)	34 (100)	0.629
	no	65 (98.5)	1 (1.5)	66 (100)	
Sleep behavior problems	yes	2 (100)	0 (0)	2 (100)	0.838
	no	96 (98.0)	2 (2.0)	98 (100)	
Waking up at night/sleep fragmentation	yes	2 (66.7)	1 (33.3)	3 (100)	0.001*
	no	96 (99.0)	1 (1.0)	97 (100)	
Inability to wake up/daytime sleepiness	yes	15 (100)	0 (0)	15 (100)	0.548
	no	83 (97.6)	2 (2.4)	85 (100)	
Total		98 (98.0)	2 (2.0)	100 (100)	–

Data presented as *n* (%). * statistically significant ($p < 0.05$).

Discussion

Today, children's sleeping habits are the focus of pediatricians and dentists. The possible associations between sleeping habits and sleep bruxism, TMD, malocclusion, and dental caries have been investigated recently, and they are still a significant area of researchers' interest.[28–30]

In the present study, the Turkish version of CSHQ was used for data collection. The questionnaire was translated into Turkish, validated and reported to be a reliable instrument for assessing the sleeping habits of Turkish children.[33] Although there are various concerns that the parent's report may differ from the child's self-report, scales based on parents' reports are frequently used in both psychiatry and pediatric practice.[34] It is noteworthy that the American Academy of Sleep Medicine considers parents' reports reliable and sufficiently objective for use in epidemiological studies.[8] The assessment of sleep bruxism is graded as: possible sleep/awake bruxism based on a self-report only; probable sleep/awake bruxism based on a self-report and clinical inspection; and definite sleep bruxism based on a self-report, clinical inspection and polysomnography.[9] The role of the family in the diagnosis of pediatric sleep bruxism is considerable, as family members typically observe the characteristic sounds produced while grinding the teeth at night.[4] A potential limitation of the present study is that the assessment of sleep bruxism was done based on the parents' reports only.

Sleep bruxism is hereditary. Muscle pain, snoring and mouth breathing are characteristic signals when detecting sleep bruxism in children. Sleep fragmentation, sleep agitation and nightmares have been reported to be possibly associated with sleep bruxism.[35,36]

In the present study, the prevalence of sleep bruxism was found to be 60%. This value is much higher than that observed in a systematic review by Machado et al., who reported that the prevalence rates for sleep bruxism varied from 5.9% to 49.6%.[18] These variations can be attributed to different diagnostic criteria used.[18] Therefore, evidence-based studies with standardized and validated diagnostic criteria are required for accurate assessment. Insana et al. reported that sleep bruxism affected more boys than girls.[37] In a study by Cheifetz et al., there was also a trend for males to be more likely to brux than females.[20] However, in the present study, no significant relationship was found between sleep bruxism and gender.

Our study revealed that sleep bruxism was associated with sleeping habits. The presence of sleep bruxism was significantly higher in children who had bedtime difficulties. Consistent with this finding, Öner et al. reported that the quality of sleep was associated with sleep bruxism in children, and that it decreased in the presence of sleep bruxism.[38]

A total of 9% of children showed TMD symptoms in the present study. The prevalence of TMD in children and adolescents varies from 16% to 68%.[39] Mostly, the study populations' subjective TMD symptoms include jaw clicking, muscle tenderness, pain during opening, and limited opening.[20] There were statistically significant associations between TMD and negative sleeping habits and sleep bruxism in the present study. Children with bedtime resistance were more likely to have TMD. In contrast to our findings, Cheifetz et al. reported that TMD were not associated with sleep bruxism, which may be attributed to different diagnostic criteria used and different study designs.[20] However, the results of another recent research are consistent with ours; Lei et al. reported that TMD were significantly associated with disturbed sleep, adversely affecting sleep quality and the quality of life.[26]

The prevalence of dental caries was very high in the present study, reflecting Turkey's unmet oral healthcare needs.[40] Subsequently, retardation in growth, school absenteeism and sleep fragmentation occur.[34] Dental caries was associated with sleep fragmentation in the present study, which is also in line with previous reports.[41,42]

The associations between negative sleeping habits and oral manifestations suggest that sleeping habits should be investigated with other diagnostic methods to confirm these findings. In this manner, the data on sleeping habits obtained when collecting the patient's history before a dental appointment could better inform parents on how to prevent sleep bruxism and TMD. Consequently, the cooperation of pediatricians, pedodontists and psychiatrists is crucial in diagnosing, treating and preventing sleep-related oral health problems.

Conclusions

In the current study, children's sleeping habits were significantly associated with sleep bruxism, TMD and dental caries. Therefore, pediatricians and pediatric dentists should collaborate to identify the causes and clinical features of sleeping habits in order to prevent the possible oral and dental damage in children.

Ethics approval and consent to participate

The current study was carried out after obtaining approval from the Human Research Ethics Committee of Istanbul Aydin University, Turkey (2020/169). The participants' parents provided written informed consent prior to the investigation.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Comparison of pain perception between computer-controlled local anesthetic delivery and the conventional syringe for inferior alveolar nerve block in children

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

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):523–529

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on February 7, 2021
Reviewed on April 11, 2021
Accepted on April 19, 2021

Published online on December 8, 2022

Abstract

Background. Local anesthesia (LA) is commonly used for pain control in clinical dental practice. However, it is often perceived as the most painful part of the treatment and the factor leading to the avoidance of dental care. Hence, research on better means of pain management is being conducted.

Objectives. The aim of the study was to evaluate and compare pain perception using the No Pain III™ computer-controlled local anesthesia delivery (CCLAD) system and the conventional syringe, for inferior alveolar nerve block (IANB) in children.

Material and methods. Thirty children aged 6–12 years were included in the study. Children were randomly allocated into 2 groups by the flip of a coin. Group A received LA by conventional syringe and group B received LA by No Pain III™, on the contralateral side. Physiological parameters including blood pressure (BP), heart rate (HR) and respiratory rate (RR) were assessed at baseline, during the deposition and after the deposition of LA. A subjective evaluation of pain perception was assessed using the Wong–Baker FACES Pain Rating Scale (WBS). The measured values were subjected to statistical analysis.

Results. A statistically significant difference was observed between group A and group B for pain perception using the WBS, systolic BP and RR.

Conclusions. The use of the No Pain III™ CCLAD system resulted in reduced pain perception and better acceptance when compared to the use of the conventional syringe, for IANB in children.

Keywords: children, pain perception, inferior alveolar nerve block, computer-controlled local anesthetic delivery system, Wong–Baker FACES Pain Rating Scale

Cite as
Shetty S, Dalvi S, Katge F, Patil D, Chimata VK, Shetty A. Comparison of pain perception between computer-controlled local anesthetic delivery and the conventional syringe for inferior alveolar nerve block in children. *Dent Med Probl.* 2022;59(4):523–529. doi:10.17219/dmp/135897

DOI
10.17219/dmp/135897

Introduction

The use of local anesthesia (LA) in dentistry has greatly reduced the pain and discomfort associated with various dental procedures in children. Local anesthesia is considered one of the best methods to perform intraoral operative and surgical procedures in children. However, delivery of LA and needle puncturing of the mucosa are uncomfortable. Local anesthesia is often perceived by children as the most painful part of treatment, and in some instances as the only painful part, which can lead to the avoidance of dental care.[1] Pain can result from the mechanical trauma of needle introduction into the site of injection, or from the sudden distension of the tissues due to the rapid discharge of syringe contents. Pain can also be caused by the stimulation with the first few drops of the LA solution.[2]

Conventional syringes are commonly used in dentistry, as their utilization is cost-efficient and less technique-sensitive. However, while using a conventional syringe, the dentist must simultaneously control the movement of the penetrating needle and drug infusion variables. If they are unable to precisely control both activities, the injection technique will be compromised and this can lead to painful insertion or inadequate deposition.[3] Several methods have been suggested to overcome conventional techniques of LA administration and to reduce pain caused by the administration of LA agents. Computer-controlled local anesthesia delivery (CCLAD) systems are one such method that has been introduced to reduce pain and anxiety of dental patients during LA delivery.[1] The unit uses a microprocessor and an electronically controlled motor to deliver the anesthetic solution. Additionally, it uses a sterile disposable handpiece that does not look like a syringe, which greatly reduces fear and anxiety. Furthermore, this new system eliminates the manual pressure required by the operator to administer injections by generating a precisely controlled anesthetic flow rate. The combination of reduced distension of tissues and controlled flow rate results in a virtually imperceptible injection.[4]

To assess pain perception during dental anesthesia, various objective and subjective parameters have been used.[5] Objective assessment can be performed by recording physiological parameters such as blood pressure (BP), heart rate (HR) and respiratory rate (RR) during the administration of LA. Subjective pain assessment can be done with the aid of non-verbal reporting, which has been used principally in clinical research to measure pain intensity.[6]

The present study was undertaken to evaluate and compare pain perception using the No Pain III™ CCLAD system and the conventional syringe, for inferior alveolar nerve block (IANB), a technique that is commonly carried out during treatment procedures in clinical pediatric dentistry. The null hypothesis was that there is no difference in pain perception between the No Pain III™ CCLAD system and the conventional syringe for IANB in children.

Material and methods

The present study was carried out in the Department of Pediatric and Preventive Dentistry of Terna Dental College, Navi Mumbai, India. Ethical clearance was obtained from the institutional Review Board of Ethics at Terna Dental College, Navi Mumbai, India (approval No. TDC/IRB-EC/95/2014).

Inclusion and exclusion criteria

The inclusion criteria for the study were children aged 6–12 years requiring LA by IANB on both sides of the mandibular arch for various dental procedures. Other criteria for inclusion in the study were a score of I according to the American Society of Anesthesiologists (ASA) Physical Status Classification System, no previous exposure to dental anesthesia and a Frankl behavior rating between 3 and 4. Exclusion criteria were children requiring unilateral IANB, patients with a Frankl behavior rating between 1 and 2, and those who were medically or mentally compromised.

Sample size calculation

The calculation of sample size was carried out using G*Power 3 analysis (v. 3.1.92; Heinrich Heine University Düsseldorf, Germany). The effect size was 0.5, the α error probability was 0.05 and power (1-β error probability) was 0.80. The calculated sample size included 30 children.

A total of 30 children aged 6–12 years who attended the outpatient department were selected for the study. Parents or guardians accompanying children were briefed about the procedure in the local language and written informed consent was obtained.

Study design

The study had a crossover design. The treatment under LA was carried out in 2 subsequent visits with a gap of 7 days. The sequence and LA administration method were randomly assigned to each child. The randomization was achieved by the flip of a coin to allocate the mode of the first local anesthetic delivery system (No Pain III™ CCLAD system or conventional syringe) to each subject. The children received LA by a single trained operator and on their subsequent visit they received the second local anesthetic delivery system (No Pain III™ CCLAD system or conventional syringe) on the contralateral side of the same arch (a crossover design).

The selected samples were divided into 2 groups. Group A underwent LA administration by conventional syringe and group B had LA administered using the No Pain III™ CCLAD system. Pre-anesthetic baseline monitoring of BP, HR and RR was performed using a Contec™ CMS6000 Patient Monitor (Contec Medical Systems Co. Ltd., Qinhuangdao, China).

All procedures were performed by a single trained operator. Topical anesthetic gel Precaine® B (Pascal International, Bellevue, USA) was applied using a cotton pellet at the site of injection. After waiting for 1 min, IANB was performed. In group A, the conventional syringe (aspirating syringes; Septodont Healthcare Pvt. Ltd., Panvel, India)[7,8] was used with the LA solution in the form of cartridge (Lignospan Special consisting of 2% lidocaine with 1:80,000 epinephrine; Septodont Healthcare Pvt. Ltd.) and with a 27-gauge needle (0.27 mm × 35 mm, Septoject™; Septodont Healthcare Pvt. Ltd.) (Fig. 1).

In group B, the No Pain III™ CCLAD system (KMG, Busan, Korea) was used for LA administration, which comprised of a disposable component, a handpiece component and a computer-controlled unit. The handpiece was an ultra-light pen-like handle that was linked to an anesthetic cartridge with plastic microtubing. The procedure was followed as per the manufacturer's instructions (Fig. 2,3). The delivery of a 1.8-mL single-use Lignospan anesthetic cartridge was done at slow speed, regulated by a pedal.

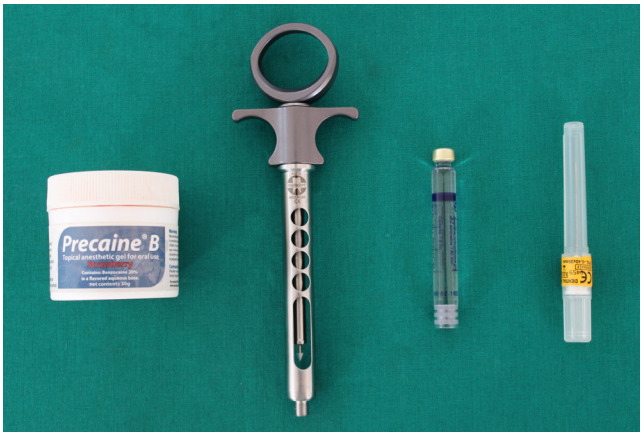

Fig. 1. Topical anesthetic gel Precaine® B, a conventional syringe (aspirating syringe), a Lignospan cartridge, and a 27-gauge needle (Septoject™) (from left to right)

Fig. 2. Computer-controlled local anesthesia delivery (CCLAD) system – No Pain III™

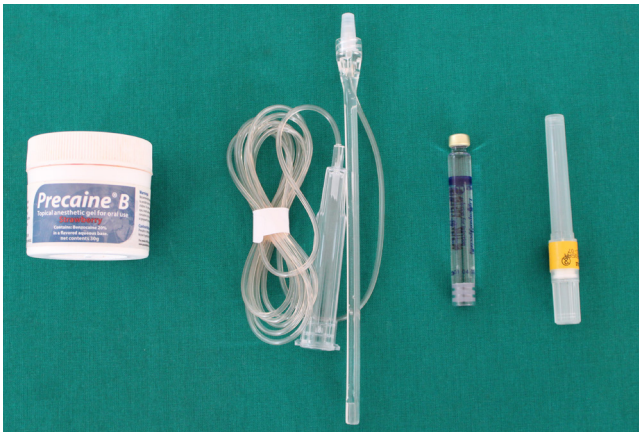

Fig. 3. Topical anesthetic gel Precaine® B, a handpiece component with a pen-like handle and plastic microtubing, a Lignospan cartridge, and a 27-gauge needle (Septoject™) (from left to right)

Blood pressure, HR and RR were recorded at baseline, during the deposition of LA and after the deposition. A subjective evaluation (self-report) of pain perception during the LA injection was assessed using the Wong–Baker FACES Pain Rating Scale (WBS). The scale consists of 6 different facial expressions numbered from 0 to 5 (no pain to intense pain). Patients were asked to select only 1 face to indicate the degree of pain they felt after the LA injection.

Statistical analysis

Obtained data was entered into a Microsoft Excel spreadsheet and subjected to statistical analysis using SPSS v. 17.0 software (SPSS Inc., Chicago, USA). A paired t-test was used to evaluate WBS scores between the 2 different groups, after the deposition of LA. Repeated measures analysis of variance (ANOVA) was used to compare vital parameters (BP, HR, RR) at baseline, during the deposition of LA and after the deposition, in both groups.

Results

The study population consisted of 30 children, 14 boys and 16 girls. Children were aged between 6 and 12 years, with a mean age of 9 ±1.8003 years. Because of the crossover study design, all 30 children were subjected to IANB using both the conventional syringe and the No Pain III™ CCLAD system.

Subjective evaluation of pain perception using the Wong–Baker FACES Pain Rating Scale

In the evaluation of children's pain perception using the WBS Scale, group B showed lower pain scores compared to group A. The difference was statistically significant ($p < 0.05$) (Table 1).

Table 1. Evaluation of pain using the Wong–Baker FACES Pain Rating Scale (WBS)

Groups	After deposition of LA	
	M	*SD*
Group A	2.866	1.502
Group B	0.467	0.681
p-value	0.002*	

*statistically significant ($p \leq 0.05$); LA – local anesthesia; *M* – mean; *SD* – standard deviation.

Assessment of physiological parameters

Tables 2–4 show intergroup comparisons of physiological parameters, including BP, HR and RR at baseline, during the deposition of LA and after the deposition.

Blood pressure

Comparison of BP values indicated that group A had increased systolic BP during the deposition of LA when compared to group B. The difference was statistically significant ($p < 0.05$) (Table 2). However, the difference in diastolic BP was not statistically significant.

Heart rate

Comparison of the mean HR values between group A and group B is shown in Table 3. No significant differences in HR were observed between both groups at various time intervals.

Respiratory rate

Comparison of RR between both groups indicated that RR increased during and after the deposition of LA in group A when compared to group B. The difference was statistically significant ($p \leq 0.05$) (Table 4).

Discussion

Pain is an unpleasant sensation that is often associated with actual or potential trauma or tissue injury.[9] Kaufman et al.[10] reported that the injection of the area in the oral cavity was directly related to pain and perceived discomfort. Palatal and IANB injections are more painful than local infiltration, mental nerve block or periodontal ligament injection.[8] However, IANB is the most frequently used injection technique for achieving LA during

Table 2. Evaluation of pain using a physiological parameter – blood pressure (BP)

Physiological parameter	Interval	Technique	*n*	*M*	*SD*	t-test	*p*-value	S/NS
Blood pressure	systolic (baseline)	conventional	30	113.900	8.113	0.587	0.560	NS
		computer-controlled	30	112.530	9.846			
	diastolic (baseline)	conventional	30	72.667	6.707	0.390	0.690	NS
		computer-controlled	30	73.433	8.439			
	systolic (during deposition of LA)	conventional	30	129.070	8.586	2.823	0.007*	S
		computer-controlled	30	122.030	10.600			
	diastolic (during deposition of LA)	conventional	30	86.033	7.876	0.843	0.400	NS
		computer-controlled	30	84.067	10.070			
	systolic (after deposition of LA)	conventional	30	123.570	7.789	2.331	0.230	NS
		computer-controlled	30	118.530	8.896			
	diastolic (after deposition of LA)	conventional	30	79.567	9.518	0.919	0.360	NS
		computer-controlled	30	77.433	8.435			

*statistically significant ($p < 0.05$); S/NS – significant/non-significant.

Table 3. Evaluation of pain using a physiological parameter – heart rate (HR)

Physiological parameter		Technique	*M*	*SD*	*p*-value	S/NS
Heart rate	baseline	conventional	104.800	12.707	0.600	NS
		computer-controlled	103.033	13.389		
	during deposition of LA	conventional	122.333	17.161	0.060	NS
		computer-controlled	114.200	16.058		
	after deposition of LA	conventional	114.900	15.775	0.060	NS
		computer-controlled	108.066	12.673		

Table 4. Evaluation of pain using a physiological parameter – respiratory rate (RR)

Physiological parameter		Technique	*M*	*SD*	*p*-value	S/NS
Respiratory rate	baseline	conventional	27.866	3.559	0.870	NS
		computer-controlled	28.033	4.657		
	during deposition of LA	conventional	35.533	4.091	0.000*	S
		computer-controlled	30.400	3.873		
	after deposition of LA	conventional	31.600	3.616	0.050*	S
		computer-controlled	28.551	4.306		

*statistically significant ($p < 0.05$).

mandibular restoration and surgical procedures. Therefore, the IANB technique was used to compare pain perception between the No Pain III™ CCLAD system and the conventional syringe.

No attempt was made to match the CCLAD and conventional groups by gender, since previous studies in children comparing CCLAD and conventional syringes have shown no difference in pain sensation between males and females.[11]

In the studies by Tahmassebi et al.[11] and Gibson et al.[12] each child was assigned to either the CCLAD or the conventional syringe group. The authors reported that the use of the CCLAD system resulted in significantly less disruptive behavior when compared to the conventional syringe.

In the current study, the children served as their own control, wherein at the first appointment one LA administration method was used, and the other method was performed on the subsequent visit. This study is in agreement with those of San Martin-Lopez et al.[13] and Langthasa et al.[14]

Pain perception was evaluated after the deposition of LA using the WBS.[15] When the 2 methods were compared using this scale, statistically significant differences were observed between group A and group B, indicating better patient acceptability towards CCLAD (No Pain III™). Since there was a difference in the mean values between both groups, the null hypothesis was rejected. These results are in accordance with studies conducted by Langthasa et al.[14] and Goyal et al.[16] In contrast, studies conducted by Asarch et al.[17] and Koyutürk et al.[18] found no difference in the pain rating between the CCLAD and the conventional syringe.

Assessment of physiological parameters

Blood pressure

Akinmoladun et al.[19] and Meyer[20] hypothesized that increased HR and alterations in BP during dental procedures are due to endogenous catecholamine release resulting from emotional stress, and are not a pharmacological effect. Meanwhile, Tolas et al.[21] and Meechan et al.[22] considered cardiovascular responses to dental treatment under LA to be influenced more by the anesthetics. In addition, pain may cause BP to rise due to the release of endogenous catecholamine.[23]

Heart rate

Changes in HR are expected to reflect patient responsiveness to procedures, especially during stressful experiences. According to Dowling,[24] HR increases in response to the application of pain. It has been suggested that mean HR increase during the deposition of LA is due to the fact that an alarm reaction is initiated by the hypothalamus. This results in vasodilatation and causes an increase in the release of endogenous epinephrine and norepinephrine that subsequently increases HR and cardiac output.[25] The above findings were in accordance with the study conducted by West et al.[26]

The results of the present study indicate that mean HR was higher during the deposition of LA by both conventional syringe and No Pain III™. In contrast to our findings, studies conducted by San Martin-Lopez et al.[13] and Bansal et al.[2] showed lower HR using a computer-controlled delivery system compared to conventional methods. These differences may be due to the pen-like design of the studies, which was virtually pain-free, more predictable and less threatening to the patients.

Respiratory rate

In agreement with the results of the present study, Nicholson et al.[27] and Langthasa et al.[14] concluded that the CCLAD system was more acceptable and less anxiety-inducing compared to the conventional method. According to Pashley et al.,[28] painful sensation during any needle injection comes from administering an anesthetic solution too rapidly or with too much force. They also stated that with a conventional syringe, the volume flow and pressure parameters cannot be precisely controlled, which results in difficult, erratic and uncomfortable injections. According to Nusstein et al.,[29] CCLAD maintains a constant positive pressure on the flow of anesthetic solution, thereby yielding a virtually pain-free needle insertion. Furthermore, the improved tactile feedback, visibility and automated aspiration achieved with CCLAD allow for concentration on needle positioning and patient interaction.[2]

Studies have been conducted using other types of computer-assisted anesthesia. The study conducted by Berrendero et al.[7] compared the Calaject CCLAD system with the conventional anesthesia. This study concluded that the majority of children reported significantly less pain with the CCLAD system.

One of the important reasons for preference towards CCLAD is that it lowers the pain of injection as well eliminates the visual stimulus of dental syringes. The expense of buying new syringes and disposable attachments, the length of injection time, the need to change work routines, and the additional space needed for the device, remain limiting factors for its widespread introduction into clinical practice.[30]

Limitations

A larger sample size should have been selected to observe changes in pain perception. Also, the difference in duration of LA deposition could have been considered. Furthermore, the objective assessment of pain perception in children using physiological parameters could have been analyzed using different types of CCLAD systems.

Conclusions

From the present study, it can be concluded that pain perception in children was reduced while using the No-Pain III^{TM} CCLAD system when compared to the conventional syringe for IANB anesthesia.

Ethics approval and consent to participate

Ethical clearance was obtained from the institutional Review Board of Ethics at Terna Dental College, Navi Mumbai, India (approval No. TDC/IRB-EC/95/2014). Written informed consent was obtained from all participants.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Effect of an experimental chitosan/casein gel on demineralized enamel under a cariogenic challenge

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):531–538

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Funding sources
The study was financially supported by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) – Programa Institucional de Bolsas de Iniciação Científica/Universidade de São Paulo (PIBIC/USP), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (No. 2011/12901-7) and the Harvard School of Dental Medicine of Harvard University, Boston, USA.

Conflict of interest
None declared

Acknowledgements
None declared

Received on April 4, 2021
Reviewed on December 1, 2021
Accepted on January 23, 2022

Published online on December 9, 2022

Cite as
Yamakami SA, Faraoni JJ, Lia NSND, Regula FB, Ohyama H, Palma-Dibb RG. Effect of an experimental chitosan/casein gel on demineralized enamel under a cariogenic challenge. *Dent Med Probl.* 2022;59(4):531–538. doi:10.17219/dmp/146038

DOI
10.17219/dmp/146038

Abstract

Background. Dental caries is considered one of the most common oral health diseases.

Objectives. The aim of the study was to evaluate the effects of an experimental chitosan/casein gel on enamel demineralization/remineralization in an environment with a high cariogenic challenge.

Material and methods. Thirty-six specimens of bovine enamel (4 mm × 3 mm × 2 mm) were ground flat and polished. Then, the specimens were immersed in acetate buffer for 43 h with half of the surface protected (serving as control) and the other half exposed. All demineralized surfaces were randomly assigned into 3 groups ($n = 12$ per group) according to the type of treatment (G1 – control, G2 – 1.5% chitosan gel with 1.5% casein, and G3 – 1.5% chitosan gel without casein), and the corresponding treatment was applied once a week for 3 weeks. The specimens were also subjected to pH cycles of demineralization/remineralization and the treatments were performed 3 times at 7-day intervals for a total of 21 days. Surface images were obtained for the analysis of initial roughness and, after the cariogenic challenge, new images were obtained to evaluate the final roughness, volume loss and wear profile using laser confocal microscopy. After the analyses, the specimens were cut and the depth of demineralization was measured. The data were analyzed using the Kruskal–Wallis analysis of variance (ANOVA) and the Tukey's test.

Results. While the chitosan gel with casein showed a similar loss to the control group ($p > 0.05$), both gels resulted in similar volume loss ($p > 0.05$). There were no statistical differences regarding the wear profile, surface roughness and depth of demineralization between the groups ($p > 0.05$).

Conclusions. The chitosan gel reduced volume loss of the demineralized enamel without significantly impacting the surface smoothness.

Keywords: chitosan, dental caries, tooth remineralization, caseins, confocal microscopy

Introduction

Dental caries is considered one of the most prevalent chronic diseases in adults and children worldwide.[1] A multifactorial etiology of dental caries involves specific microorganisms, fermentable carbohydrates, the dental surface, characteristics inherent to the host, and time of exposure. All of these factors play a role in the dynamic processes of demineralization and remineralization that occur on the dental surface.[1] If demineralization occurs continuously, the lesion may progress from an initial decalcification to a white spot lesion until an irreversible loss of the mineral structure occurs, which can be visualized in the form of a cavity lesion.[2,3]

If found at an early stage, lesions can be reversed noninvasively through the use of remineralizing agents.[4] Thus, research on the use of remineralizing agents is important as it can be helpful in preventing cavity formation. Remineralizing agents should meet some requirements,[5] including being safe for human use, displaying efficacy of bioactive compounds, promoting rapid precipitation in partially demineralized teeth, becoming a stable and resistant phase against the attack of bacteria and other acidic agents, remaining active on both the surface and subsurface of the lesion, and having the ability to diffuse through the biofilm and lesion. As of today, there has not been an agent that meets all of the aforementioned characteristics.

Several studies have shown that the formation of white spot lesions is directly attributable to the accumulation and prolonged retention of visible bacterial biofilm,[6] as well as the presence of *Abiotrophia defective* spp., *Actinomyces*, *Actinobaculum*, *Aggregatibacter*, *Bergeyella*, *Campylobacter gracilis* spp., *Cardiobacterium hominis* spp., Clostridiales, *Corynebacterium*, *Fusobacterium*, *Gemella*, *Granulicatella*, *Haemophilus parainfluenzae*, *Kingella*, *Lautropia mirabilis* spp., *Leptotrichia*, *Neisseria*, *Porphyromonas*, *Prevotella melaninogenica* spp., *Rothia*, *Streptococcus*, *Nanosynbacter lyticus* spp., and *Veillonella*,[7–9] among others. Traditionally, the topical application of fluoride has been the most commonly used method to prevent enamel demineralization[6] and promote a surface less susceptible to acid degradation.[10] However, most of the current fluoride regimens depend on patient adherence and collaboration, and those who would benefit most from the application of supplemental fluoride due to poor oral hygiene are also the least likely to comply with this treatment.[11] For this reason, finding alternative treatments has been a major challenge in the field of remineralization research. However, interesting results have been obtained using arginine, xylitol gums, self-assembling peptides, enamel matrix proteins, crystalline calcium phosphates, polyphosphate systems, unstable calcium phosphates, and stable calcium phosphates, such as casein derivatives.[12–19]

Preventive therapies have been refined to curb demineralization, favor remineralization, and, therefore, halt lesions of active caries.[12] An example of one such preventive therapy is casein, a milk-derived phosphoprotein, which has shown a beneficial effect in preventing and inhibiting the onset of the disease. Casein phosphopeptide (CPP) can bind to phosphate and calcium ions in the dental structure.[20,21] It is thought that this compound is able to intervene in the dynamics of the demineralization/remineralization process, reducing demineralization and increasing the opposite process during an acid challenge of the dental surface.[22] The bioavailability of these remineralizing components inhibits acidic attacks on the tooth surface, thereby enhancing the dynamic remineralization process.[22]

Chitosan is a biopolymer with a high nitrogen content that can function as a carrier to transport calcium and phosphate ions during the biomineralization process.[23] Chitosan has been widely used in the medical field and, although relatively new to dentistry, the potential it holds is promising.[24] On top of promoting the remineralization process, it can also bind to the surface of *Streptococcus mutans*, reducing the availability of these bacteria to bind to others and to colonize the dental surface. Consequently, the formation of dental plaque biofilm is significantly reduced.[25] Moreover, chitosan is positively charged, which allows it to adhere to negatively charged surfaces, such as demineralized enamel, and form a protective film against acidic attacks.[24]

Our study aimed to evaluate the effects of an experimental chitosan/casein gel on enamel demineralization/remineralization in an environment with a high cariogenic challenge. To our knowledge, this is one of the first studies to evaluate enamel demineralization/remineralization with a combination of 1.5% chitosan and 1.5% casein. The null hypotheses included the following: (i) wear profile and surface roughness would not vary after treatment with a combination of chitosan and casein; (ii) time would not influence the enamel roughness analysis after the experimental treatment.

Material and methods

Experimental design

The study involved the experimental treatment with chitosan gel on demineralized enamel in 3 groups (G1 – control, G2 – 1.5% chitosan gel with 1.5% casein, and G3 – 1.5% chitosan gel without casein). The experimental units consisted of 36 enamel specimens obtained from the buccal surfaces of bovine incisors (n = 12 per group). The response variables were volume loss, surface wear and surface roughness. They were evaluated using 3D confocal laser scanning microscope (OLS 4000 LEXT; Olympus Inc., Waltham, USA), and depth of the demineralization lesion, which was measured by means of optical microscopy (Axiostar Plus; Carl Zeiss, Oberkochen, Germany).

Sample preparation

Bovine incisors were freshly extracted and stored in a 0.1% thymol solution (pH = 7.0) at 4°C. The incisors were cleaned with a scaler and water/pumice slurry in dental prophylaxis cups. Teeth with hypoplastic stains, extensive cracks or marked wear were discarded. The teeth were sectioned using an IsoMet™ Low Speed Saw (Isomet 1000; Buehler, Lake Bluff, USA) with a water-cooled diamond disc (Extec Corp., Enfield, USA) in order to obtain enamel slabs measuring 4 mm high × 3 mm wide × 2 mm thick.[26]

The surfaces of the specimens were ground flat, finished and polished using a polishing machine (APL-4; Arotec Indústria e Comércio, Cotia, Brazil) with 400-, 600- and 1,200-grit sandpaper and felt disks impregnated with 0.3-µm and 0.05-µm alumina (Arotec Indústria e Comércio). The dentin surface was also corrected to remove unevenness across the samples. Next, the specimens were immersed in an ultrasonic bath with deionized water (Ultrasonic Cleaner T-1449-D; Odontobrás Indústria e Comércio de Equipamentos Médicos Odontológicos LTDA, Ribeirão Preto, Brazil) for 10 min to remove the polishing debris.[26]

All specimens were covered with a composite resin (3M™ Filtek™ Z350; 3M, St. Paul, USA) to protect all surfaces and only part of the external surface (3 mm) was not covered with resin.[26] This surface was divided in half, with half of the enamel surface (control area) covered with composite resin (without adhesive application) and the other half exposed to a cariogenic challenge.

Initial cariogenic challenge

The artificial caries lesions (white spot formations) were induced by immersing the specimens in 1 L of 50 mM acetate buffer solution (1.28 $mmol^{-1}$ $Ca(NO_3)_2 \cdot 4H_2O$, 0.74 $mmol/L^{-1}$ $NaH_2PO_4 \cdot 2H_2O$, 0.03 µgF, pH 5.0) for 43 h, according to the protocol described by Queiroz et al.[27] After the cariogenic challenge, the specimens were analyzed using a confocal laser scanning microscope for initial measurements and topographic images.

Surface treatment

After the cariogenic challenge,[27] the specimens were stored in artificial saliva[28] for 24 h and randomly assigned to 3 groups. The corresponding experimental treatments were applied: G1 – no treatment, G2 – 1.5% chitosan gel (75–85% deacetylated; Sigma-Aldrich Brasil Ltda., Barueri, Brazil) with 1.5% casein (cat. No. C3400, casein from bovine milk; Sigma-Aldrich Brasil Ltda.) (composition: distilled water, 1.0% glacial acetic acid, 1.5% chitosan powder, casein powder; pH 5.0), and G3 – 1.5% chitosan gel without casein (75–85% deacetylated, Sigma-Aldrich Brasil Ltda.) (composition: distilled water, 1.0% glacial acetic acid, 1.5% chitosan powder; pH 5.0). For groups G2 and G3, the gels were actively applied to the enamel surface with a microbrush (Microbrush® Regular 2.0 mm; Vigodent SA Indústria e Comércio, Rio de Janeiro, Brazil) for 3 min, followed by 2 min of further contact before removal with jets of deionized water.

After each treatment, the specimens were stored in artificial saliva for 6 h.[28] The treatments were performed 3 times at 7-day intervals for a total of 21 days. Between treatments, a pH cycle was carried out in a demineralizing/remineralizing solution[27] for the entire 21-day period.

pH cycling

Twenty-four hours after the end of treatment, the specimens were placed in a demineralizing solution (DES) for 4 h. Then, they were moved to a remineralizing solution (RE) for 20 h[27] at a temperature of 37°C to simulate a high caries risk situation. After each 7-day interval, the specimens were washed with deionized water and re-treated according to each group protocol. After treatment, the specimens were washed as outlined above and the pH cycle was restarted.

The DES consisted of 2.0 $mmol/L^{-1}$ $Ca(NO_3)_2 \cdot 4H_2O$, 2.0 $mmol/L^{-1}$ $NaH_2PO_4 \cdot 2H_2O$, 0.075 $mmol/L^{-1}$ acetate buffer, and 0.02 ppm F (pH 4.7).[27] The RE consisted of 1.5 $mmol/L^{-1}$ $Ca(NO_3)_2 \cdot 4H_2O$, 0.9 $mmol/L^{-1}$ $NaH_2PO_4 \cdot 2H_2O$, 0.150 $mmol/L^{-1}$ KCl, 0.1 mol/L^{-1} Tris, and 0.03 ppm F (pH 7.0).[27] The solutions were applied at a volume ratio per area of 6.25 mL/mm^2 (50 mL) and 3.12 mm^2 (24 mL), respectively. The demineralizing and remineralizing solutions were replaced every 4 days. After 21 days, the specimens were kept in the RE for 24 h, completing the experimental period in 22 days.[17] After that, the specimens were analyzed using a confocal laser scanning microscope to obtain images of the enamel surface.

Volume loss, surface roughness and wear profile analysis

Images were captured using a ×5 objective lens, obtaining a ×107 total optical zoom. After the acquisition of the images, volume loss (µm) was calculated using the difference between the surface ($µm^3$) of the plane of the reference area (control) and the structure lost below its plane. Surface roughness analysis (Sa-µm) was carried out on both the control and demineralized areas to compare the different patterns of surface texture after treatment. For the wear profile analysis (Rv-µm), the control and demineralized areas were calculated using the length of the wear line (in µm) between them (Fig. 1). The same specimens were used for morphological evaluation captured at the end of the pH cycle in relation to the control area, with a ×100 objective lens and a ×2137 optical zoom.

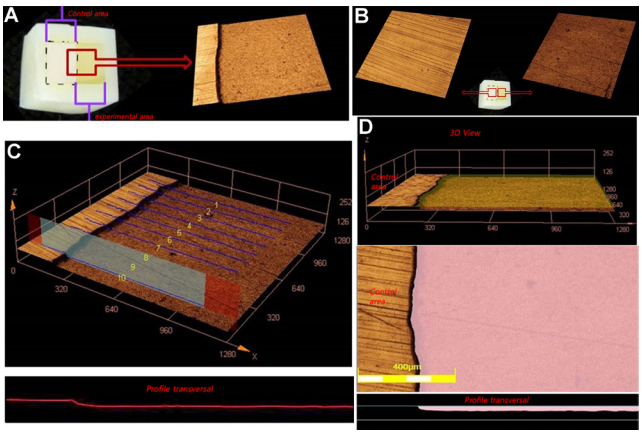

Fig. 1. Confocal laser scanning microscope images and analyses

A – specimen with control area and experimental area after the removal of protection; B – surface roughness of control and experimental area; C – 3D images of wear profile analysis (10 reads of the image, with the control area as a reference point); D – volume loss analysis in 3D images; volume analysis is marked in pink (observed in transversal profile).

Depth of demineralization

After the images were captured using the laser confocal scanning microscope, the specimens were individually embedded into an acrylic resin and longitudinally sectioned using a low-speed water-cooled diamond saw (Isomet 1000; Buehler) to obtain 0.5-mm thick slices. Next, the slices were polished with 600- and 1,200-grit aluminum oxide paper to achieve a thickness of 150 µm. Each slice was then placed in an ultrasonic cleaner with distilled water for 10 min. In the end, 2 sections were obtained per specimen and taken for the analysis under an optical microscope (Axiostar Plus; Carl Zeiss). Images were obtained with ×40 magnification and captured using a digital camera coupled to the microscope. Measurements of the demineralization depth (µm) of the initial white spot lesion and the white spot lesion after the demineralizing pH cycle were obtained using AxioVision® software LE v. 4.3 (Carl Zeiss).

Statistical analysis

The data was analyzed for normality and homogeneity, and data distribution was non-normal only in the case of surface roughness. Therefore, the Kruskal–Wallis test was performed. For wear profile, volume loss and depth of demineralization, one-way analysis of variance (ANOVA) was used. For surface roughness, an ANOVA was employed to compare the different time points of the treatment (white spot, after treatment, after cycling). For differentiation of the means, the Tukey's test was performed for all variables ($p < 0.05$).

Results

The analysis of volume loss revealed that the experimental chitosan gel without casein group was similar to the experimental chitosan gel with casein ($p > 0.05$). The 2 groups significantly differed from the control group, which showed a higher volume loss (Fig. 2A–C). For the wear profile and surface roughness, all groups showed similar values ($p > 0.05$; Table 1).

For the surface roughness analysis at different time points (Fig. 3), a statistically significant difference was observed between the initial and final evaluation for all groups ($p < 0.05$), with a significant increase in values (Table 2).

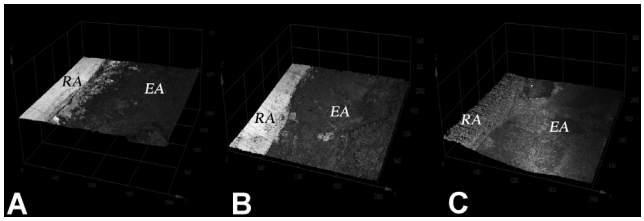

Fig. 2. Wear profile between the reference area (RA) and the experimental area (EA) among the groups

A – control; B – experimental chitosan gel with casein; C – experimental chitosan gel without casein.

Table 1. Mean and standard deviation of the volume loss [µm], wear profile [Rv-µm] and surface roughness [Sa-µm] of the different groups

Group	Volume loss	Wear profile	Surface roughness
G1 – control	15.15 ±9.79^{B}	4.10 ±1.26^{C}	0.96 ±0.39^{C}
G2 – chitosan/casein gel	10.66 ±9.21^{AB}	3.66 ±1.14^{C}	1.05 ±0.37^{C}
G3 – chitosan/casein-free gel	3.88 ±3.80^{A}	3.24 ±1.68^{C}	0.87 ±0.39^{C}

The values in the columns have been compared. The same capital letters indicate statistical similarity ($p > 0.05$).

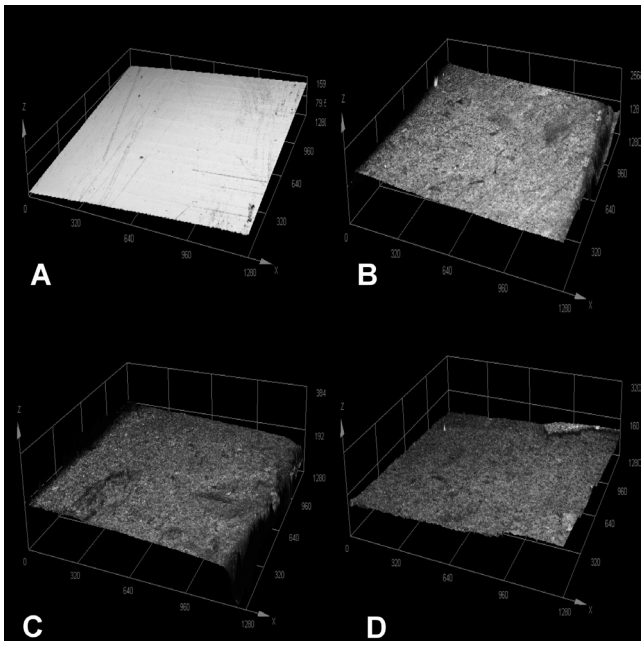

Fig. 3. Topography of the different groups after the pH cycle

A – surface roughness before the pH cycle/surface treatment; B – control; C – experimental chitosan gel with casein; D – experimental chitosan gel without casein.

Table 2. Mean and standard deviation of surface roughness [Sa-µm] at different time points

Time point	G1	G2	G3
White spot	0.59 ±0.39^{AB}	0.53 ±0.14^{AB}	0.52 ±0.26^{A}
After treatment	0.40 ±0.35^{A}	0.45 ±0.21^{A}	0.44 ±0.19^{A}
After cycling	0.96 ±0.39^{B}	1.05 ±0.37^{B}	0.87 ±0.39^{B}

The same capital letters indicate statistical similarity ($p > 0.05$). G1 – control; G2 – 1.5% chitosan gel with 1.5% casein; G3 – 1.5% chitosan gel without casein.

The 3 groups presented similar behavior concerning demineralization depth (Table 3 and Fig. 4). No experimental treatment was able to inhibit the process. In the comparison between the white spot and treated areas, the data showed that for all groups there was no significant increase in the demineralization depth of the treated areas.

Table 3. Mean and standard deviation of the demineralization depth of the white spot lesion, treated area (experimental) and the difference between them (in µm)

Area	G1	G2	G3
White spot lesion	0.09 ±0.03^{A}	0.08 ±0.03^{A}	0.08 ±0.03^{A}
After pH cycling	0.12 ±0.03^{B}	0.11 ±0.04^{B}	0.13 ±0.03^{B}
Difference	0.04 ±0.02^{C}	0.03 ±0.02^{C}	0.04 ±0.02^{C}

The same capital letters indicate statistical similarity ($p > 0.05$).

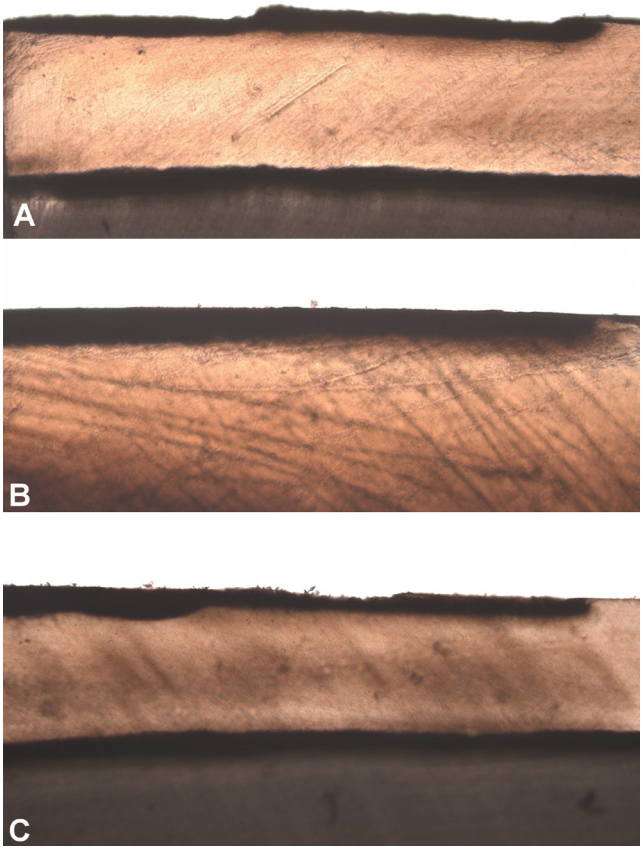

Fig. 4. Depth demineralization lesion

A – control; B – experimental chitosan gel with casein; C – experimental chitosan gel without casein.

Discussion

Dental caries is the result of an imbalance in the dynamics of the enamel remineralization and demineralization processes, mainly due to a low oral pH after the release of acid by facultative anaerobic bacteria.[6,7] To simulate this condition, the current study subjected dental enamel to an intense cariogenic challenge that provided a high risk for caries. Accentuated enamel loss, including the formation of cavities, was observed in some specimens.

The substrate used in the present study was bovine teeth enamel. This methodology was based on previous studies that employed this substrate for studies of minimally invasive processes in enamel.[29] Moreover, its use is supported by recent studies, which verified that the microstructure of bovine enamel is very similar to human enamel,[30] making its use feasible for research in this area. Additionally, it has been observed that the use of this substrate in the microbial caries model showed similar behavior to human teeth.[31]

To suspend or minimize the structural loss in high-risk caries, an experimental chitosan/casein treatment was employed, as literature has shown that casein, a milk protein, is similar in function to proteins responsible for the biomineralization of the tooth.[20,32] Casein phosphopeptide, in particular, can bind to surfaces such as plaque, soft tissue and dentin, as well as provide a reservoir of bio-available calcium and phosphate in the saliva and on the surface of dental structure.[20,32] Under oral acid conditions, CPP considerably increases the solubility of calcium phosphate by stabilizing amorphous calcium phosphate (ACP) through the presence of phosphorylated serine groups in its structure.[33] The process of remineralization of the subsurface occurs through the dissociation of the CPP-ACP complex and slows the release of calcium and phosphate ions as the pH in the plaque decreases producing a supersaturation state that reduces the demineralization process.[33,34] The large calcium reservoir within the plaque delays the diffusion of free calcium ions and provides a source of calcium for remineralization, thus restricting mineral loss during a cariogenic episode.[22,33,35] Incorporating casein peptides into enamel plaques increases the enamel's calcium and phosphate content, thereby depressing its demineralization and improving remineralization.[22,32,33] Since the effectiveness of casein has been demonstrated by several studies,[34,36,37] it was suggested to combine the remineralizing property of casein with the multi-beneficial properties of chitosan.

The experimental gels were produced on a chitosan base (with or without casein) and prevented the continuity of the mineral loss in the enamel specimens and caused little volume loss in this group, without interfering with demineralization depth. Therefore, the first null hypothesis was accepted. This result can be explained since chitosan, besides possessing a strong positive charge at a low pH, can absorb other structures with a negative zeta potential, such as enamel,[38] thus protecting the organic layer against cariogenic challenges.[38,39]

In an oral environment, the caries process produces lactic and acetic acids that infiltrate the interprismatic spaces, which results in a continuous decrease in oral pH (range 5.0–5.5) that consequently leads to mineral loss by a binding of the positive hydrogen ions (H^+) of the acid to the negative phosphate (PO_4^{3-}) and hydroxyl ions (OH) of the enamel structure that transformed in water as well as HPO_4^{2-}, until the moment of saturation.[40] The chitosan amino groups can decrease mineral loss by apprehending the acid's hydrogen ions and creating a positively charged protective layer that prevents the diffusion of hydrogen ions into the mineral surface.[3,38,41] Chitosan disrupts the H^+ ions of the acid solution, inhibiting the demineralization process and increasing the pH of the solution.[42] The chitosan-based layer formed by the reaction of these biopolymer molecules with the enamel surface leads to coverage of at least a few nanometers[43] of a ubiquitous chitosan layer.[44] The variation in the sample surface may explain the high standard deviation in volume loss found in this study. This is corroborated by Ruan et al.[45] who demonstrated the efficacy of an amelogenin-containing chitosan hydrogel as a biomaterial for the biomimetic reconstruction of the enamel structure. The employment of nano-complexes of phosphorylated chitosan (Pchi-ACP)[41] and ACP on enamel lesions had a remineralization effect significantly higher than that of fluoride.[46] In addition, chitosan in a fluoride-containing varnish significantly inhibited the enamel demineralization process.[47] As mentioned above, chitosan can be widely used, regardless of the material type, to minimize dental demineralization.

However, contrary to expectations, the results of the present study did not demonstrate significant differences in volume loss or in the wear profile of enamel in the experimental chitosan group with casein when compared to the chitosan group without casein. The promising effects of casein on the enamel demineralization process were not demonstrated in this study. On the other hand, it was observed that casein reduced the therapeutic effect of chitosan, increasing the intensity of the mineral loss due to the demineralization process, and produced greater volume loss, similar to the control group. It is possible that casein could have lost affinity for enamel under the severe acidic conditions,[48] and may have affected the performance of the chitosan. As far as we know, few studies have examined the efficacy of chitosan associated with casein in enamel remineralization under the conditions similar to this study. Therefore, it is difficult to make any comparisons. One study found that casein was not effective in remineralizing early enamel caries at the subsurface level.[49] Moreover, casein demonstrated a lower efficacy than fluoride in remineralizing early enamel caries at the surface level.[50–52] Although CPP-ACP was able to remineralize the early caries lesion, low hardness values were found in those studies, suggesting that the remineralization process was not efficient enough to increase the hardness values. Chitosan added to the CPP-ACP (GC Tooth Mousse) had no additional effect on tooth enamel remineralization.[53]

Although the demineralization depth in the remaining tissue was the same, structural loss and cavity formation were different, with the chitosan gel without casein exhibiting better surface integrity. However, no difference was observed among the control, chitosan gel with and without casein groups regarding the surface roughness. The only difference was found in the first and final treatment; that is, after the cycling and conclusion of the treatment, thus rejecting the second hypothesis of this study. This result is probably due to the active application of the agents with the microbrush, which favors a smoother surface of the demineralized enamel. As the demineralizing/remineralizing process and mineral loss were continuous, this procedure probably favored a rougher surface, regardless of the treatment performed. These results will lead to further investigations of chitosan gel formulations, as there is still a promising potential for the use of chitosan-based materials in the remineralization process of white spot lesions.

It is known that the demineralization process promotes mineral loss of the hydroxyapatite crystals, leading to the appearance of white spot lesions due to a loss of the optical properties of the hard tissues.[21] Thus, if a treatment is not effective, demineralization is greater, as shown in this study, where the 3 groups showed a similar increase in the demineralization levels, and only the experimental treatment of chitosan gel without casein presented a satisfactory result regarding lower enamel structure loss. Due to the lack of studies on the interaction between both materials, it is necessary to conduct more studies focused on the improvement and cohesion of materials with a preventive effect, testing new components that add value to their clinical properties. Additionally, necessary reformulations can be performed to improve materials' properties against the enamel demineralization process.

Conclusions

Chitosan seems to be the major component responsible for reducing the volume loss of demineralized enamel, yet it did provide a slight alteration in surface smoothness. In this study, no additive effect of casein on the demineralized enamel surface has been demonstrated.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Association of the self-reported socioeconomic and health status with untreated dental caries and the oral hygiene level in adult patients

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

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):539–545

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Funding sources
Funding grant from the University of Rijeka, Croatia (grant No. 818101218).

Conflict of interest
None declared

Acknowledgements
None declared

Received on March 22, 2021
Reviewed on June 7, 2021
Accepted on June 14, 2021

Published online on December 7, 2022

Abstract

Background. Dental caries is a multifactorial disease and its management requires a thorough analysis of its etiological factors.

Objectives. The present study used a multivariate approach to investigate the associations of socioeconomic and health-related determinants with untreated tooth decay and level of oral hygiene in adult individuals.

Material and methods. A cross-sectional study involved 597 adult patients. Health and socioeconomic status were assessed using a self-administered structured questionnaire. The presence of decayed teeth was recorded clinically using the World Health Organization diagnostic thresholds. Oral hygiene level was estimated using the plaque index. Multiple linear regression analysis was used to explore the associations of socioeconomic and health-related variables with the number of decayed teeth and level of oral hygiene.

Results. Socioeconomic and health-related variables explained 34.1% of the observed variation in the number of decayed teeth ($p < 0.001$) and 19.2% of the observed variation in the plaque index ($p < 0.001$). Analysis revealed several significant associations for both decayed teeth and plaque index scores. Males had 2.3 more untreated decayed teeth than women and an increased plaque index score of 0.3 units (unique contributions of 6.6 and 4.2%, respectively). An increase in self-assessed household economic status decreased the average number of decayed teeth by 1.3 and the plaque level score by 0.13 (unique contributions of 3.13% and 1.46%, respectively). Smokers presented with 1.78 more decayed teeth than non-smokers (unique contribution of 2.1%) and an increase in the plaque index by 0.48 units (unique contribution of 8.5%).

Conclusions. Untreated dental caries and dental plaque severity share the same socioeconomic and health-related determinants.

Keywords: smoking, dental caries, oral hygiene, dental plaque index, socioeconomic factors

Cite as
Peršić Bukmir R, Paljević E, Pezelj-Ribarić S, Brekalo Pršo I. Association of the self-reported socioeconomic and health status with untreated dental caries and the oral hygiene level in adult patients. *Dent Med Probl.* 2022;59(4):539–545. doi:10.17219/dmp/138908

DOI
10.17219/dmp/138908

Introduction

The World Health Organization (WHO) defines dental caries or tooth decay as a significant public health problem and the most widespread noncommunicable disease worldwide.[1] The general level of caries varies significantly between European countries, and its prevalence in Croatia is high. The decayed, missing and filled teeth (DMFT) index of both 12-year-old children and adults in this country significantly exceeds the average DMFT index of the European population.[2] A recent study conducted on Croatian schoolchildren reported that one third of participants had gingivitis, while half of them had caries.[3] The consequences of a high caries prevalence are severe and can have a cumulative effect in adulthood. Dental caries and its potential consequences, endodontic and periapical disease, were shown to be the most frequent causes of permanent tooth loss in Croatia.[4] Although the loss of teeth can also be attributed to the treatment approach of dentists, views of patients, and accessibility and standard of dental care, it is important to treat teeth with active caries as early as possible.

Dental caries in adults is a multifactorial disease and its management requires thorough identification of its etiological factors, as well as recognition of its cumulative nature.[1,5] A growing amount of evidence indicates that general and oral health are influenced by socioeconomic status (SES). It seems that socioeconomic factors have an indirect influence through environmental factors and impact disease processes through psychosocial stress and health-related habits.[6] Educational background, SES and gender have already been identified as factors influencing oral health.[7,8] Previous investigations have reported that level of education, employment status, household income, smoking habits, dental service usage, gender, daily medications, and marital status seem to contribute to tooth decay in adults.[7–10] Also, a clear socioeconomic gradient in health behavior has been established, indicating that individuals with lower educational levels report a higher frequency of health-compromising behaviors.[11]

As a recent study showed that an absence of pain was the most common justification given for leaving decayed teeth (DT) untreated, it seems that the merits of treatment may be outweighed by other priorities.[12] Considering the detrimental effects of untreated caries not only on dentition, but on overall life quality as well, it is important to identify the reasons for leaving teeth with active caries untreated in adults.

Poor oral hygiene results in an accumulation of dental plaque, which harbors bacteria and their toxins. The role of dental plaque in dental caries disease is well known.[13] Age, gender, SES, and birth-rank were identified as significant predictors of oral hygiene status in schoolchildren.[14] Considering the cumulative effects of poor oral hygiene on caries status, it may be presumed that similar social predictors can be significant in adulthood. Furthermore, a recent study identified oral hygiene, education and employment status as significant predictors for untreated decay, indicating the need to pay attention to oral hygiene in socially vulnerable groups in order to promote oral health.[15] The connection between oral and systemic health is one of the most significant problems faced by the medical and dental scientific community.[16] A recent study reported a significant association of self-reported health with dentate status, and confirmed the connection between oral and systemic health. These results emphasize the importance of preserving natural dentition as a global goal to improve systemic health.[17]

The hypothesis of the present study was that untreated dental caries and dental plaque severity share the same socioeconomic and health-related determinants. Therefore, this research used a multivariate approach to investigate and quantify the associations of self-reported socioeconomic and health status with the number of untreated DT and the level of oral hygiene in adult individuals.

Material and methods

The present investigation is a part of a larger cross-sectional study on apical periodontitis risk indicators and their influence on periapical status in adult patients. It received approval from the institutional Ethical Committee of the Clinical Hospital Center, Rijeka, Croatia (No. 003-05/13-01/03).

The sample for the present survey was drawn from 1072 eligible patients older than 18 years who attended the University Dental Clinic at Rijeka Clinical Hospital Centre, Rijeka, Croatia, for the first time and presented consecutively within a 2-year period. General practitioners from 3 counties referred these patients to the Dental Clinic since it is the only healthcare institution in the area providing full specialist dental care through the health insurance system.

The sample and the criteria for inclusion and exclusion were previously described by Peršić Bukmir et al.[18] Patients were excluded if they refused to take part in the study, received endodontic treatment within previous 2 years, had seven or fewer remaining teeth, and/or suffered from periodontal disease. Additionally, 2 patients who did not complete the questionnaire were excluded. Criteria developed by Machtei et al. were used for establishing the presence of periodontal disease.[19] Application of the exclusion criteria provided a sample comprised of 597 participants – 190 males (31.8%) and 407 females (68.2%). All participants agreed to be included in the study by signing an informed consent form. The investigation was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

Data was acquired through clinical examination and a self-administered questionnaire filled in by the participants. The structured questionnaire was used to obtain

data on participant health condition, health-related habits and SES. Clinical examinations were carried out in a dental chair under standard light. Oral hygiene levels were assessed utilizing the plaque index (PI) in accordance with the Sileness and Löe criteria.[20] Four surfaces of 6 teeth were examined (16, 12, 24, 36, 32, and 44). No disclosing solution or tablets were used in order to avoid interference with caries registration. After cleaning and drying with compressed air, teeth were examined using a dental mirror and a community periodontal index (CPI) probe. All teeth, with the exception of impacted teeth and third molars, were recorded. To avoid uncertainties regarding early caries detection, diagnostic thresholds according to the WHO were applied. A diagnosis of caries was established only in the presence of cavitated lesions.[21]

One of the authors who underwent calibration for the clinical diagnosis of dental caries and PI collected the clinical data. The calibration was performed according to WHO recommendations.[21] An evaluation of diagnostic intra-examiner reliability was performed through double scoring of 30 randomly selected participants with a 1-week time interval for dental caries and 1 h for dental plaque. The intra-examiner agreement scores produced kappa values of 0.92 for the clinical diagnosis of dental caries and 0.85 for plaque assessment.

To explore the associations of socioeconomic and health-related variables with untreated DT and the level of oral hygiene, 2 multiple linear regression models were employed. The 1st used DT as an outcome variable, as it provides a measure of more recent untreated disease experience. This variable was also used in a previous study.[22] In the 2nd model, PI was used as an outcome variable. An overview of the socioeconomic and health-related predictor variables tested in both models is presented in Table 1.

Table 1. Predictor variables tested in multivariate regression analysis and distribution of 597 participants according to observed variables

Variable		Registration and codes	*n* (%)
Socioeconomic variables	age	continuous variable	–
	gender	0 = female	407 (68.2)
		1 = male	190 (31.8)
	level of education	1 = low	19 (3.2)
		2 = medium	343 (57.4)
		3 = high	235 (39.4)
	self-assessed economic status of household	1 = below the average	98 (16.4)
		2 = average	369 (61.8)
		3 = above the average	130 (21.8)
	residency	0 = urban	134 (22.4)
		1 = rural	463 (77.6)
	marital status	0 = single	298 (49.9)
		1 = cohabiting	299 (50.1)
Health-related variables	smoking behavior	0 = no, occasionally	473 (79.2)
		1 = everyday smoker	124 (20.8)
	complementary health insurance	0 = no	125 (20.9)
		1 = yes	472 (79.1)
	number of dental visits during the last year	1 = <2	225 (37.7)
		2 = 3–10	257 (43.0)
		3 = >10	115 (19.3)
	number of visits to family doctor during the last year	1 = <2	359 (60.1)
		2 = 3–10	179 (30.0)
		3 = >10	59 (9.9)
	dental visit to private practice during the last year	0 = no	418 (70.0)
		1 = yes	179 (30.0)
	dentist providing dental care through health insurance system	0 = no	25 (4.2)
		1 = yes	572 (95.8)
	family doctor providing care through health insurance system	0 = no	15 (2.5)
		1 = yes	582 (97.5)
	self-perceived general health	1 = excellent	114 (19.1)
		2 = very good	230 (38.5)
		3 = good	150 (25.1)
		4 = satisfying	103 (17.3)

Statistical analysis

Statistica, v. 13.0 software (StatSoft Inc., Tulsa, USA) was used to perform the statistical analysis. The level of statistical significance was set at $p < 0.05$. Testing for a normal distribution was accomplished with the Lilliefors test. Considering that the data was not distributed normally, median and interquartile range (IQR) were used as measures of central tendency and dispersion. To test for differences between the groups in continuous variables, the Mann–Whitney U test was chosen. To examine the associations between the dependent variables (number of DT and PI) and predictor variables, multiple linear regression analysis (backward model) was used.

Results

The median age for all participants was 34 years, with an IQR of 24.0–47.0. Most of the sample consisted of females (68.2%). No significant age difference between male and female participants was found (Mann–Whitney test, $p = 0.511$). The median number of teeth present in the sample was 26 per person, with an IQR of 24–28. The average values for DT and PI were 5.0 (IQR 2.0–8.0) and 0.8 (IQR 0.4–1.25), respectively. Figure 1 shows the distribution of the number of DT per person. Only 69 participants (11.6%) had no teeth with untreated decay.

Multiple linear regression analysis was applied to identify possible socioeconomic and health-related determinants associated with the DT and PI scores. The variables demonstrating the best fit are presented in Tables 2 and 3.

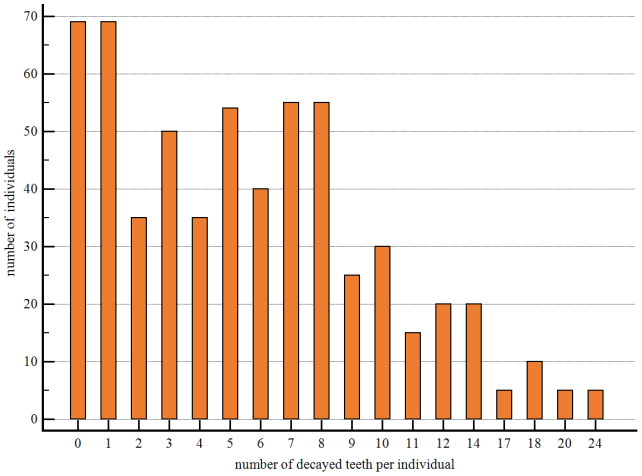

Fig. 1. Distribution of the number of decayed teeth per person

Socioeconomic and health-related variables explained 34.1% of the observed variation in the number of untreated DT (Table 2; $p < 0.001$) and 19.2% of the observed variation in PI (Table 3; $p < 0.001$). Seven variables were significantly associated with DT scores, and the most important was a dentist providing dental care through the health insurance system, followed by the number of dental visits during the last year, gender, and a dental visit to a private practice during the last year. These variables accounted for 6–9% of the variability (Table 2). Six variables were significantly associated with PI scores. In this case, smoking behavior and a dental visit to a private practice during the last year accounted for a major part of variability with unique contributions of 8.5% and 7.7%, respectively (Table 3). Analysis revealed the same 5 significant associations for both DT and PI scores.

It was observed that an increase in self-assessed household economic status was related to a decrease the average number of DT by 1.3 and the PI score by 0.13 (unique contributions of 3.13% and 1.46%, respectively). Participants who visited the dentist more often presented with more DT. However, they had lower PI scores. Although the number of dental visits during the previous year accounted for a major part of the variability in DT scores

Table 2. Association of socioeconomic and health-related variables with the number of decayed teeth (DT)

Independent variables	B	*SE*	*p*	Sr
Constant	11.935	–	–	–
Age	–0.003	0.013	0.817	–0.010
Self-assessed economic status of household (1 = below average; 2 = average; 3 = above the average)	–1.296	0.299	<0.001	–0.177
Self-perceived general health (1 = excellent; 2 = very good; 3 = good; 4 = satisfying)	–0.357	0.185	0.054	–0.080
Number of dental visits during the last year (1 = less than 2; 2 = 3–10; - 3 = more than 10)	1.657	0.230	<0.001	0.286
Number of visits to family doctor during the last year(1 = less than 2; 2 = 3–10; 3 = more than 10)	0.472	0.299	0.116	0.065
Family doctor providing care through health insurance system (0 = no; 1 = yes)	–1.531	1.612	0.343	–0.039
Dentist providing dental care through health insurance system (0 = no; 1 = yes)	–3.784	0.494	<0.001	–0.302
Dental visit to private practice during the last year (0 = no; 1 = yes)	–2.362	0.380	<0.001	–0.249
Residency (0 = rural; 1 = urban)	–2.008	0.380	<0.001	–0.213
Gender (0 = female; 1 = male)	2.310	0.360	<0.001	0.256
Smoking behavior (0 = no or occasionally; 1 = yes, every day)	1.782	0.501	<0.001	0.145

Explained variance (R^2-adjusted) = 0.341; B – regression coefficient; *SE* – standard error of B coefficient; Sr – semi partial correlation indicates the unique contribution to number of decayed teeth.

Table 2. Association of socioeconomic and health-related variables with plaque index

Independent variables	B	*SE*	*p*	Sr
Constant	1.212	–	–	–
Self-assessed economic status of household (1 = below average; 2 = average; 3 = above the average)	–0.130	0.044	0.003	–0.121
Level of education (1 = low; 2 = medium; 3 = high)	–0.125	0.047	0.008	–0.110
Number of dental visits during the last year (1 = less than 2; 2 = 3–10; 3 = more than 10)	–0.075	0.035	0.032	–0.089
Dentist providing dental care through health insurance system (0 = no; 1 = yes)	0.217	0.126	0.087	0.071
Dental visit to private practice during the last year (0 = no; 1 = yes)	–0.398	0.057	<0.001	–0.278
Residency (0 = rural; 1 = urban)	0.110	0.061	0.073	0.074
Gender (0 = female; 1 = male)	0.298	0.059	<0.001	0.205
Smoking behavior (0 = no or occasionally; 1 = yes, every day)	0.477	0.065	<0.001	0.291

Explained variance (R^2-adjusted) = 0.192. B – regression coefficient; *SE* – standard error of B coefficient; Sr – semi partial correlation indicates the unique contribution to plaque index.

(unique contribution of 8.17%), it accounted for a low proportion of the variability in PI scores (unique contribution of 0.79%).

A visit to a private dental practice during the previous year reduced the number of teeth with untreated caries as well as the PI. Participants who visited a private dentist had on average 2.4 less DT and their PI was reduced by 0.4 units (unique contributions of 6.2% and 7.7%, respectively). Males were associated with a higher number of DT and a higher PI level (unique contributions of 6.6% and 4.2%, respectively). On average, males had 2.3 more untreated DT than women and their PI score was increased by 0.3 units. Everyday smokers presented with 1.78 more DT than persons who did not smoke or smoked occasionally (unique contribution of 2.1%). Smoking on daily basis resulted in an increase in the PI by 0.48 units and accounted for major part of the variability (unique contribution of 8.5%).

Level of education was identified as a significant predictor only for oral hygiene. A negative association was established between education and PI, implying that participants with a higher education level have lower plaque levels. However, this variable accounted for a lower proportion of variability (unique contribution of 1.2%). Participants who did not have access to a dentist providing dental care through the health insurance system had on average 3.8 more DT (unique contribution of 9.1%). Participants living in urban areas had significantly fewer untreated carious teeth than participants living in rural areas (on average 2 teeth less; unique contribution of 4.5%).

Discussion

The present study identified the same 5 socioeconomic and health-related predictors for the severity of untreated dental caries and oral hygiene level: gender, self-assessed household economic status, number of dental visits during the last year, a dental visit to a private practice during the last year, and smoking behavior.

A commonly used measure for dental caries is the DMFT index. This is a sum of the number of decayed (D), missing (M) and filled (F) teeth (T), and is a relevant tool for the assessment of caries status in a population.[2] In the present study, the number of DT was used as an outcome variable for several reasons. First, in a cross-sectional design, it is impossible to be sure that all presently filled and missing teeth were preceded by tooth decay. Furthermore, while the M and F components reflect a consequence of disease and its treatment outcome, the number of DT may be a better measure of disease without the influence of dental treatment.[22] In the present study, caries was recorded according to the WHO criteria, which means that it was diagnosed at advanced stage and a possible underestimation of untreated disease in the surveyed sample should be considered.

One of the main limitations of this study is that, unlike the community-based studies where samples are drawn from randomly selected residents of a certain area, our sample comprised of patients referred by their general practitioners to a dental clinic. The high active caries prevalence can be attributed to the clinic-based design of the study. Therefore, the present results should be interpreted carefully regarding general population. Nonetheless, as to our knowledge, no similar study has been conducted in Croatia or in the neighboring countries. Thus, these results can make a contribution to the planning of public dental health measures.

Our results demonstrated a difference in active caries disease prevalence across gender. Men experienced a significantly higher burden of untreated dental decay and had on average 2.3 more DT than women. Also, male participants had a significantly lower level of oral hygiene. There is a plethora of studies reporting more positive dental attitudes and habits in female than male participants, namely more regular visits to the dentist, and more frequent brushing and use of dental floss.[23,24] The fact that the present sample comprised of a considerably smaller proportion of male participants can be attributed to the lower utilization of dental services by males.

The influence of social gradient on dental caries prevalence has been previously reported.[6,25] It is assumed that socioeconomic factors can affect the disease process indirectly through behavioral patterns and lifestyle.[26] Many variables have been used in studies in this field to describe socioeconomic differences in various populations. However, no consensus regarding which variables are most valid for describing SES has been reached. In the present study, self-assessed household economic status was used as an indicator of socioeconomic well-being. An increase in self-assessed household economic status was significantly associated with a decreased average number of DT and better oral hygiene. Our results also revealed an association between educational background and oral hygiene – participants with a higher education level had better oral hygiene. Several studies have reported that a lower educational level is a risk factor for DT.[7,8,27] Although the present study did not demonstrate an association between education and the severity of active caries, it is possible that educational background may influence caries prevalence indirectly through dental habits, such as oral hygiene.

Participants who visited the dentist more often presented with more DT and better oral hygiene. It is possible that persons with more carious teeth seek dental care more often, but also may adopt a higher standard of oral hygiene. The variable of a dentist providing dental care through the health insurance system was the most significant predictor for active caries severity, accounting for 9.1% of the variability in the number of DT. Participants who did not have access to a dentist providing dental care through the health insurance system had on average 3.8 more DT.

An interesting finding was that participants living in rural areas had on average 2 untreated carious teeth more than those living in urban areas. A survey investigating the reasons for permanent tooth extractions in urban and rural populations of Croatia reported that in rural areas, people more often lost teeth because of endodontic and periapical disease.[4] Therefore, more teeth were lost in the rural population due to the consequences of untreated dental caries. Even though we have no scientific explanation for this, it may be hypothesized that patients living in rural areas have lower accessibility to dental care or a lack of motivation for dental visits and treatments.

Smoking on a daily basis was a significant predictor for both untreated dental caries and plaque severity. Moreover, it accounted for major part of the variability in oral hygiene level (unique contribution of 8.5%). This is in line with previous reports. [9,10] Bernabé et al. reported the relationship between daily smoking and DT over a 4-year period. Smokers had poor dental attendance, and exhibited a high sugar consumption and infrequent tooth brushing.[10]

This study has several limitations, including its cross-sectional, clinic-based design and a lack of questionnaire validation. Cross-sectional studies do not allow for an estimation of the cause–effect relationship. Therefore, a conclusion that the relationships between socioeconomic and health status and untreated DT and level of oral hygiene are causal cannot be derived from the present data. Due to the clinic-based study design, it is likely that the prevalence of caries is higher than that expected for the general population. Another consequence of the clinic-based design is a greater prevalence of female participants in the sample. Although this may reflect the greater conscientiousness of women in the usage of dental care and attending check-ups,[28] it may also represent a study limitation. Different studies have used a plethora of variables to index socioeconomic and health status in various populations. In the present study, the data related to the health condition and SES of the participants was acquired using a structured questionnaire designed for this research. One of the limitations of this study is a lack of questionnaire validation. Such validation is related to its generalizability, adaptation and semantic equivalence. The lack of a cross-culturally validated research instrument can cause difficulties when comparing the results between studies.[29]

The intent of this study was to relate socioeconomic and health variables with the severity of untreated carious disease and the level of oral hygiene in adult users of specialist dental care. Bearing in mind the limitations of this study, the results should be carefully interpreted. However, our hypothesis that untreated dental caries and dental plaque severity share the same socioeconomic and health-related determinants can be confirmed. Dental caries in adults is a multifactorial disease and its management requires a thorough identification of its etiological factors. While the role of dental plaque in dental caries has been well established, understanding the etiology of caries demands information other than that merely related to the biological mechanisms in the individual.

Conclusions

The results revealed a socioeconomic gradient for untreated dental caries and oral hygiene level, indicating more untreated carious teeth and worse oral hygiene in the case of lower SES. This study emphasizes the need to educate adults on oral hygiene improvement and the early treatment of dental caries, as well as its associated diseases. These measures should particularly target socially vulnerable groups and the inhabitants of rural regions.

Ethics approval and consent to participate

The present study received approval from the institutional Ethical Committee of the Clinical Hospital Center, Rijeka, Croatia (No. 003-05/13-01/03).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Impact of dietary habits on the incidence of oral diseases

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

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):547–554

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
The authors thank Dr. hab. Agnieszka Pac for providing valuable assistance in the evaluation of statistical data.

Received on January 1, 2021
Reviewed on March 11, 2021
Accepted on March 22, 2021

Published online on December 12, 2022

Abstract

Background. Diet is a factor that can modify the course of caries, dental erosion and periodontal diseases.

Objectives. The aim of this study was to examine the impact of dietary habits and the anthropometric parameters on oral health.

Material and methods. 50 females and 45 males aged 19–21 years were examined in a cross-sectional study. Oral health was assessed utilizing selected dental indices: approximal plaque index (API), bleeding on probing (BoP), community periodontal index (CPI), and DMFT (D – decayed, M – missing, F – filled, T – teeth). In addition, dental erosion was assessed. Anthropometric measurements included body mass, height, body mass index (BMI), waist circumference, skinfold thickness, fatty and lean body mass, body fat percentage, and total body water. The frequency of consumption of food products was determined with the use of the Questionnaire on Food Products Frequency Intake. Student's *t* tests, the χ^2 tests and Pearson's correlation coefficients were used to analyze the results.

Results. The average DMFT was 9.92, API was 52.97% and BoP was 20.46%. Dental erosion was observed in 44.21% of cases. A total of 11.58% of the study population were classified as CPI 0, 30.53% as CPI 1 and 57.89% as CPI 2. The consumption of crisps and cereal products increased caries ($p = 0.003$). Dental erosion was associated with the consumption of fruit, vegetables, meat, fish, and alcoholic beverages. The consumption of sugar, sweets and alcoholic beverages increased API and BoP. Caries rarely occurred in people who ate fruit and vegetables on a daily basis. The anthropometric parameters were associated with oral hygiene, gingivitis and body weight disorders ($p < 0.05$).

Conclusions. Rational nutrition not only plays a role in the development of general systemic diseases, but also has an effect on oral health. Besides providing instructions on oral hygiene, dentists should also assess the eating habits of their patients.

Keywords: nutritional status, diet, students, oral health

Cite as
Kantorowicz M, Olszewska-Czyż I, Lipska W, et al. Impact of dietary habits on the incidence of oral diseases. *Dent Med Probl.* 2022;59(4):547–554. doi:10.17219/dmp/134749

DOI
10.17219/dmp/134749

Introduction

Maintenance of oral health is an important factor in the preservation of overall health.[1] Tooth loss can lead to a change in eating habits, which, in turn, increases the risk of certain systemic diseases.[2,3]

Although since the 1970s there has been a steady decline in the prevalence of caries,[4] this disease and its complications remain the most common causes of tooth loss. World Health Organization (WHO) studies clearly indicate that children and young people, as well as the majority of adults in highly developed countries, suffer from dental caries.[4,5] The formation of carious lesions depends on dental plaque, carbohydrates, a susceptible tooth surface, and time. Other risk factors include a difficult family situation, an imbalanced diet and poor dietary habits.[6] Dental plaque bacteria use carbohydrates to produce acids responsible for the destruction of dental hard tissues.[4,6] Apart from caries, another growing problem is tooth loss caused by chronic periodontitis.[4] Researchers have examined the influence of nutrients on the human inflammatory-immune response and found that macro- and microelements affect the pro- and anti-inflammatory cytokine cascade.[7,8] High-calorie food rich in refined sugars can also lead to chronic inflammation in the body.[7] An independent, inverse correlation exists between the consumption of omega-3 unsaturated fatty acids and the progression of periodontal disease, especially in the elderly.[8]

Dental erosion occurs as a result of the chemical and biochemical effects of extrinsic and intrinsic acids, the biochemical action of proteolytic enzymes, and the piezoelectric effect on the organic dentin matrix.[9] The main exogenous factor responsible for the onset and development of erosive lesions is the excessive consumption of foods and beverages with an acidic pH.[10] The erosive effect of low pH foods depends on the frequency and method of their consumption as well as immediate teeth brushing before and after food intake. The erosive potential of meals increases during and after physical exertion as a result of the reduced secretion of saliva.[10]

The aim of this study was to assess oral health in relation to dietary habits and selected anthropometric parameters in first-year university students.

Material and methods

This study protocol was approved by the Ethics Committee of Jagiellonian University, Kraków, Poland (approval No. KBET/77/B/2014). Informed consent was provided by all study participants. This was a cross-sectional study, with a total number of 50 female and 45 male volunteers aged 19–21 years. The participants were first-year students at higher education institutions. The exclusion criteria were any chronic systemic diseases and a current habit of smoking. The participants' medical and dental histories were recorded. The latter covered current complications in the oral cavity.

Dental examination

The following periodontal parameters were recorded: approximal plaque index (API; in %) and bleeding on probing (BoP; in %). The API was assessed by recording the presence or absence of dental plaque in approximal interdental spaces. The BoP index was determined for the entire mouth by recording the presence or absence of bleeding 10 s after probing. The API and BoP were expressed as a percentage of approximal sites with plaque/bleeding sites in relation to all sites examined. The DMFT index (D – decayed, M – missing, F – filled, T – teeth) was implemented to evaluate dental caries. The occurrence of dental erosion in dental hard tissue was also assessed. The epidemiological examination of the periodontium was based on the community periodontal index (CPI) and measured as follows: 0 – no gingival bleeding in sextant, 1 – bleeding on probing in at least 1 place in sextant, 2 – presence of supragingival calculus in sextant and/or factors favoring retention of dental plaque, 3 – periodontal pocket depth in sextant 3.5–5.5 mm, 4 – presence of at least 1 periodontal pocket in sextant with a depth of 5.5 mm or more.

Anthropometric measurements

In every participant, the following basic measurements were taken: body weight and height and body mass index (BMI). The following ranges of BMI were specified: <18.5 kg/m^2 – underweight, 18.5–24.9 kg/m^2 – proper weight, 25.0–29.9 kg/m^2 – overweight, and >30.0 kg/m^2 – obesity. The waist circumference (in centimeters) was also measured. Fatty body mass (FM; in kilograms), body fat percentage (% FM), lean body mass (fat-free mass (FFM); in kilograms), and total body water (TBW; in liters) were determined using the infrared interactance method with a Futrex Body Composition Analyzer Model 6100/XL 6100/ZL (Futrex Inc., Hagerstown, USA). The thickness (in millimeters) of the triceps skin-fat fold, subscapular skin-fat fold and suprailiac skin-fat fold were measured with the use of a Harpenden Skinfold Caliper (Cambridge Scientific Instruments, Cambridge, USA). All measurements were taken by the same investigator trained in this area.

Assessment of dietary habits

The frequency of consumption and preferences for certain foods were assessed using a modified Questionnaire on Food Products Frequency Intake. This questionnaire was recommended by the Polish National Food and Nutrition Institute (http://knozc.pan.pl).

Statistical analysis

For variables with a normal distribution, the following were calculated: mean (*M*), standard deviation (*SD*), minimum, and maximum. For variables with a non-normal distribution, median (*Me*), range, minimum, and maximum were calculated. Normal distribution of variables was tested with the Kolmogorov–Smirnov test. Quantitative variables for 2 groups were compared using Student's *t* test or the χ^2 test (based on Yates' correction for continuity in 2 × 2 tables). Correlations between 2 quantitative variables were assessed with Pearson's product-moment correlation coefficient. A significance level of $p < 0.05$ was adopted.

Statistical calculations were performed with R, v. 3.2.3 statistical software (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Results

The opportunity to participate in the project was announced among students and a total of 95 individuals (50 females and 45 males) aged between 19 and 21 years volunteered. The mean DMFT index for females was 10.08, while for males it was 9.73 (overall mean: 9.92). Dental erosion was present in 44.21% of the participants (in 52% of females and 35.56% of males). The mean API for males was 34.73%. Within the group of females, half of the participants had an API lower than 78% and half had a value higher than this, with a range between 8% and 100%. The overall API was 52.97%. The mean BoP among females was 22.02% compared to 18% for males (the mean BoP for the whole study population was 20.46%). Regarding CPI, 11.58% of the study population were classified as CPI 0, 30.53% as CPI 1 and 57.89% as CPI 2. Further

Table 1. Association between the frequency of consumption of various products and approximal plaque index (API)

Consumption of food products		*M*	*SD*	*SEM*	*p*-value
1. Milk and dairy products	not every day	57.2	27.6	3.7	0.105
	every day	47.1	32.6	5.2	
2. Eggs	≤ 3 times a week	54.2	30.4	3.4	0.330
	4 times or more a week	45.4	27.9	7.7	
3. Meat and fish, including low-meat dishes	not every day	59.2	32.6	4.2	0.007*
	every day	42.3	21.5	3.6	
4. Animal fats	not every day	52.1	31.2	4.8	0.803
	every day	53.7	29.4	4.1	
5. Vegetable fats, including hydrogenated fats	not every day	62.3	30.5	4.1	0.001*
	every day	40.2	24.6	3.9	
6. Raw fruit and vegetables	not every day	58.7	29.0	4.4	0.083
	every day	48.0	30.4	4.3	
7. Crisps and other similar products	≤ 3 times a month	53.3	32.7	4.6	0.905
	once a week or more often	52.6	27.2	4.1	
8. Vegetable or fruit juice	≤ 3 times a week	53.8	29.7	4.2	0.772
	4 times or more a week	52.0	30.7	4.6	
9. Potatoes	≤ 3 times a week	53.8	31.9	3.8	0.675
	4 times or more a week	50.8	25.1	4.9	
10. Legumes	never	49.4	30.0	4.2	0.214
	I consume	57.1	29.9	4.5	
11. Cereal products and associated products	not every day	57.5	34.7	6.9	0.385
	every day	51.4	28.3	3.4	
12. Sugar and sweets	not every day	43.4	31.7	6.2	0.056
	every day	56.6	28.8	3.5	
13. Soft drinks	≤ once a week	58.4	31.2	4.4	0.062
	2 times or more a week	46.9	27.9	4.2	
14. Alcoholic beverages	≤ 3 times a month	62.8	30.5	4.4	0.001*
	once a week or more often	42.5	26.1	3.8	
15. Other beverages	not every day	73.1	25.0	8.3	0.034*
	every day	50.9	29.9	3.2	

Student's *t* test for independent samples for women and men in relation to API (data presented as percentage). * statistically significant; *M* – mean; *SD* – standard deviation; *SEM* – standard error of the mean.

analysis showed that within the group of females there was a higher percentage of sextants with CPI 2 and a lower percentage with CPI 0 in comparison with males (p = 0.004).

Association between the frequency of consumption of food products and the clinical dental parameters

The API of the female participants depended on the consumption of meat and fish (p = 0.005), vegetable fats (p = 0.001) and cereal products (p = 0.022). Females who consumed these products on a daily basis had a lower API. Males who ate raw fruit and vegetables (p = 0.034) and cereal products (p = 0.016) every day had lower API values, while those who consumed sugar or sweets on a daily basis had higher API values (p = 0.042). When females and males were analyzed as one group, results of the Student's t test for independent samples revealed statistically significant changes in the API with regard to the consumption of the following products: meat, fish, vegetable fats, and alcoholic and non-alcoholic beverages (Table 1).

The BoP index of female participants depended on the consumption of vegetable fats (p = 0.01) and was lower when these were consumed daily. The same indicator for males depended on the consumption of raw fruit and vegetables (p = 0.001) as well as alcoholic beverages (p = 0.046). Males who ate raw fruit and vegetables on a daily basis had a lower BoP index in comparison with those who consumed them more rarely (p = 0.001), and those who drank alcohol less than once a week also had a lower BoP. Concerning BoP for males and females (combined), the Student's t test for independent samples revealed statistically significant results in regard to the consumption of the following products: milk and dairy products, raw fruit and vegetables, and juice (vegetable or fruit; Table 2).

Table 2. Association between the frequency of consumption of various products and bleeding on probing (BoP)

Consumption of food products		*M*	*SD*	*SEM*	*p*-value
1. Milk and dairy products	not every day	23.7	17.4	2.3	0.032*
	every day	16.1	15.7	2.5	
2. Eggs	≤ 3 times a week	21.3	16.9	1.9	0.304
	4 times or more a week	16.0	17.7	4.9	
3. Meat and fish, including low-meat dishes	not every day	21.3	15.8	2.0	0.570
	every day	19.2	19.2	3.2	
4. Animal fats	not every day	19.6	16.6	2.5	0.613
	every day	21.3	17.5	2.4	
5. Vegetable fats, including hydrogenated fats	not every day	23.3	18.0	2.4	0.063
	every day	16.7	15.0	2.4	
6. Raw fruit and vegetables	not every day	26.1	18.4	2.8	0.003*
	every day	15.7	14.2	2.0	
7. Crisps and other similar products	≤ 3 times a month	19.4	16.5	2.3	0.504
	once a week or more often	21.8	17.8	2.7	
8. Vegetable or fruit juice	≤ 3 times a week	23.8	17.5	2.5	0.046*
	4 times or more a week	16.8	15.8	2.4	
9. Potatoes	≤ 3 times a week	21.1	16.9	2.0	0.592
	4 times or more a week	19.0	17.6	3.5	
10. Legumes	never	20.3	17.6	2.5	0.882
	I consume	20.8	16.6	2.5	
11. Cereal products and associated products	not every day	18.9	16.4	3.3	0.583
	every day	21.1	17.3	2.1	
12. Sugar and sweets	not every day	16.3	14.7	2.9	0.138
	every day	22.1	17.7	2.1	
13. Soft drinks	≤ once a week	21.6	17.5	2.5	0.532
	2 times or more a week	19.4	16.7	2.5	
14. Alcoholic beverages	≤ 3 times a month	18.8	13.8	2.0	0.307
	once a week or more often	22.4	19.9	2.9	
15. Other beverages	not every day	29.9	16.2	5.4	0.084
	every day	19.6	16.9	1.8	

Student's t test for independent samples for women and men in relation to BoP (data presented as percentage). * statistically significant.

Students who consumed raw fruit and vegetables on a daily basis had a lower DMFT score than those who consumed them less frequently (p = 0.042), while eating crisps more than once a week was associated with a higher DMFT (p = 0.012). Daily consumption of cereal products led to a higher DMFT in both females (p = 0.043) and males (p = 0.018). With regard to the DMFT score for males and females (combined), the Student's t test for independent samples showed statistically differences in relation to the consumption of raw fruit and vegetables, crisps and cereal products (Table 3).

The χ^2 test for the female participants showed no statistically significant differences in dental erosion based on the frequency of consumption of any of the investigated products. Among the male participants, the presence of dental erosion depended on the consumption of meat, fish (p = 0.024), and fruit and vegetable juices (p = 0.004). Dental erosion occurred more frequently in students who consumed meat and fish daily, and juices at least 4 times a week. With regard to males and females (combined), the presence of dental erosion depended solely on the consumption of alcoholic beverages. Those who drank alcohol more often than once a week were less likely to have erosive defects (p = 0.046).

Association between body mass components and the clinical dental parameters

Bleeding on probing and DMFT depended on BMI (p = 0.02, p = 0.04) and were higher in overweight or obese individuals in comparison with those with normal weight. The mean BoP in participants of proper weight was 18.9%, as compared to 30.3% in the case of overweight or obese students. The DMFT score in students with the

Table 3. Association between the frequency of consumption of various products and DMFT

Consumption of food products		*M*	*SD*	*SEM*	*p*-value
1. Milk and dairy products	not every day	10.1	5.2	0.7	0.738
	every day	9.7	4.0	0.6	
2. Eggs	≤ 3 times a week	9.9	4.7	0.5	0.945
	4 times or more a week	10.0	4.9	1.4	
3. Meat and fish, including low-meat dishes	not every day	9.6	4.2	0.5	0.323
	every day	10.5	5.4	0.9	
4. Animal fats	not every day	10.5	5.1	0.8	0.303
	every day	9.5	4.4	0.6	
5. Vegetable fats, including hydrogenated fats	not every day	10.3	4.9	0.7	0.413
	every day	9.4	4.5	0.7	
6. Raw fruit and vegetables	not every day	11.4	4.8	0.7	0.004*
	every day	8.6	4.3	0.6	
7. Crisps and other similar products	≤ 3 times a month	8.6	4.0	0.6	0.003*
	once a week or more often	11.4	5.0	0.7	
8. Vegetable or fruit juice	≤ 3 times a week	10.1	4.9	0.7	0.751
	4 times or more a week	9.8	4.5	0.7	
9. Potatoes	≤ 3 times a week	9.8	4.4	0.5	0.655
	4 times or more a week	10,3	5,5	1,1	
10. Legumes	never	10.4	4.7	0.7	0.290
	I consume	9.4	4.7	0.7	
11. Cereal products and associated products	not every day	7.5	4.1	0.8	0.002*
	every day	10.8	4.6	0.5	
12. Sugar and sweets	not every day	10.1	5.1	1.0	0.839
	every day	9.9	4.6	0.6	
13. Soft drinks	≤ once a week	9.7	4.6	0.7	0.671
	2 times or more a week	10.1	4.8	0.7	
14. Alcoholic beverages	≤ 3 times a month	10.2	4.7	0.7	0.512
	once a week or more often	9.6	4.7	0.7	
15. Other beverages	not every day	10.1	5.1	1.7	0.897
	every day	9.9	4.7	0.5	

Student's t test for independent samples for women and men in relation to the DMFT index. * statistically significant; DMFT – D – decayed, M – missing, F – filled, T – teeth.

proper body weight amounted to 9.5, as compared to 12.3 for overweight and obese participants.

With regard to male participants, a statistically significant relationship was observed between the API index on the one hand, and waist measurement (p = 0.009) and skin-fat fold thickness over the triceps brachii muscle (p = 0.022) on the other hand. Likewise, only in males did waist measurement (p = 0.021) and FM% (p = 0.039) have any significant influence on BoP. These were positive correlations.

Discussion

In the present study, we examined oral health of young students in relation to dietary habits and nutritional status. The limitations of the study were the age of the participants (the study group consisted only of students), a modest sample size and the absence of a control group.

The DMFT score was lower for those females and males who consumed raw fruit and vegetables on a daily basis. According to Trzcionka and McDowell, in order to protect oneself against dental caries, it is important to consume products containing polyphenols, of which raw fruit and vegetables (apples in particular) are the main sources.[11] Another important factor in preventing dental caries are the physical characteristics of an individual's diet.[11] Hard consistency of food has a positive effect on the self-cleaning capacity of the oral cavity. The cariogenic effect of nutrition stems from, among other things, the consumption of soft foods – mushy, glutinous foods, which favor the build-up of dental plaque in retention places and generally worsen hygiene conditions in the oral cavity.

The current results showed that the consumption of crisps and cereal products had a negative impact on hard dental tissue. Likewise, Johansson et al. identified crisps as products associated with an increased incidence of dental caries.[5] A study by Monteagudo et al. showed that the consumption of cereal products was associated with a lower incidence of dental caries.[6] Additionally, Trzcionka and McDowell claimed that cariostatic properties can only be identified in raw cereal grains – on account of the phosphorane present in them.[11]

Our observations are in accordance with the results of other reports, namely that the main factor responsible for the occurrence of erosive lesions is the consumption of low pH foods. The results of a study by Waszkiel showed that 30% of the respondents with dental erosion consumed citrus juice several times a day, while 20% did so several times a week. Moreover, 70% of persons with erosions ate fruit.[12] The current results showed that dental erosions occur more frequently in students who consumed meat and fish on a daily basis. This contradicts observations made by Herman that vegetarians are more likely to suffer from enamel erosion – 39% in comparison with 24% in the control group.[13] Unhealthy dietary habits, such as the consumption of stimulants and supplements, and alcohol abuse, are among the risk factors for non-carious lesions.[10] However, we found a lower incidence of erosion among students who more often drank alcoholic beverages.

Al-Zahrani noted the positive effects that dairy products have on periodontal tissue.[14] According to our results, the consumption of dairy products had a positive effect on oral health – the BoP index for male and female participants combined was lower in those individuals who consumed dairy products on a daily basis. These results are in line with the findings of Dietrich et al., who reported that supplementation with vitamin D reduces the susceptibility of gums to inflammation.[15] Likewise, we found that the consumption of raw fruit and vegetables and juice had a positive effect on the structure of the periodontium (lower BoP). These are major sources of vitamin C. Kuzmanova et al. observed lower levels of vitamin C in the plasma of patients with periodontitis in comparison with a control group.[16]

We found that female students who consumed vegetable fats on a daily basis had lower BoP values as compared with the average values for this indicator. Vegetable oils are the main source of omega-3 unsaturated fatty acids, which have, among other things, anti-inflammatory properties, and which the human body is unable to synthesize independently.[8]

The current data also indicates that the consumption of alcoholic beverages by males has a negative effect on oral health and results in a higher BoP index as compared to the average values for this indicator. Tezal et al. showed a statistically significant linear relationship between the quantity of alcoholic beverages consumed and the severity of periodontitis.[17] The harmful mechanisms involved in alcohol consumption may depend on its direct inhibitory effect on bone metabolism as well as on the toxic action of osteoblasts.[18]

We found lower API values in young female students who consumed meat, fish, vegetable fats, and cereal products daily. Young men who consumed raw fruit and vegetables and cereal products on a daily basis also had lower API values in comparison to the average values for this indicator. Higher API values in male participants were associated with the daily consumption of sugar and sweets.

A number of studies have also confirmed the positive impact of wholegrain products on oral health. According to Merchant et al., consumption of such food reduces the risk of periodontitis.[19] There has been an increase in the prevalence of periodontitis among young people aged 18–25 years, a trend associated with the addition of sugar to foods.[20] In our study, more than half of those surveyed (62.1%) consumed refined sugar every day and had a higher API. Baumgartner et al. asserted that an increase in the supply of refined sugar results in increased gum bleeding.[21]

The results of the present study showed that the BoP and DMFT indices depended on BMI and were higher in students with an unsuitable body mass. No correlation was found between API and BMI. These outcomes are partly

convergent with a study conducted by Konopka et al., who observed a correlation between BMI, API and BoP.[22] The API indicates the effectiveness of cleaning of interdental spaces. Poorer hygiene causes bacterial plaque to settle, which may lead to the development of gingivitis and, subsequently, chronic periodontitis.

Our results show that the parameters of fatty tissue in the body correlate with oral tissue health. In the case of male participants, the greater the waist measurement, the higher the BoP and API indices. The API of the study participants was affected by the skin-fat fold thickness over the triceps brachii muscle, while BoP was shaped by FM%. In both cases, the greater the values of these parameters, the worse the health of the periodontal tissue. Other authors have singled out an increase in body mass and adipose tissue content in the body as factors that favor and exacerbate the course of chronic periodontitis.[1,23–26] According to Salekzamani et al., patients with periodontitis have greater waist measurements in comparison with healthy individuals and patients with gingivitis.[23] According to Benguigui et al., the plaque index and the presence of deep periodontal pockets are statistically associated with an increase in BMI.[24] In their own study, Suvan et al. showed that a higher BMI may be regarded as a factor explaining the poorer response of certain patients to non-surgical periodontal treatment.[25] Among patients with an increased BMI, Konopka et al. observed higher API and BoP, predisposing these individuals to the onset of periodontitis.[22] Ekuni et al. came to similar conclusions in a study on Japanese students and, according to their results, the higher the BMI, the higher CPI values.[26]

Our results show that the consumption of sugar, sweets and alcoholic beverages had a negative impact on periodontal tissues. Eating crisps and cereal products increased caries, and consumption of sugar, sweets and alcoholic beverages had a negative impact on periodontal tissue health. Dental erosion was associated with the consumption of fruit, vegetables, meat, fish, and alcoholic beverages.

Conclusions

The consumption of unhealthy products has a negative impact on dental and periodontal tissue health. Finally, poor dietary habits may have a harmful influence on selected clinical and anthropometric parameters. Further research is warranted to systematize the function of macro- and micro-nutrients in relation to periodontal tissues and overall oral health.

Ethics approval and consent to participate

This study protocol was approved by the Ethics Committee of Jagiellonian University, Kraków, Poland (approval No. KBET/77/B/2014). Informed consent was provided by all study participants.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Gingival fluid and saliva concentrations of selected non-enzymatic antioxidants in periodontitis

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):555–564

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Funding sources
This work was supported by Wroclaw Medical University, Poland (STM.B050.17.009).

Conflict of interest
None declared

Acknowledgements
None declared

Received on December 16, 2021
Reviewed on March 3, 2022
Accepted on April 5, 2022

Published online on December 16, 2022

Abstract

Background. Due to their low specificity, non-enzymatic antioxidants play a significant role in the protection of organisms against free radicals. They are normally sourced from the diet, and independently react with oxidizing molecules and their products.

Objectives. The study aimed to determine the concentrations of selected non-enzymatic antioxidants (uric acid (UA), reduced glutathione (GSH) and polyphenols) in the gingival fluid and saliva of patients diagnosed with periodontitis according to the current criteria.

Material and methods. This prospective case–control study included 50 patients with periodontitis, who were divided into 2 groups depending on disease severity, along with 25 healthy controls. Unstimulated saliva, stimulated saliva and gingival crevicular fluid (GCF) were collected from all subjects, and non-enzymatic antioxidant concentrations were determined.

Results. Significantly lower concentrations of all tested non-enzymatic antioxidants were observed in the gingival fluid as well as in the unstimulated and stimulated saliva of patients with periodontitis ($p < 0.05$). Moreover, the concentration of GSH was a parameter that differentiated the various degrees of periodontitis ($p < 0.05$). A significantly lower concentration of GSH was found in the stimulated saliva of patients with moderate progression as compared to those with fast progression of the disease ($p < 0.05$).

Conclusions. The continuation of research on the GSH concentrations in the gingival fluid and saliva may be useful in the context of biomarkers for periodontitis progression.

Keywords: periodontal disease, gingival crevicular fluid, salivary diagnostics

Cite as
Toczewska J, Maciejczyk M, Zalewska A, Konopka T. Gingival fluid and saliva concentrations of selected non-enzymatic antioxidants in periodontitis. *Dent Med Probl.* 2022;59(4):555–564. doi:10.17219/dmp/148051

DOI
10.17219/dmp/148051

Introduction

Non-enzymatic (low-molecular-weight) antioxidants are characterized by much lower specificity as compared to enzymatic antioxidants. For this reason, these substances play a much greater role in protecting organisms against free radicals; they inhibit oxidation processes by reacting with oxidizing agents and the intermediate products of oxidation. Such interventional antioxidants reduce free radicals on their own through propagation or termination. Most of them are exogenous compounds supplied in the diet. They are divided into hydrophobic antioxidants, which protect the inside of the cell membranes, and hydrophilic antioxidants, which are active in the aqueous environment of the cell.[1] Among the most important non-enzymatic antioxidants are uric acid (UA), reduced glutathione (GSH) and polyphenols.

Uric acid participates in the capture of hydroxyl radicals, lipid peroxides and singlet oxygen. It limits the processes associated with free radicals by creating complexes with iron, copper and manganese ions, which stabilizes the reduced form of vitamin C. The compound is also responsible for 70–80% of the antioxidative potential of saliva; therefore, it is considered the most important antioxidant of the oral cavity.[2,3] However, in high concentrations and in the presence of copper ions, UA and its derivatives may be highly cytotoxic. In such conditions, it has been shown that UA may intensify lipid peroxidation, and therefore act as a pro-oxidant.[4,5]

Reduced glutathione is composed of 3 amino acid residues (γ-glutamyl–cysteinyl–glycine). It is most often oxidized to glutathione disulfide, via a non-enzymatic or enzymatic pathway, which can then be reduced by glutathione reductase or can be actively removed from the cell. Furthermore, GSH is responsible for maintaining the thiol groups of proteins in a reduced form, and for reactions with organic peroxides, hydrogen peroxide, free radicals, xenobiotics, and protein disulfides.[6]

Polyphenols differ in terms of structure, mass, and physiochemical and biological properties. In animal organisms, they are not synthesized, but are absorbed from plant foods. Their antioxidant activity consists in, among other things, inhibiting the activity of enzymes responsible for the formation of reactive oxygen species (ROS), chelating the metals catalyzing the reactions of ROS formation, binding and inactivating the formed free radicals, intensifying the activity of antioxidant enzymes, and increasing the concentrations of other low-molecular-weight antioxidants.[7] Due to the significant exposure of the oral cavity to environmental and diet-related stress, polyphenols reach high concentrations in the mucous membrane, increase the antioxidant activity of biological fluids in the oral cavity and show antibacterial activity against periopathogens in vitro.[8]

In periodontitis, the excessive secretion of ROS and oxidative stress occur due to the exposure of (mostly) neutrophils to periopathogens and their products. This leads to periodontal tissue damage through the intensification of such processes as lipid peroxidation in the gingival tissue, gingival crevicular fluid (GCF) and saliva. Furthermore, it causes protein and deoxyribonucleic acid damage, and changes the functional activity of the proteins found in GCF and saliva.[9] It has been suggested that the chronic occurrence of such processes may result in the depletion of the antioxidant capacity of the enzymatic and non-enzymatic systems. It is manifested as a significant decrease in the activity of preventive and interventional antioxidants as well as in the total antioxidant capacity of GCF and saliva.[9,10] Non-enzymatic antioxidants, which can be supplied exogenously and, as a consequence, can be applied in treatment to reduce the effects of oxidative stress, are particularly important with regard to the abovementioned processes. However, there is no data concerning the antioxidant properties of GCF or saliva with respect to the new criteria for the classification of periodontal disease, established during the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.[11] Classification into stages and grades refers to the severity of the disease at the time of treatment and the treatment plan complexity. Grades provide information about the characteristics of the disease, the rate of its progression, risk assessment, and the analysis of possible treatment failure as well as the evaluation of the impact of periodontopathy and its treatment on the general condition of the patient.[11]

The current study aimed to determine the concentrations of selected non-enzymatic antioxidants (UA, GSH and polyphenols) in the GCF and saliva of patients diagnosed with periodontitis according to the current criteria. Additionally, correlations between the concentrations of these antioxidants in gingival fluid and saliva and the parameters of the clinical condition of the periodontium were evaluated.

Material and methods

Patients

This prospective study involved 50 patients treated for periodontitis at the Department of Periodontology of Wroclaw Medical University, Poland. The diagnosis was made based on a clinical examination, according to the current definition of periodontitis.[11] All patients were Polish Caucasians aged 20–55 years. The study group with periodontitis was divided into 2 subgroups – stage III or IV, or grade B or C.

The control group was composed of 25 persons with a clinically healthy periodontium (bleeding on probing (BoP) <10%, pocket depth (PD) ≤3 mm) who matched the study group in terms of age and gender, and who had been

admitted to the Academic Dental Clinic in Wroclaw for treatment.

The exclusion criteria for both the study and control groups were as follows: age below 20 or above 55 years; systemic comorbidities associated with oxidative stress (cancers, diabetes, hypertension, rheumatoid arthritis, kidney diseases, lung diseases, or thyroid diseases); pregnancy; use of any medications or supplements during the 3 months preceding the study; smoking; number of teeth below 15; occurrence of clinical lesions on the oral cavity mucosa; and periodontal treatment less than a year before the study. The research was approved by the Bioethics Committee at Wroclaw Medical University (KB-559/2018), and was conducted between February 19, 2018 and August 30, 2019.

Material collection

The methods of Toczewska et al. were followed throughout the study.[12,13] The material collected for analysis included total mixed unstimulated saliva and stimulated saliva, with both types of samples collected via spitting. All samples were taken between 8 a.m. and 10 a.m. Saliva was collected in a sitting position, with the head slightly inclined downward, and with minimal facial and labial movements. There was an initial 5-minute adaptation period prior to collection. The saliva accumulated at the base of the oral cavity was spat into a sterile Falcon® test tube, which was placed in a container filled with ice. To avoid possible contamination from other sources, the oral cavity was rinsed two times with room-temperature distilled water before saliva was collected. Unstimulated saliva was spat to a maximum volume of 5 mL, within no more than 10 min.

Stimulated saliva was collected at 5-minute intervals. The secretion of saliva was stimulated by administering 10 µL of 2% citric acid (Sigma-Aldrich, Poznan, Poland) on the tongue every 30 s.[14,15] The volume of saliva was measured using an automated Eppendorf® pipette, with an accuracy of 0.1 mL. Immediately after collection, the samples were centrifuged (5,000 × g, 20 min, 4°C). An antioxidant (10 µL of 0.5 M-butylated hydroxytoluene (Sigma-Aldrich) per 1 mL of saliva) was then added to the supernatant fluid, and the content was frozen at –80°C and stored for no more than 3 months for further analysis.[16,17] The salivary flow was calculated over a 1-minute period by dividing the volume of saliva by the time necessary for its secretion, and was expressed in mL/min.[14]

After selecting the clinically deepest periodontal pockets, GCF was collected using PerioPaper Strips® (Oraflow Inc., New York, USA). The region was dried with compressed air and isolated from saliva by employing cotton dental rollers. PerioPaper Strips contaminated with blood or saliva were discarded. Before and after collecting the material, the strips were placed in Eppendorf test tubes and weighed on an analytical balance to determine the volume of GCF.[12,13] The supernatant fluid (10 µL of 0.5 M-butylated hydroxytoluene per 1 mL of saliva) was added to GCF and the samples were frozen at –80°C.[16,17]

Clinical trial

The clinical trial was conducted using a mouth mirror, a HuFriedy® periodontometer (Warsaw, Poland), which was calibrated every 1 mm, and an artificial light source. The following clinical parameters were assessed: number of preserved teeth; modified plaque index (PI)[18]; approximal plaque index (API)[19]; mean PD measured at 6 points of each tooth; mean interproximal PD for all teeth measured at 4 points of each tooth; number of sites with PD > 5 mm; mean clinical attachment level (CAL) measured at 6 points of each tooth; BoP index[20]; papillary bleeding index (PBI)[21]; maximum value of tooth mobility assessed with the use of Periotest® (Medizintechnik Gulden, Modautal, Germany); and mean value from the indications of Periotest for all teeth.

Enzymatic antioxidant activity

The biochemical tests of saliva and gingival fluid were conducted in the Experimental Dentistry Laboratory at the Medical University of Bialystok, Poland. All measurements were conducted in duplicate and were standardized to total protein content. On the day of the measurements, the samples of saliva and GCF were slowly thawed at 4°C. The saliva and GCF samples were then mixed with a vortex mixer immediately before analysis.

To extract gingival fluid, the strips were placed in an Eppendorf test tube containing 0.02 M phosphate-buffered saline (PBS) solution (pH 7.0) (Sigma-Aldrich) in the proportion of 1 strip/500 µL PBS, and were mixed for 30 s with a vortex mixer before being centrifuged (3,000 × g, 5 min, 4°C). The supernatant was preserved for testing.[12,13] Gingival fluid was used for all experiments on the same day.

The concentration of GSH was determined using a colorimetric method based on the reduction of 5,5'-dithiobis-(2-nitrobenzoic acid) (Sigma-Aldrich) to 2-nitro-5-mercaptobenzoic acid under the influence of GSH contained in the test sample.[22] The absorbance of the 2-nitro-5-mercaptobenzoic acid product was measured at a wavelength of 412 nm and its concentration was calculated from a reference curve for GSH. The measurements were conducted in duplicate and the values were expressed in µg/mg of total protein.

The concentration of UA was measured using the QuantiChrom™ Uric Acid Assay Kit (DIUA-250; BioAssay Systems, Hayward, USA). This method consists in the reaction of 2,4,6-tripirydyl-s-triazine with the iron ions (3+) contained in UA in the test sample. Changes in the absorbance of the obtained complex were measured at a wavelength of 690 nm.

Total polyphenol content (TPC) was determined with the use of the Folina-Ciocâlteu (FC) reagent (Pol-Aura, Roznowo, Poland), which is a mixture of phosphotungstic acid and phosphomolybdic acid. As a result of the reaction of FC with phenols, a blue product with a maximum absorbance of 760 nm was obtained.[23] Total polyphenol content was calculated from a reference curve for gallic acid and the values were expressed as μg/mg of total protein.

Statistical analysis

The 2 groups were compared using the Mann–Whitney *U* test, whilst the analysis of the 3 groups (with regard to different stages of the disease) was conducted using the Kruskal–Wallis one-way analysis of variance (ANOVA) followed by Dunn's post-hoc test. Spearman's rank-order correlation was used to assess associations between the variables. The threshold for statistical significance was set at $p < 0.05$, while in the correlation analysis, the threshold was $p < 0.02$. All analyses were conducted with the use of the Statistica software, v. 13.1. (TIBCO Software Inc., Palo Alto, USA).

Results

The patients' general and periodontal data is presented in Table 1.

In comparison with the control group, the concentrations of GSH in the study group were significantly lower in both biological fluids. This was especially evident in unstimulated saliva and gingival fluid ($p < 0.001$), and regarded all patients with periodontitis, at both stages. A significantly lower concentration of GSH was observed in the gingival fluid of those at the most severe stage of periodontitis (stage IV) as compared to stage III patients ($p = 0.039$) (Fig. 1).

In both types of saliva and in gingival fluid, the concentrations of UA were significantly lower in both periodontitis subgroups as compared to patients with a clinically healthy periodontium ($p < 0.001$). The concentrations of UA in these fluids did not differentiate the advancement of periodontitis (Fig. 2).

In the unstimulated saliva and gingival fluid of patients at both stages of periodontitis, TPC was significantly lower as compared to the control group ($p < 0.001$). In stimulated saliva, this difference was significant for all

Table 1. General and periodontal data of the study participants

Variable	Control group (*n* = 25)			Stage III subgroup (*n* = 32)			Stage IV subgroup (*n* = 18)			Whole study group (both stage III and stage IV) (*n* = 50)		
	M ±*SD*	*Me*	min–max	*M* ±*SD*	*Me*	min–max	*M* ±*SD*	*Me*	min–max	*M* ±*SD*	*Me*	min–max
Age [years]	40 ±9.72	39	20–55	43 ±8.86	44	20–55	45 ±8.08	48	29–55	44 ±8.54	45	20–55
Gender n (%) M	12 (48)			17 (53)			7 (39)			24 (48)		
Gender n (%) F	13 (52)			15 (47)			11 (61)			26 (52)		
Unstimulated SF [mL/min]	0.43 ±0.20	0.4	0.2–1.0	0.40 ±0.21	0.4	0.1–1.0	0.41 ±0.21	0.4	0.1–0.9	0.40 ±0.21	0.4	0.1–1.0
Stimulated SF [mL/min]	1.83 ±0.76	1.6	0.4–3.4	1.30 ±0.56	1.3	0.3–2.6	1.37 ±0.63	1.3	0.6–3.0	1.33 ±0.58	1.3	0.3–3.0
Protein in unstimulated saliva [μg/mL]	644.2 ±201.3	668.3	300.5–1,101.0	862.2 ±233.2	821.2	481.0–1,387.0	967.9 ±513.1	839.6	23.5–1,847.1	900.0 ±356.4	827.0	23.5–1,847.1
Protein in stimulated saliva [μg/mL]	584.7 ±172.9	599.0	235.7–946.3	589.8 ±186.2	610.3	28.9–926.4	494.7 ±227.6	537.1	43.7–811.9	555.8 ±204.5	585.2	28.9–926.4
Protein in GCF [μg/mL]	39.1 ±21.9	31.5	8.4–91.7	131.2 ±70.3	130.8	36.8–337.0	181.1 ±124.5	131.1	45.5–445.6	149.4 ±95.4	131.1	36.8–445.6
Number of teeth	26 ±2.85	28	19–28	27 ±1.19	27	24–28	22 ±4.03	24	15–28	25 ±3.39	26	15–28
PI	22.6 ±16.9	20	0–79	46.3 ±25.6	47	9–100	47.8 ±28.4	40.5	0–100	46.8 ±26.3	43.5	0–100
API	37.9 ±16.5	32	14–68	63.2 ±22.1	64	29–100	73.8 ±25.2	82	22–100	67.0 ±23.6	70.5	22–100
BoP [%]	11.9 ±7.4	9.0	0.7–26.0	44.9 ±28.7	41.0	4.0–100.0	59.2 ±28.5	57.5	17.0–100.0	50.0 ±29.2	43.0	4.0–100.0
PD [mm]	1.8 ±0.3	1.7	1.2–2.3	3.2 ±0.7	3.2	2.1–5.3	3.9 ±0.5	4.1	2.7–4.7	3.5 ±0.7	3.5	2.1–5.3
CAL [mm]	2.2 ±1.2	1.7	1.0–5.2	4.9 ±1.3	5.0	2.7–8.1	6.1 ±1.9	6.1	3.0–10.1	5.3 ±1.6	5.4	2.7–10.1

M – mean; *SD* – standard deviation; *Me* – median; min – minimum; max – maximum; M – male; F – female; SF – saliva flow; GCF – gingival crevicular fluid; PI – plaque index; API – approximal plaque index; BoP – bleeding on probing; PD – pocket depth; CAL – clinical attachment level.

persons from the study group (p = 0.016) and for those with stage IV periodontitis (p = 0.028). Total polyphenol content did not differ significantly with regard to different stages of periodontitis (Fig. 3).

Comparisons were made between the concentrations of the 3 non-enzymatic antioxidants in both types of saliva and in the gingival fluid of patients with grade B or C (stage II or stage IV, respectively) periodontitis. The results indicated a significantly lower concentration of GSH in the GCF obtained from participants with periodontitis of moderate progression a compared to those with fast progression of the disease (p = 0.039).

Total polyphenol content in saliva and gingival fluid as well as the clinical condition of the periodontium were positively correlated across the entire study group. Two significant positive correlations were observed between TPC in unstimulated saliva and the advancement of gomphosis, according to the measurements conducted with the use of Periotest (for the maximum value: R = 0.33, p = 0.020, and for the mean value: R = 0.33, p = 0.018).

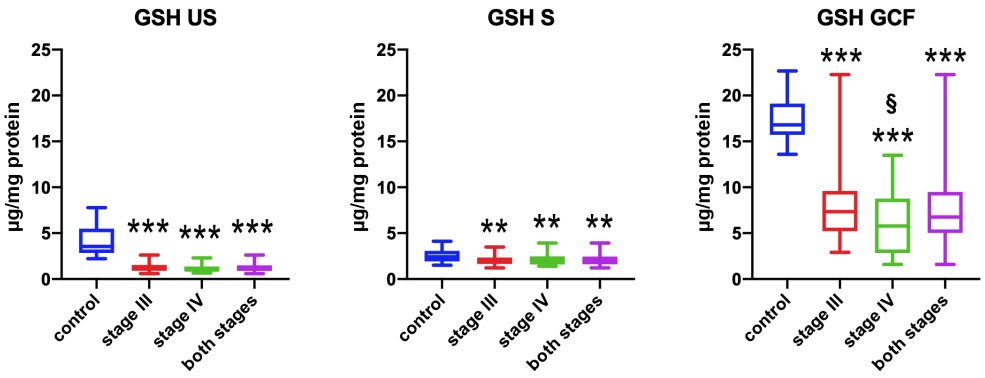

Fig. 1. Comparison of the concentrations of reduced glutathione (GSH) in saliva and gingival crevicular fluid among the study subgroups and the control group
US – unstimulated saliva; S – stimulated saliva; ** $p < 0.01$ vs. control group; *** $p < 0.001$ vs. control group; § $p < 0.05$ vs. stage III.

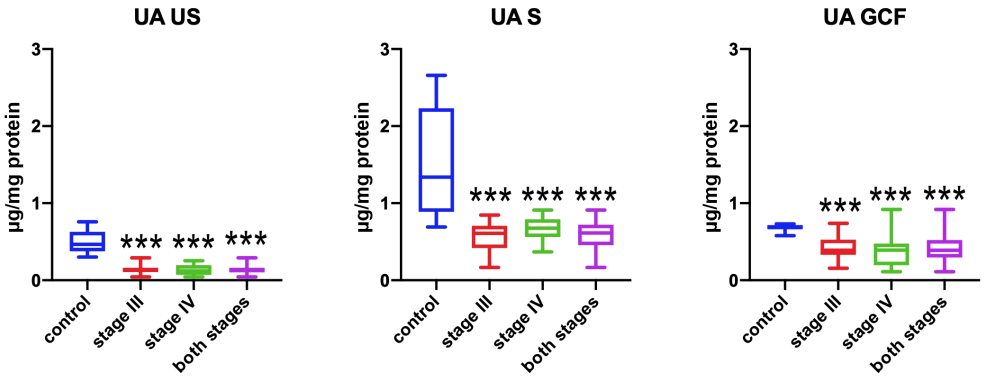

Fig. 2. Comparison of the concentrations of uric acid (UA) in saliva and gingival crevicular fluid among the study subgroups and the control group
*** $p < 0.001$ vs. control group.

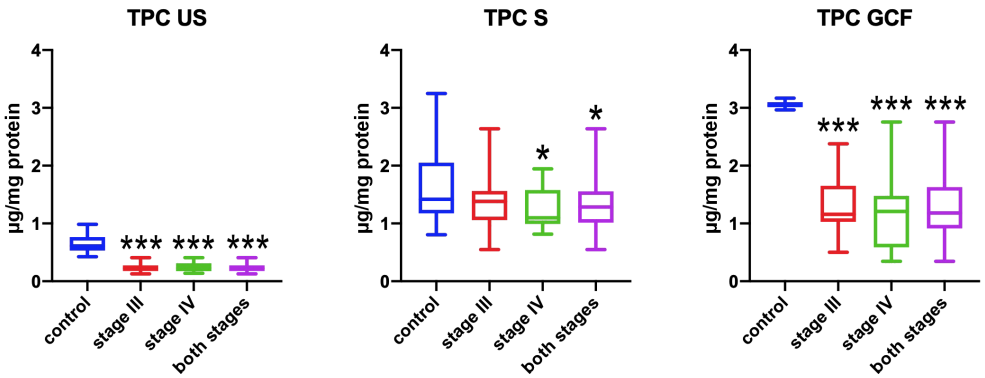

Fig. 3. Comparison of total polyphenol content (TPC) in saliva and gingival crevicular fluid among the study subgroups and the control group
* $p < 0.05$ vs. control group; *** $p < 0.001$ vs. control group.

A significant negative correlation between the concentration of UA in stimulated saliva and the number of preserved teeth was also revealed (R = –0.36, p = 0.018) (Table 2). In patients with the most advanced stage of periodontitis, there were significant positive correlations between the concentration of UA and TPC in gingival fluid and the value of API (R = 0.53, p = 0.015, and R = 0.55, p = 0.013, respectively) (Table 3). The assessment of relationships between antioxidant concentrations revealed strong correlations between GSH and UA in unstimulated and stimulated saliva (R = 0.54 and R = 0.55, $p < 0.001$), between UA and TPC in unstimulated saliva (R = –0.38, p = 0.010), and between GSH and TPC in stimulated saliva (R = –0.81, $p < 0.001$).

Table 2. Correlations between the clinical periodontal variables and the activity of non-enzymatic antioxidants in the whole group (all persons with periodontitis)

Variable	GSH US	UA US	TPC US	GSH S	UA S	TPC S	GSH GCF	UA GCF	TPC GCF
Age	–0.148460	–0.008252	–0.177784	–0.072552	0.109466	–0.230409	0.015517	0.059522	0.089190
Genetic factors	–0.018081	–0.138714	0.029198	0.051856	0.038329	0.108275	0.055430	0.248201	0.221901
Number of teeth	–0.072690	0.065000	–0.127808	–0.076507	**–0.360093**[2]	0.046340	0.250244	0.115265	0.106950
PI	0.027708	–0.052361	0.100997	0.143385	–0.046838	0.157111	–0.049051	0.099796	0.056841
API	0.033389	0.198481	0.030847	–0.246361	–0.172175	–0.304828	–0.018852	0.142544	0.131745
BoP	0.094921	–0.028941	0.148465	–0.006576	–0.075105	–0.074121	–0.191422	–0.068440	–0.113778
PBI	0.108934	0.080807	0.074978	–0.119344	–0.129393	–0.153836	–0.216316	0.041060	–0.002099
PD mean	0.013274	–0.078999	0.055139	–0.062376	–0.104320	–0.057834	–0.129956	–0.064719	–0.063855
PD mean/interproximal	–0.027305	–0.062779	–0.007020	–0.081205	–0.137780	–0.090657	–0.104097	–0.006734	–0.010070
PD > 5 mm	0.025488	–0.069966	–0.020372	–0.079563	–0.124136	0.006460	–0.217784	–0.204375	–0.190553
Percentage of measurement points with CAL > 0 mm	0.179388	0.094392	0.061920	–0.133478	0.211135	–0.195932	0.039784	0.105488	0.122348
Percentage of teeth with CAL ≥ 5 mm interproximal	0.050480	0.006736	0.065255	–0.092878	0.053428	–0.125751	0.008053	0.008348	0.029867
CAL > 5 mm	0.021037	0.008913	0.101542	0.045825	0.125765	0.006458	–0.072949	–0.127637	–0.097594
CAL ≥3 mm interproximal	0.145713	0.125467	0.056151	–0.227495	–0.060581	–0.113802	0.079004	0.044290	0.059834
Periotest max value	0.193351	0.001812	**0.328707**[1]	0.169847	0.221484	0.064697	0.006061	–0.100777	–0.092821
Periotest mean value	0.202671	0.010572	**0.334870**[2]	0.229882	0.300676	0.084066	–0.050270	–0.095171	–0.079257

GSH – reduced glutathione; UA – uric acid; TPC – total polyphenol content; PBI – papillary bleeding index; max – maximum; [1] p = 0.020, [2] p = 0.018.

Table 3. Correlations between the clinical periodontal variables and the activity of non-enzymatic antioxidants in the stage IV periodontitis subgroup

Variable	GSH US	UA US	TPC US	GSH S	UA S	TPC S	GSH GCF	UA GCF	TPC GCF
Age	–0.067651	–0.241889	–0.229929	0.014952	–0.034398	–0.362565	–0.014066	–0.015825	0.008289
Genetic factors	0.024398	0.140028	0.043574	–0.076980	–0.024056	0.286972	0.365655	0.416213	0.433555
Number of teeth	–0.004973	–0.042773	–0.056907	–0.206719	–0.444051	–0.022289	–0.132512	–0.337502	–0.351123
PI	0.066710	0.074076	0.155827	0.364850	0.456620	0.218290	0.083041	0.247357	0.237523
API	0.047971	0.343405	–0.009800	0.120546	0.137593	–0.521740	0.499782	**0.532983**[3]	**0.545045**[4]
BoP	0.447882	0.117820	0.311818	0.230162	0.130868	–0.047268	–0.098767	–0.089880	–0.111784
PBI	0.425767	0.192931	0.294317	–0.010540	0.041743	–0.219603	–0.028107	0.153557	0.133986
PD mean	0.228502	–0.143708	–0.062666	–0.158452	–0.203932	0.106117	–0.081094	0.046056	0.063421
PD mean/interproximal	0.213760	–0.103169	–0.102448	–0.160000	–0.215121	–0.025074	–0.120440	0.030132	0.042185
PD > 5 mm	0.219632	–0.352248	–0.121942	–0.151888	–0.289393	0.129507	–0.250220	–0.200979	–0.197968
Percentage of measurement points with CAL > 0 mm	0.169035	0.067223	–0.043957	–0.012395	0.286250	–0.187455	0.330986	0.419869	0.436543
Percentage of teeth with CAL ≥ 5 mm interproximal	0.122760	0.073988	–0.029193	–0.170918	–0.139044	–0.096637	0.087316	0.248905	0.265806
CAL > 5 mm	0.121398	0.108824	–0.044378	0.116718	0.038013	0.208977	–0.116718	0.009026	0.024069
CAL ≥3 mm interproximal	0.155828	0.100074	–0.039127	–0.269535	–0.298160	0.120766	0.140474	0.167795	0.148232
Periotest max value	0.181373	0.294118	0.299248	0.216762	0.148375	–0.129507	–0.083370	–0.025574	–0.033847
Periotest mean value	0.149510	0.247241	0.160211	0.352632	0.232843	–0.055882	0.016674	0.030839	0.028582

[3] p = 0.015, [4] p = 0.013.

Discussion

The data relating to the concentrations of the most frequently tested non-enzymatic antioxidants in periodontitis in the gingiva, gingival fluid, saliva, and blood, are presented in Table 4.[24–38] Results and observations from the current study as well as from other studies are quite unambiguous and indicate that in periodontitis, non-enzymatic antioxidant concentrations are significantly reduced in saliva and gingival fluid. The most homogenous results were obtained for GSH; it has been consistently shown in numerous studies to be significantly decreased in gingival fluid as compared to individuals with a healthy periodontium.[24,30,34] Such decreases have also been observed in saliva and plasma,[27] and, for glutathione, in serum.[36] In the current study, a correlation was observed between the clinical advancement of periodontopathy (and its duration) and a decreased concentration of GSH in gingival fluid (significantly lower in stage IV as compared to stage III).

Glutathione is secreted to GCF by epithelial cells and neutrophils, and under physiological conditions, its concentration in GCF is 1,000 times higher than it is found in plasma.[39] However, its concentration is reduced in patients with periodontitis due to a strong respiratory burst, the destruction of the epithelium and the degradation of proteins by periopathogens. The greatest ability to metabolize glutathione to hydrogen sulfide is shown by *Treponema denticola*, *Fusobacteria* (*nucleatum*, *periodonticum*, and *necrophorum*), *Parviromonas micra*, and *Prevotella tannerae*.[40] In the gingival tissue that is inaccessible to periopathogens, the concentration of reduced and oxidized glutathione may even be elevated.[27,29] Using gas chromatography in combination with mass spectrometry, Chen et al. conducted an analysis of 349 metabolites of gingival fluid in patients with generalized aggressive periodontitis.[36] The secondary nature of the decrease in the concentration of glutathione and its reduced form in relation to the advancement of periodontitis was also indicated by the possibility of significantly improving its secretion to GCF as a result of non-surgical periodontal treatment.[34] In our opinion, the lowest concentrations of GSH in the unstimulated saliva of patients with periodontitis stem from a single source, which is the outflow of GSH from periodontal pockets together with gingival fluid and the degrading activity of periopathogens in saliva. The observation of significantly lower concentrations of GSH in GCF in the moderate grade of periodontitis progression as compared to fast progression can be explained by the slower course of the former and the exhaustion of the antioxidative potential of GSH.

Uric acid is secreted into saliva by passive diffusion from blood and its concentration depends on the volume of the secreted saliva, as previously demonstrated.[41] It is estimated that UA is responsible for approx. 70% of the total antioxidative potential of saliva.[19] Uric acid, which is an end product of purine metabolism, is produced as a result of a reaction that also generates ROS. For this reason, salivary hyperuricemia would not be beneficial. The UA concentration in both types of saliva in patients with periodontitis was significantly lower as compared to the control group, which was also observed in other studies,[25,33] though this difference was not confirmed by 2 other publications.[26,32] However, it should be noted that neither of the abovementioned studies took CAL into account when defining periodontitis, and the basic inclusion criterion was a radiological image.

In the current study, a significant decrease was observed in the concentration of UA in the GCF obtained from periodontitis patients in comparison with clinically healthy sites. With the use of the most popular colorimetric uricase–peroxidase method for the evaluation of the UA concentration, Narenda et al. did not show significant differences in its concentration in GCF between the chronic and aggressive periodontitis groups and the control group (in the control group, the UA concentrations in blood serum and gingival fluid were identical, i.e., 5.11 ±0.54 mg/dL).[37] It is possible that these contradictions stem from the application of different methods for the determination of the UA concentration. Nonetheless, a significant reduction in the concentration of UA in gingival fluid and saliva in periodontitis is probably due to its increased activity against ROS in the dental pocket and the entire oral cavity. Indeed, this is indirectly indicated by the positive correlation between its concentration in gingival fluid and the presence of plaque in interdental spaces in stage IV periodontitis. Moreover, there is also a possibility of significantly increasing the concentration of UA in saliva as a result of non-surgical periodontal treatment.[32]

Positive correlations between UA and GSH concentrations may be indicative of the synergy of non-enzymatic antioxidant cooperation in protection against periodontal oxidative stress. However, the findings regarding hyperuricemia in peripheral blood in periodontitis and the possibility of significant reductions thereof as a result of scaling and root planing combined with the administration of exogenous antioxidants are seemingly contradictory to the above observations.[35,38,42] Nonetheless, hyperuricemia in GCF and saliva plays a completely different role in periodontitis than it does in the peripheral vascular bed. In the latter case, it can be a sign of immunological-metabolic dysregulation, linking the clinical status of the periodontium to systemic pathologies.[43]

Polyphenols are plant metabolites that are not synthesized endogenously. Therefore, their concentration in vivo reflects the supply and absorption of these compounds from food. They include a number of biologically active substances (e.g., flavonoids and phenolic acids), many of which have antioxidant properties. Apart from their direct interventional activity against ROS, these compounds also participate in intercellular signaling that promotes the activity of enzymatic antioxidants, such as heme oxygenase, and inhibit enzymes in ROS and reactive nitrogen species production pathways.[44]

Table 4. Comparison of the data relating to the non-enzymatic antioxidant concentrations in periodontitis

Authors, year and country	Biological material	Assessment method	Size and age [years] of the studied groups	*p*-value for periodontitis group	Other data
Chapple et al.[24] 2002, the UK	GCF	GSH – NADPH reduction	P: 60 (mean age: 46.1) HP: 10 (mean age: 46.9)	↓ GSH $p < 0.022$	–
Sculley and Langley-Evans[25] 2003, the UK	unstimulated saliva	UA – enzymatic Asc – Butts and Mulvihill	severe P: 46 (mean age: 59.6) HP: 46 (mean age: 60.3)	↓ UA $p < 0.050$ Asc ns	decrease in UA depends on the severity of periodontitis
Diab-Ladki et al.[26] 2003, Libya	stimulated saliva	UA – enzymatic Asc – Molina-Diaz	severe P: 17 (30–45) HP: 20 (30–45)	UA ns Asc ns	–
Panjamurthy et al.[27] 2005, India	gingiva, plasma	GSH – Beutler Asc – Omaye vit. E – Desai	CP: 25 (25–35) HP: 25 (25–35)	gingiva ↑ GSH $p = 0.001$ plasma ↓ GSH, Asc, vit. E $p = 0.001$	–
Tsai et al.[28] 2005, Taiwan	unstimulated saliva	TG – spectrophotometric acidification	CP: 13 (NA) HP: 9 (NA)	↓ TG $p < 0.050$	no significant correlation TG–GPx
Borges et al.[29] 2007, Brazil	gingiva	GSH – Beutler TG – Tietze GSSG – TG–GSH	CP: 9 (mean age: 52.9) HP: 9 (mean age: 51.1)	GSH ns TG ns ↑ GSSG $p = 0.020$	–
Grant et al.[30] 2010, the UK	GCF	GSH – NADPH reduction	CP: 20 (mean age: 43.6) HP: 20 (mean age: 44.3)	↓ GSH $p < 0.001$	periodontal treatment improved the concentration of GSH (ns)
Karim et al.[31] 2012, India	GCF, unstimulated and stimulated saliva	thiol groups – Ellman	P: 23 (20–55) HP: 23 (20–55)	GCF ns saliva ns	–
Novakovic et al.[32] 2014, Serbia	unstimulated saliva	UA – enzymatic	CP: 21 (mean age: 39.1) HP: 21 (mean age: 35.2)	UA ns lack of significant correlations with periodontitis	periodontal treatment improved the concentration of UA ($p < 0.001$)
Miricescu et al.[33] 2014, Romania	unstimulated saliva	UA – enzymatic	CP: 20 (mean age: 51.3) HP: 20 (mean age: 18.6)	↓ UA $p < 0.050$	–
Savita et al.[34] 2015, India	GCF	GSH – gas chromatography	CP: 20 (30–50) HP: 20 (30–50)	↓ GSH $p < 0.001$	periodontal treatment improved the concentration of GSH ($p < 0.001$)
Banu et al.[35] 2015, Saudi Arabia	plasma	UA – enzymatic	CP: 40 (40–65) HP: 20 (40–65)	↑ UA $p = 0.001$	significant positive correlation with transaminases
Chen et al.[36] 2018, China	GCF, serum	G, vit. E – gas chromatography	AgP: 20 (maen age: 28.4) HP: 20 (mean age: 25.7)	GCF, serum ↓ G $p < 0.001$ GCF ↑ vit. E $p = 0.00003$	–
Narendra et al.[37] 2018, India	GCF, serum	UA – enzymatic	CP: 46 (mean age: 47.1) AgP: 32 (mean age: 25.7) HP: 50 (mean age: 36.6)	GCF ns serum ns	–
Gharbi et al.[38] 2019, Tunisia	serum	UA – enzymatic	P: 80 (20–60) HP: 50 (20–60)	↑ UA $p < 0.050$	–
Authors' own study	GCF, unstimulated and stimulated saliva	GSH – Ellman UA – FRAP assay	P: 50 (mean age: 43.6) HP: 25 (mean age: 40.3)	GCF ↓ GSH, UA saliva ↓ GSH, UA	in severe periodontitis, in GCF there is a positive correlation between UA and API; in both types of saliva there is a positive correlation between GSH and UA

NAPDH – nicotinamide adenine dinucleotide phosphate hydrogen; Asc – ascorbate; vit. E – vitamin E; TG – total glutathione; GSSG – oxidized glutathione; G – glutathione; FRAP – ferric-reducing/antioxidant power; P – periodontitis; HP – healthy patients; CP – chronic periodontitis; AgP – aggressive periodontitis; GPx – glutathione peroxidase; NA – data not available; ns – statistically non-significant.

There are no studies available in the literature investigating TPC in gingival fluid or saliva in periodontitis. Studies on antioxidant phenolic components with regard to periodontopathy conducted to date have been randomized clinical studies on coenzyme Q and catechins as well as in vitro and animal studies.[44] A significant reduction in TPC in GCF was observed in our patients with periodontitis, though the stage and grade of periodontitis did not have a significant impact on TPC. It seems that the antioxidative activity of polyphenols develops in the periodontal pocket, similar to UA, in response to stimulation by plaque bacteria (a significant positive correlation between TPC in GCF and API in stage IV periodontitis was found). Meanwhile, a strong pro-oxidative impulse in the dental pocket is responsible for a significant reduction in TPC in the gingival sulcus. Regardless, fluctuations in salivary TPC may be of limited value due to the possible activity of flavonoids that are commonly found in food.

Lower values of TPC were observed in the unstimulated saliva of patients with periodontitis. In addition, the concentration correlated directly with the electronic measurement of tooth mobility. This pioneering research on the impact of the periodontal condition on TPC should be continued, with the attention paid to determining antioxidant concentrations in serum. Furthermore, other antioxidants, such as resveratrol, apigenin and kaempferol, should be investigated. Such research may lead to recommendations for the introduction of antioxidant supplementation into periodontal treatment protocols.

The majority of studies on non-enzymatic antioxidants in periodontal diseases have been conducted with regard to ascorbate and α-tocopherol. Some of them showed a significant decrease in the ascorbate concentration in the serum and plasma of individuals with periodontitis,[27,45] depending on the severity of periodontopathy.[46] However, periodontitis does not have a significant impact on the ascorbate concentration in saliva.[25,26] Researchers have also observed a significant decrease in the α-tocopherol concentration in plasma[27]; however, unlike with vitamin C, its high concentration in serum was not associated with a rare occurrence of the most severe clinical form of periodontal disease.[46] In the analysis of the gingival fluid metabolome in patients with generalized aggressive periodontitis, the concentrations of ascorbate and α-tocopherol were over 18 times and 6 times higher, respectively, in comparison with a clinically healthy periodontium.[36]

Salivary redox biomarkers are being increasingly used in clinical practice, both in the diagnosis of systemic diseases and in the diseases of the oral cavity.[10,47–52] Unfortunately, in the current study, they did not differentiate between the grades of periodontitis (except for GSH), which indicates that their diagnostic value is low. However, due to the significant impact of oxidative stress on the pathogenesis of periodontitis, further studies on a larger population of patients are needed.

Conclusions

A significant decrease in the concentrations of all the studied non-enzymatic antioxidants in saliva and gingival fluid from periodontitis patients may be indicative of a strong oxidative impulse associated with inflammatory and destructive processes in dental pockets. Further studies concerning the GSH concentration in gingival fluid and saliva may be useful in the context of periodontitis progression biomarkers. The model of periodontitis progression which is currently being considered provides the basis for the local application of exogenous non-enzymatic antioxidants, such as polyphenols resveratrol and curcumin, to inhibit signaling that initiates and exacerbates the disease.[53]

Ethics approval and consent to participate

The research was approved by the Bioethics Committee at Wroclaw Medical University, Poland (KB-559/2018). Written informed consent was obtained from all participants.

Data availability

The article contains complete data used to support the findings of this study.

Consent for publication

Not applicable.

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Original paper

Effect of non-surgical periodontal therapy on the salivary levels of omentin-1, a novel adipokine biomarker in periodontitis: A clinico-biochemical study

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):565–571

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on November 16, 2021
Reviewed on December 24, 2021
Accepted on January 7, 2022

Published online on December 19, 2022

Abstract

Background. Biomarkers are emerging, advanced diagnostic tools for the assessment of periodontal disease progression. Omentin-1 is an anti-inflammatory adipocytokine, which has been observed and studied in the saliva of periodontitis patients. Non-surgical periodontal therapy (NSPT) is considered a vital part of periodontal disease treatment.

Objectives. The study aimed to evaluate the interventional effect of NSPT on the levels of salivary omentin-1 in healthy (H) and chronic periodontitis (CP) patients.

Material and methods. A total of 60 participants were selected and equally divided into 2 groups (group A: H participants, group B: CP patients). After obtaining verbal and written consent, whole unstimulated saliva was collected from all participants and analyzed for omentin-1 levels using enzyme-linked immunosorbent assay (ELISA).

Results. Mean salivary omentin-1 levels were elevated and found to be significantly higher in group A (95.80 ±26.65) compared to group B (61.97 ±24.53). In group B, there was a substantial rise in omentin-1 levels from baseline to the 6th week of follow-up ($p < 0.001$). Thus, NSPT had a positive influence on salivary omentin-1 levels in the treatment group.

Conclusions. Salivary omentin-1 levels may serve as diagnostic and prognostic indicators of periodontal disease progression, and may be used to assess therapeutic outcomes in periodontitis patients.

Keywords: omentin-1, periodontitis, saliva, biomarker, non-surgical periodontal therapy

Cite as
Patil RS, Kalburgi NB, Koregol AC, Vinayaka AM, Puttarevanna T, Hannahson P. Effect of non-surgical periodontal therapy on the salivary levels of omentin-1, a novel adipokine biomarker in periodontitis: A clinico-biochemical study. *Dent Med Probl.* 2022;59(4):565–571. doi:10.17219/dmp/145593

DOI
10.17219/dmp/145593

Introduction

Chronic periodontitis (CP) is a multifactorial, immunoinflammatory disease that affects the vital periodontal tissues supporting the tooth. Although bacterial microflora is the main causative factor in periodontal disease progression, eventually the host's immune response causes the release of cytokines (e.g., interleukin (IL)-4, IL-10 and IL-35, as well as adipokines, such as omentin-1) that have anti-inflammatory properties controlling further destruction.[1] Therapeutic modalities such as scaling and root planing still remain the "gold standard" in non-surgical periodontal therapy (NSPT) and lead to significant improvements in clinical parameters.[2,3]

Advancements in oral and periodontal diagnostic research are heading towards more sensitive and objective tools such as biomarkers, which help to overcome the limitations of traditional diagnostic tools.[4] A biomarker or biologic marker is a substance that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacological responses to a therapeutic intervention.[5] Thus, a biomarker for a disease can play vital roles in the diagnosis, monitoring of therapeutic outcomes and drug discovery.[6]

Researchers concerned with advancements in periodontal disease diagnostics are currently investigating the possible use of oral fluids, such as saliva, for disease assessment. Major salivary gland secretions include proteins and peptides that are responsible for maintaining the integrity of the oral cavity. Salivary components also play a major role in the formation of oral biofilm and host defense; hence, they are associated with the establishment and progression of periodontal disease. A series of initiatives by the National Institute of Dental and Craniofacial Research (NIDCR) has given compelling reasons for the use of saliva as a diagnostic fluid for monitoring periodontal diseases.[7] Salivary proteins and RNAs have been used in the detection of oral cancer[8] and Sjögren's syndrome.[9] The analyses of the salivary proteomes and transcriptomes are now at the cutting edge of translational and clinical applications in periodontal diseases.[7]

Although adipocytes (fat cells) occupy a large fraction of salivary gland tissue, little is known about their significance in periodontal disease.[10] Many studies[11–15] have reported that adipocytes are able to express cytokines such as adipokines, including salivary leptin, adiponectin and omentin-1.

Salivary omentin-1, a novel anti-inflammatory adipokine, inhibits inflammation via multiple cellular signaling pathways and molecular mechanisms. This adipokine inhibits tumor necrosis factor alpha (TNF-α)-induced cyclooxygenase-2 (COX-2),[16] superoxide production[17] and the expression of adhesions molecules in endothelial cells, blocking the extracellular regulated protein kinase (ERK)/nuclear factor kappa B (NF-κB) pathway.[18] Moreover, omentin-1 plays an anti-inflammatory role in endothelial cells by promoting the AMPK/AKT pathway directly via suppressing the expression of proinflammatory mediators, including TNF-α, IL-6 and monocyte chemotactic protein-1 (MCP-1) in macrophages.[19] In addition, omentin-1 promotes the PI3K/AKT signaling pathway that induces the proliferation of human osteoblasts (hOBs).[20] Therefore, salivary omentin-1 appears to be a significant regulator of bone remodeling.

In light of the above findings and the paucity of studies evaluating the relationship between periodontal disease and omentin-1, this clinico-biochemical trial aimed to evaluate, compare and correlate the levels of salivary omentin-1 in healthy (H) and CP patients before and after NSPT. The study assessed the validity of omentin-1 as an early diagnostic tool and explored its potential uses for the monitoring of periodontal treatment results.

Material and methods

Preliminary plan and ethics statement

This study was carried out as a prospective, double-blinded, controlled clinical trial. It was approved by the institutional Review Board of the P.M. Nadagouda Memorial Dental College and Hospital, Bagalkot, India, before initiation (approval No. PMNMDCH/1534/2018-19).

The study was carried out in agreement with the ethical standards established by the Declaration of Helsinki. Each patient was given a detailed verbal and written description of the study and a signed consent form was obtained from all of the participants.

Inclusion and exclusion criteria

The patients were assessed at the Ambulatory Care Unit in the Department of Periodontics (P.M. Nadagouda Memorial Dental College, Bagalkot, India), in accordance with the 1999 American Academy of Periodontology guidelines for periodontal disease classification.[21] Patients of both sexes, within the age range of 35–60 years and suffering from chronic generalized periodontitis were included in the study. Patients with systemic diseases that could influence periodontal conditions, who underwent periodontal therapy in the past 6 months, who took any systemic medications known to affect the periodontal status, who were pregnant or lactating, who used tobacco in any form, or had a history of radiotherapy were excluded from the study.

Sample size calculation

The required sample size was calculated using the following formula[22]:

$$n = \frac{2(Z_\alpha - Z_\beta)^2 \quad [s]^2}{d^2}$$

where:
n – sample size;
Z_α – Z variate of alpha error =1.96;
Z_β – Z variate of beta error =0.84;
s – standard deviation;
d – difference between the means for the 2 groups.

After the calculation, the estimated smallest sample size was approx. 58. A total of 60 patients were recruited in order to compensate for a 20% dropout of participants who might fail to follow-up.

Periodontal examinations

The oral screening was performed to clinically assess the participants both at baseline and at the 6th week after NSPT. The gingival index (GI),[23] oral hygiene index simplified (OHI-S),[24] sulcus bleeding index (SBI),[25] pocket probing depth (PPD), and clinical attachment level (CAL) were recorded, and unstimulated whole saliva samples (for the evaluation of omentin-1 levels) were collected by a single examiner who was blinded to the patient's condition.

Collection of unstimulated whole saliva

A total of 1.5 mL of unstimulated whole saliva was collected from each participant. Salivary samples were collected between 9 and 11 am to minimize circadian influences.[26] During sample collection, patients were comfortably seated with eyes open, head tilted slightly forward, protected from any stimulation. They made minimal orofacial movements in order for saliva to accumulate in the floor of the mouth. Participants were then instructed to spit into a 1.5-mL Eppendorf tube every 60 s for 10 min or when the participant experienced an urge to swallow the fluid accumulating in the floor of the mouth.[27] Samples were centrifuged for 20 min at 1000 g at 2–8°C to remove any particulate matter, sealed firmly and sent to the Maratha Mandal's Central Research Laboratory (Belgaum, India) where they were stored at –80°C until enzyme-linked immunosorbent assay (ELISA) testing.

Periodontal therapy

After the unstimulated saliva sampling, CP patients underwent thorough subgingival scaling and root planing using ultrasonic scalers (Woodpecker™, Guilin, China). Root planing was carried out using either 4R-4L or 2R-2L Columbia universal curettes (Hu-Friedy, Chicago, USA) via established techniques. Oral hygiene instructions were given to all individuals, particularly regarding regular tooth brushing, the use of the modified bass technique, and suitable devices for interdental cleaning, such as dental floss and interdental brushes.

Biochemical evaluation

An ELISA kit (ELK Biotechnology Co. Ltd., Wuhan, China) was used to determine omentin-1 levels in the collected saliva and a sandwich enzyme immunoassay was carried out. Samples were added to a microtiter well plate where an enzyme–substrate reaction gave rise to a color change that was measured spectrophotometrically at a wavelength of 450 ±10 nm.

Statistical analysis

The data obtained from the clinical and biochemical evaluations is presented as mean ± standard deviation ($M \pm SD$). The GI, OHI-S, SBI, PD, and CAL data was analyzed using the Student's t-test. Correlations between the variables in both groups were evaluated using the Pearson's test. Comparisons of categorical variables were made using the χ^2 tests. For all statistical tests, the significance level was set at $p < 0.05$, keeping α error at 5%, β error at 20%, and giving the study a power of 80%.

Results

A total of 60 participants aged 18–60 years were recruited in the study. No notable differences were observed in the distributions of age and gender (mean age in group A: 38.37 ±8.45 years; and group B: 40.60 ±10.25 years; $p = 0.361$; gender ($p = 0.791$)), as depicted in Tables 1 and 2, respectively.

Table 1. Distribution of subjects according to age

Group	Age [years] *M* ±*SD*	*p*-value
A (*n* = 30)	38.37 ±8.45	0.361
B (*n* = 30)	40.60 ±10.25	

A – healthy patients; B – chronic periodontitis patients; *M* – mean; *SD* – standard deviation.

Table 2. Intergroup comparison according to gender using the χ^2 test

Gender	Group A *n*	Group B *n*	Total *n*	*p*-value
M	19	18	37	0.791
F	11	12	23	
Total	30	30	60	

F – female; M – male.

Clinical parameters

A significant reduction ($p \leq 0.001$) was observed in the GI, OHI-S, SBI, PPD, and CAL in the CP patients at 6 weeks after NSPT. Intragroup comparisons between CP patients at baseline and 6 weeks after NSPT showed a statistically significant difference in the mean values for GI, OHI-S, SBI, PPD, and CAL ($p = 0.000$), as presented in Table 3.

An intergroup comparison of omentin-1 levels showed a statistically significant difference ($p = 0.000$) in mean salivary omentin-1 levels between healthy participants (95.80 pg/mL) and CP patients (43.10 pg/mL).

Intergroup comparisons between healthy participants and CP patients at baseline showed significant differences in the statistical mean values for GI, OHI-S, Bleeding on probing (BoP), PPD, and CAL ($p = 0.000$).

Correlation between salivary omentin-1 levels and various parameters

A statistically significant moderate and negative correlation was seen between age and the expression of omentin-1 ($r = -0.420$, $p < 0.05$) in CP patients at 6 weeks after NSPT, indicating that as the value of one variable increases, the other reduces (Table 4). However, healthy participants and CP patients showed a statistically non-significant correlation between age and the salivary expression of omentin-1 ($r = 0.098$, $r = -0.315$ at baseline, respectively; $p > 0.05$).

Comparisons of salivary omentin-1 levels between the genders of the participants in both groups showed highly significant differences ($p < 0.01$), with higher values in healthy group females. Higher values of omentin-1 were noted in males than in females in both groups (i.e., CP patients at baseline and 6 weeks after NSPT); however, the difference was not statistically significant ($p > 0.05$; Table 5).

Salivary omentin-1 levels when correlated with the clinical parameters (GI, OHI-S, BoP, PPD, CAL) in healthy participants, CP patients at baseline, and CP patients 6 weeks after NSPT, showed statistically non-significant correlations with either a slightly positive or negative relationship (Table 6).

Table 4. Statistically significant, moderate, negative correlation between the salivary levels of expression of omentin-1 and age in chronic periodontitis (CP) subjects at 6 weeks after non-surgical periodontal therapy (NSPT)

Group	Parameter	Correlation (*r*)
CP patients 6 weeks after NSPT	salivary omentin-1	–0.420*
	age	

* statistically significant ($p < 0.05$).

Table 5. Correlation between the salivary levels of expression of omentin-1 and gender in healthy participants and chronic periodontitis (CP) subjects

Group	Gender	*n*	Salivary omentin-1 [pg/mL] *M ±SD*	*p*-value (*t* test)
Healthy participants	M	19	85.66 ±19.27	0.004**
	F	11	113.30 ±29.31	
CP at baseline	M	18	46.36 ±5.48	0.360
	F	12	38.20 ±6.89	
CP after 6 weeks	M	18	66.93 ±27.22	0.179
	F	12	54.52 ±18.47	

** highly statistically significant ($p < 0.01$).

Table 3. Intergroup and intragroup comparisons of the numerical outcome variables between healthy participants, chronic periodontitis (CP) patients and CP patients at 6 weeks after non-surgical periodontal therapy (NSPT) (*t* test)

Group	Parameter				
	GI	OHI-S	SBI	PPD [mm]	CAL [mm]
Healthy participants	0.89 ±0.16	0.61 ±0.20	0.86 ±0.13	–	–
CP patients at baseline	2.27 ±0.45	4.13 ±0.98	3.21 ±0.68	3.04 ±1.87	3.35 ±1.70
CP patients at 6 weeks	1.12 ±0.34	0.89 ±0.68	1.45 ±0.47	1.34 ±0.97	1.76 ±1.27
Healthy participants vs. CP patients	T= –15.73	T = –19.238	T = –18.454	–	–
	p = 0.000**	*p* = 0.000**	*p* = 0.000**	–	–
CP patients vs. CP patients 6 weeks after NSPT	T = 13.647	T = 19.423	T = 14.854	T = 7.744	T = 9.237
	p = 0.000**	*p* = 0.000**	*p* = 0.000**	*p* = 0.000**	*p* = 0.000**
Healthy participants vs. CP patients 6 weeks after NSPT	T = –3.286	T = –2.101	T = –6.550	–	–
	p = 0.002**	*p* = 0.040*	*p* = 0.000**	–	–

GI – gingival index; OHI-S – oral hygiene index simplified; SBI – sulcus bleeding index; PPD – pocket probing depth; CAL – clinical attachment loss; * statistically significant ($p < 0.05$); ** highly statistically significant ($p < 0.01$).

Table 6. Correlation between the salivary levels of expression of omentin-1 and the clinical parameters in both groups (Pearson's test)

Group	Parameter	GI	OHI-S	BoP	PPD	CAL
Healthy participants	salivary omentin-1	0.295	–0.028	–0.058	–	–
CP patients at baseline		0.225	–0.196	0.258	–0.035	–0.118
CP patients 6 weeks after NSPT		–0.016	–0.099	0.115	0.078	–0.190

BoP – bleeding on probing; $r < 0.2$ – slight correlation, negligible relationship; $r = 0.2–0.4$ – low correlation, weak relationship; $r = 0.4–0.7$ – moderate correlation, substantial relationship; $r = 0.7–0.9$ – high correlation, marked relationship.

Discussion

The present study was undertaken to evaluate, compare and correlate the levels of salivary omentin-1 with the severity of periodontal disease as assessed by clinical parameters in healthy participants and CP patients at baseline and 6 weeks after NSPT.

The mean age of the healthy participants (38.37 ±8.45 years) was lower than that of CP patients (40.60 ±10.25 years; Table 1); however, this difference was not statistically significant. This finding is in accordance with previous studies conducted by Dogan et al.,[1] Balli et al.[15] and Bagwe et al.,[28] which showed no statistically significant age differences among healthy and CP participants (i.e., indicating an equal distribution as per randomization). Statistically significant moderate and negative correlations were observed between age and the expression of omentin-1 (gingival crevicular fluid (GCF); $p < 0.05$) in the CP group 6 weeks after NSPT, which suggests that the expression of omentin-1 decreases with age (Table 4). This finding is in line with the study by Bagwe et al.,[28] which showed higher levels of omentin-1 in healthy and older age group individuals. Decreased levels of omentin-1 may be supported by the fact that greater numbers of individuals with diabetes or rheumatoid arthritis are in the age groups of 41–59 years[29,30] and 51–69 years,[31] respectively, which suggests that the downregulation occurs in aged individuals due to other physiological conditions along with CP.

There was no notable difference in the gender distribution (23 female and 37 male participants; Table 2) in our study, indicating that there was no considerable variation in distribution as per randomization in both groups. Comparisons of omentin-1 expression across gender (Table 5) showed highly significant differences among males and females in the healthy group, with higher omentin-1 levels seen in females. In contrast, higher values were observed in males than females in both the CP at baseline and CP 6 weeks after NSPT groups; however, these values were not statistically significant. To the best of our knowledge, there are no direct studies available in periodontal literature to compare with our results. These findings are in accordance with Luque-Ramírez et al.,[32] who studied sexual differences in the circulating levels of adipokines that were caused by the differential effects of sex hormones on adipose tissue. Along with de Souza Batista et al.[33] who studied levels of plasma omentin-1 and gene expression in obesity, they found higher plasma omentin-1 levels in lean women than in lean men.

The GI, OHI-S, BoP, PPD, and CAL represent measures of the severity of the inflammatory burden within the gingival tissues and are indicative of periodontal diseases.[34,35] In the present study, we found significantly increased scores in all of these clinical parameters (GI: 2.27 ± 0.45, OHI-S: 4.13 ±0.98, SBI: 3.21 ±0.68, PPD: 3.04 ±1.87 mm, CAL: 3.35 ±1.70 mm). Also, intergroup comparisons showed statistically significant differences in the clinical parameters between healthy participants, CP patients at baseline, and CP patients at 6 weeks after NSPT (Table 3). These results are consistent with a study by Sato et al.,[36] which showed higher scores in clinical parameters that could have been the result of the elimination of local etiological factors and reduced inflammation by NSPT.

The present study showed significantly higher levels of salivary omentin-1 in healthy participants (95.80 ±26.65 pg/mL) than in CP patients at baseline (43.10 ±23.47 pg/mL). These findings are similar to the results reported by Bagwe et al.[28] who observed increased levels of omentin-1 in GCF and serum. A study by Sarhat et al.[37] also showed higher levels of omentin-1 in the serum of healthy participants as compared to CP patients, thereby suggesting an anti-inflammatory activity for omentin-1. Also, previous studies have shown that insulin and inflammation are closely linked[38]; hence, decreased levels of omentin-1 in CP patients confirm its anti-inflammatory role.

Correlations between salivary omentin-1 levels and clinical parameters in healthy participants (Table 6) showed a slightly positive and negligible relationship with GI, and a slightly negative and negligible relationship with OHI-S and BoP. The values were not statistically significant ($p > 0.05$). Correlations of salivary omentin-1 levels with clinical parameters in CP participants at baseline showed a slightly positive and negligible relationship with GI and BoP, and a slightly negative and negligible relationship with OHI-S, PPD and CAL. These results were also statistically non-significant. The results for both healthy participants and CP patients at baseline were in contrast to the studies by Dogan et al.[1] and Balli et al.,[15] which showed statistically significant and negative correlations with CAL and GI, suggesting an improvement in the periodontal health condition. Correlations of omentin-1 lev-

els with clinical parameters in CP patients at 6 weeks after NSPT showed a slightly positive and negligible relationship with BoP and PPD, and slightly negative and negligible relationships with GI, OHI-S and CAL. The values were not statistically significant. The weak correlations between the levels of omentin-1 and clinical parameters suggest that a larger sample size is required for a more precise and accurate assessment of the relationship between both variables.

Limitations

This research involved certain limitations, such as a smaller sample size and short duration of the study. The smaller sample size and various other differences, such as race and population variations, do not allow these findings to be generalized to the entire population. Therefore, further long-term clinical investigations using a larger sample size, multiple centers and various races are required to confirm our findings.

Future perspectives

The results of our study suggest that salivary omentin-1 levels can serve as reliable biomarkers for the diagnosis and prognosis of periodontal disease, as well as the assessment of treatment outcomes. The levels of omentin-1 decline in various pathological conditions. Thus, appropriate steps taken to maintain its adequate levels, such as weight loss,[39] an olive oil-rich diet[40] or aerobic training,[41] may guarantee a long and healthy life. Treatment with atorvastatin and certain anti-diabetic drugs, such as metformin or pioglitazone, is also effective at increasing endogenous omentin-1 levels by improving insulin sensitivity.

These results may contribute to the development of omentin-1-based medicines, such as omentin-1 analogs and omentin-1 receptor agonists, to combat various inflammatory conditions, including periodontitis and metabolic disorders.

Conclusions

The present research evaluated the effects of NSPT on the levels of salivary omentin-1 in periodontally healthy participants and CP patients. Within the constraints of this study, it can be stated that lower salivary omentin-1 levels were identified in CP patients. They were associated with increased levels of periodontal parameters. Higher salivary omentin-1 levels after NSPT were also concomitant with an improvement in the patient's periodontal health status. Taken together, it may be concluded that omentin-1 has an anti-inflammatory role in periodontitis, and its expression may have a potential role in the immunopathogenesis of CP. Hence, omentin-1 can serve as a biomarker for the early detection and diagnosis of periodontitis, which helps in meticulous treatment planning and the development of proper therapeutic modalities that not only enhance the maintenance of periodontal health, but also improve overall systemic well-being.

Ethics approval and consent to participate

The present study was approved by the institutional Review Board of the P.M. Nadagouda Memorial Dental College and Hospital, Bagalkot, India (approval No. PMNMDCH/1534/2018-19). Written informed consent was obtained from all participants.

Data availability

All data generated and/or analyzed during this study is included in this published article.

Consent for publication

Not applicable.

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Original paper

Oral health-related quality of life (OHRQoL) in Polish adults with periodontal diseases, oral mucosal diseases and dental caries

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):573–581

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on November 25, 2021
Reviewed on January 22, 2022
Accepted on January 27, 2022

Published online on December 30, 2022

Cite as
K. Wąsacz, M. Chomyszyn-Gajewska, D. Hukowska. Oral health-related quality of life (OHRQoL) in Polish adults with periodontal diseases, oral mucosal diseases and dental caries. *Dent Med Probl.* 2022;59(4):573–581. doi:10.17219/dmp/146195

DOI
10.17219/dmp/146195

Abstract

Background. With the development of medicine and extending the human lifespan, the next challenge for healthcare providers is to improve the quality of life. Oral Health Impact Profile (OHIP) is a worldwide known questionnaire that is used for assessing oral health-related quality of life (OHRQoL).

Objectives. The aim of the present study was to assess the impact of periodontal diseases, oral mucosal lesions and dental caries on OHRQoL among Polish adults.

Material and methods. A cross-sectional study consisting of an intraoral clinical examination and a questionnaire was conducted among 250 adult patients seeking dental treatment at the University Dental Clinic (UDC) in Cracow, Poland. The obtained clinical data included the number of decayed, filled and missing teeth (DMFT), the presence of fixed or removable dental prostheses, the type and size of oral mucosal diseases, periodontal data based on a visual examination as well as the approximal plaque index (API) and modified sulcus bleeding index (mSBI) scores, and the patient's dental history. A modified OHIP questionnaire was used, which had been previously validated amongst patients with periodontal and oral mucosal diseases.

Results. In patients reporting problems with oral mucosa, the OHIP-14 scores in relation to oral mucosa and other soft tissues were higher, and the scores in relation to the teeth were lower than in patients who did not suffer from oral mucosal diseases (0.86 (0.25–1.81) vs. 0.29 (0–1.00); $p < 0.001$, and 0.39 (0.07–1.07) vs. 0.68 (0.29–1.29); $p = 0.048$, respectively). Among patients looking for treatment due to caries and other dental problems, the OHIP-14 scores relating to dentures were higher and the scores relating to oral mucosa were lower than in patients who did not report such problems (2.07 (0.96–2.15) vs. 0.64 (0–1.38); $p = 0.043$, and 0.14 (0–0.56) vs. 0.57 (0.14–1.31); $p = 0.001$, respectively). Among patients noticing prosthetic problems, the OHIP-14 scores relating to dentures were higher than in those who did not suffer from such issues (2.07 (1.23–2.36) vs. 0.64 (0–1.36); $p = 0.004$).

Conclusions. The symptoms reported by patients with periodontal diseases, oral mucosal lesions and dental caries influenced their OHRQoL. The proper prophylaxis and treatment of these diseases are important to avoid the worsening of OHRQoL.

Keywords: periodontal diseases, oral mucosal diseases, caries, OHIP-14, OHRQoL

Introduction

With the development of medicine and technology, leading to the extension of the human lifespan, the subsequent challenges for healthcare providers in dentistry are to advance diagnostic processes and consider patient well-being. Medical and dental history, a clinical examination, and additional diagnostic tests (e.g., radiography, cone-beam computed tomography (CBCT), ultrasound imaging, and dental photography) allow the dentist to make an adequate diagnosis and plan alternative treatment options.[1–3] Furthermore, simulating the possible treatment outcomes may be advantageous for patient psychological well-being[4] and may improve patient–dentist communication. It is particularly important for dentists to consider the development of technologies and devices in each field of dentistry. The use of modern appliances may help to reduce the dose of radiation emitted during the examination and decrease the biological risk related to ionizing radiation.[5] The development of non-invasive diagnostic methods, such as ultrasonography (USG), can also help to minimize biological risk to the patient. Owing to scientific progress, it has become possible to overcome the existing limitations of some examinations, and new indications for their use have emerged. Ultrasonography seems to be the best tool for use in the differential diagnosis of bone lesions, such as periapical lesions or tumors,[6–8] and may be useful in planning periodontal and peri-implant surgeries, or for evaluating the stability of tissues after such procedures.[5,9,10] Furthermore, USG may be an additional tool for the examination of disc displacements in the temporomandibular joint (TMJ).[11] The gold standard examination with regard to a disc displacement in TMJ and its differentiation from other diseases, such as coronoid process hypertrophy,[12] is magnetic resonance imaging (MRI),[13] which is also radiation-free.

In diagnostic and therapeutic processes, the patient's individual expectations and experience should be taken into consideration in order to respect their well-being. Oral health-related quality of life (OHRQoL) is a complex and multidimensional concept describing the influence of the oral cavity condition on an individual's well-being and quality of life. To assess OHRQoL properly, it is necessary to use tools developed and validated for a specific population, with regard to its age, native language and diseases. Until now, many such questionnaires in many language versions have been developed for use in children (e.g., Early Childhood Oral Health Impact Scale (ECOHIS),[14–17] Child Perceptions Questionnaire (CPQ)[18–20]), adolescents (Oral Impact on Daily Performance (OIDP)[21,22]) and adults (Oral Health Impact Profile (OHIP),[23] Geriatric Oral Health Assessment Index (GOHAI),[24,25] Liverpool Oral Rehabilitation Questionnaire (LORQ),[26] the World Health Organization Quality of Life (WHOQOL) assessment tool[27]).

The OHIP is a worldwide known questionnaire used for assessing OHRQoL. It was developed and validated in 1994 by Slade and Spencer to investigate the social impact of oral disorders on well-being.[23] Initially, the questionnaire consisted of 49 items (OHIP-49), but to facilitate its usage in clinical settings, Slade created a shortened version (OHIP-14) that has been shown to be as reliable as the primary form.[28] The OHIP-14 captures 7 dimensions that have affected people's life and health over the previous 12 months. This includes functional limitations, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap.[28] Each dimension is determined by 2 items (yes/no); for example, it may ask participants if they have had any trouble pronouncing any words because of problems with their teeth, mouth or dentures.

To adapt the OHIP questionnaire to other populations, the original English version was translated into other languages, including Polish,[29] Spanish,[30] Greek,[31] Turkish,[32] and Korean,[33] adapted and validated.

Until now, the link between many specific oral disorders, such as caries,[34–38] oral mucosal diseases,[39–47] periodontal diseases,[36,48–55] tooth wear,[56,57] tooth loss,[58,59] and temporomandibular disorders (TMD)[60,61], and general diseases, including diabetes,[51,53] rheumatic diseases,[62] leukemia,[63] and renal diseases,[64] and OHRQoL has been thoroughly researched among adults.

The aim of this study was to appraise the impact of periodontal diseases, oral mucosal lesions and dental caries on OHRQoL among Polish adults looking for treatment at a specialized university clinic.

Material and methods

A cross-sectional study was conducted on 250 adult patients seeking dental treatment at the Department of Periodontology, Dental Prophylaxis and Oral Pathology of the University Dental Clinic (UDC) in Cracow, Warsaw. Ethical approval was obtained from the Ethics Committee of the Jagiellonian University Medical College in Cracow (No. 122.6120.354.2016). The patients were given detailed information on the study and informed written consent was obtained from each of the enrolled participants. The exclusion criteria were as follows: under 18 years of age; and the lack of consent for participation in the study.

Data was collected by conducting an intraoral clinical examination and a questionnaire survey. Clinical data was obtained through an examination conducted by one dentist, using artificial light, a dental mirror and a WHO periodontal probe. The obtained data included the number of decayed, filled and missing (due to any reason, excluding third molars) teeth (DMFT), the presence of fixed or removable dental prostheses, the type and size of oral mucosal diseases, periodontal data based on a visual examination as well as the approximal plaque index (API) and modified sulcus bleeding index (mSBI) scores, and the patient's dental history. More data was collected from the self-completed quality of life (QoL), OHRQoL and OHIP-14 questionnaires, with the results of the latter being analyzed, and patients were asked about their reasons for visiting the UDC.

Statistical analysis

Data analysis was conducted using the R software, v. 4.1.1 (https://www.r-project.org/).[65] The significance level for all statistical tests was set at 0.05. The Mann–Whitney *U* test was used to compare quantitative and ordinal variables between two groups. The relationship between two quantitative and/or ordinal variables was assessed with Spearman's coefficient of correlation. Quantitative variables were summarized as median (interquartile range) (*Me* (*IQR*)).

Results

A group of 250 patients was enrolled in the study (age: 18–82 years; mean age: 52.16 ±15.85 years; females: 65.2%) (Fig. 1). They all underwent an intraoral clinical examination and self-completed the questionnaire.

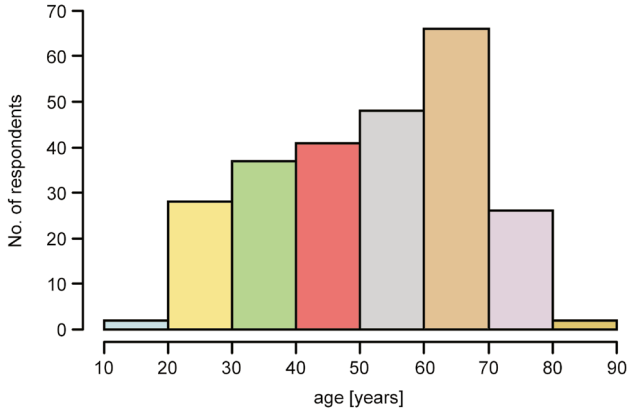

Fig. 1. Age structure of the patients

A modified OHIP-14 questionnaire was used, which had been validated amongst patients with periodontal and oral mucosal diseases and caries.[66] The adjustments involved: 1) asking about all of the items separately in relation to the teeth (subscale 1), oral mucosa and other soft tissues (e.g., gingiva, the tongue) (subscale 2) and dentures (subscale 3); and 2) adding 2 additional answers, i.e., 'I don't know' and 'not applicable'. The changes were implemented to explore detailed OHRQoL and, according to the authors' current knowledge, they had never been used before in studies on the OHIP questionnaire.

The patients were divided into 5 groups depending on their reason for visiting the UDC: group 1 – periodontal diseases (117 (46.8%)); group 2 – oral mucosal diseases (95 (38.0%)); group 3 – caries and other dental problems (33 (13.2%)); group 4 – prosthetic treatment (12 (4.8%)); and group 5 – follow-up (25 (10.0%)) (Fig. 2).

The mean number of missing teeth (due to any reason, excluding third molars) among the respondents was 8.34 ± 8.36, and only 43.7% had all of the missing teeth replaced. The types of prostheses used are shown in Fig. 3.

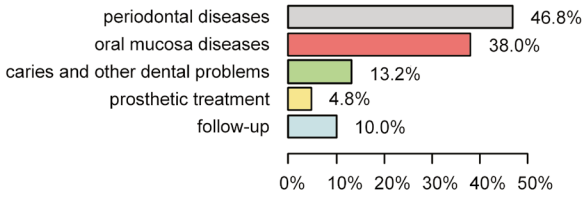

Fig. 2. Reason for visiting the University Dental Clinic (UDC)
Percentages do not sum up to 100%, as each patient could have several reasons for the visit (a multiple-choice question).

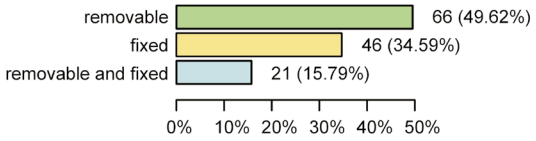

Fig. 3. Prostheses used in the respondents with missing teeth

The OHIP-14 items were rated on a Likert-type scale as never (0), almost never (1), sometimes (2), fairly often (3), or almost all of the time (4). The scale referred to the frequency of the occurrence of the symptoms or problems related to the teeth (subscale 1), oral mucosa (subscale 2), or dentures (subscale 3). The higher the OHIP-14 score was, the worse OHRQoL was assumed.

There was a significantly higher subscale 2 score and a significantly lower subscale 1 score in group 2 than in any other group (0.86 (0.25–1.81) vs. 0.29 (0–1.00); $p < 0.001$, and 0.39 (0.07–1.07) vs. 0.68 (0.29–1.29); $p = 0.048$, respectively (Fig. 4). There was no significant difference in the OHIP-14 scores within subscale 3 between these groups of respondents.

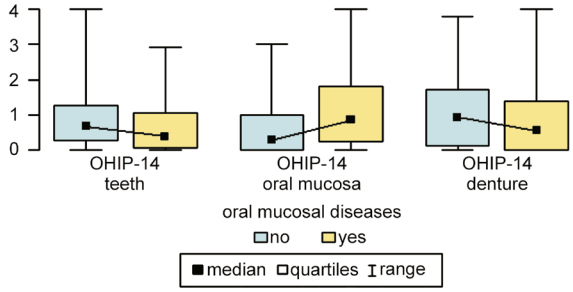

Fig. 4. Modified Oral Health Impact Profile (OHIP-14) scores in the group of patients reporting oral mucosal diseases vs. patients without such complaints

Patients suffering from caries and other dental problems (group 3) had a significantly higher OHIP-14 score within subscale 3 and a significantly lower score within subscale 2 as compared to other respondents (2.07 (0.96–2.15) vs. 0.64 (0–1.38); $p = 0.043$, and 0.14 (0–0.56) vs. 0.57 (0.14–1.31); $p = 0.001$) (Fig. 5).

In group 4 (patients looking for prosthetic treatment), the OHIP-14 score within subscale 3 was significantly higher than among other patients (2.07 (1.23–2.36) vs. 0.64 (0–1.36); $p = 0.004$) (Fig. 6).

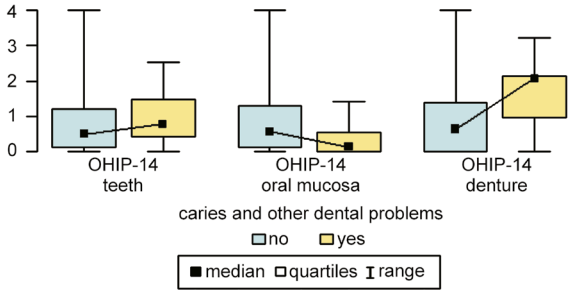

Fig. 5. Modified Oral Health Impact Profile (OHIP-14) scores in the group of patients suffering from caries and other dental problems vs. patients without such complaints

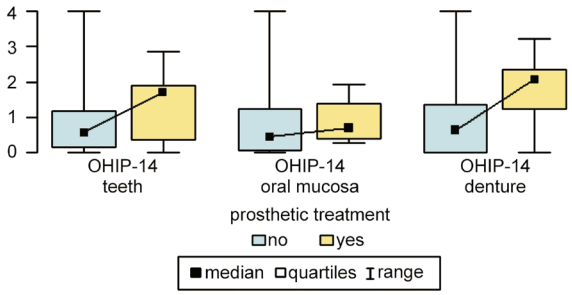

Fig. 6. Modified Oral Health Impact Profile (OHIP-14) in the group of patients looking for prosthetic treatment vs. patients without such needs

In group 1 (patients with periodontal diseases) and group 5 (follow-up), there were no statistically significant differences observed within any subscale in comparison with other participants ($p > 0.05$).

There was a statistically significant ($p < 0.05$) positive correlation ($r > 0$) between the number of missing teeth and the OHIP-14 scores within subscales 2 and 3 (Fig. 7 and Fig. 8).

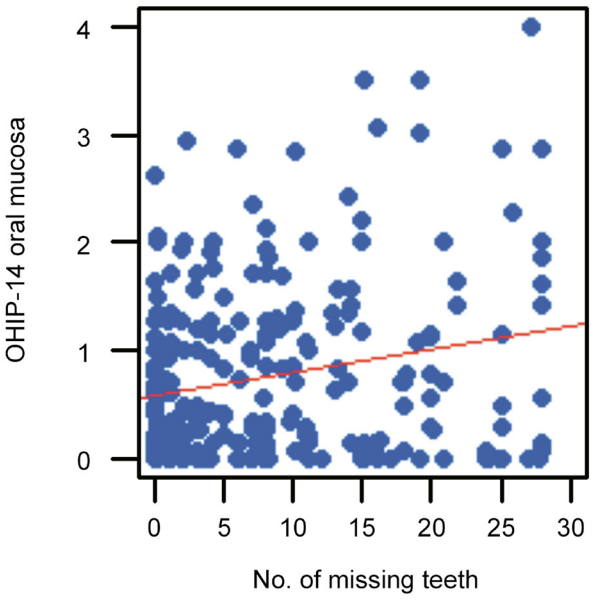

Fig. 7. Correlation between the number of missing teeth and the OHIP-14 score within subscale 2 (oral mucosa)

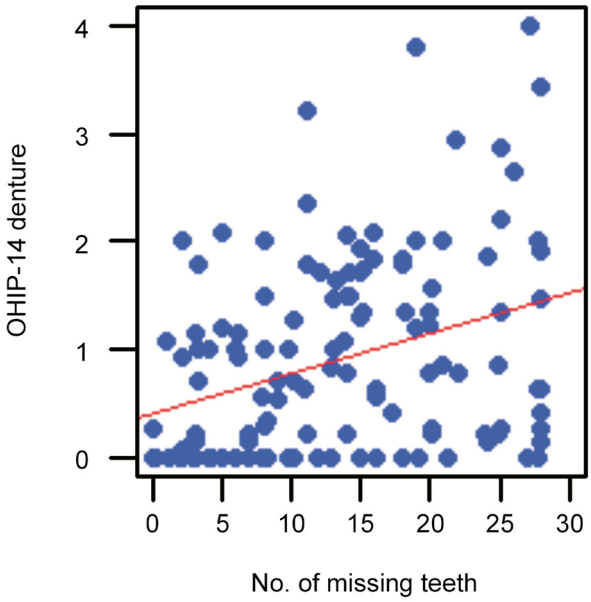

Fig. 8. Correlation between the number of missing teeth and the OHIP-14 score within subscale 3 (denture)

Discussion

The most prevalent oral diseases are dental caries, periodontal diseases, tooth loss (having 9 or fewer teeth),[67] and cancers (of the lips and of the oral cavity).[68] They remain a significant global public health concern and have a serious socio-economic impact.[68,69] This is especially true in low-income and middle-income countries, where the prevalence of these diseases remains high and the financing of oral healthcare is low.[68,70] Untreated oral diseases have many negative consequences on personal life, including suffering from pain, impaired quality of life, school absenteeism, and decreased productivity at work.[68]

Dental caries is a multifactorial disease involving interactions between the hard tissues of the tooth, the biofilms formed on the tooth surface, and sugars that cause tooth demineralization.[71] The disease is conditioned by genes and the salivary flow.[71] It occurs in 60–90% of children and in nearly 100% of adults.[70] Caries may occur in children under 6 years of age, in their deciduous teeth, and is called early childhood caries (ECC).[71,72] In epidemiological studies, the international decayed, missing and filled teeth (DMFT) index is used for assessing caries at the individual and population level.[71] Caries is preventable and the application of preventive measures generates significantly lower costs than the treatment of the disease.[71,73] Such measures include proper oral hygiene (tooth brushing and interdental hygiene), the daily and professional use of fluoride, the reduction of the amount and frequency of sugar intake, saliva stimulation, and the use of antibacterial agents.[71,73,74] Biofilm engineering, through the use of pre- and probiotics, seems to have a long-term anticariogenic effect.[73]

The most common periodontal disease is periodontitis. This is an inflammatory, chronic and multifactorial disease that leads to the destruction of connective tissue and the bone supporting the teeth, and is a result of interactions between host inflammatory immune responses and the bacterial biofilm.[75–77] Untreated periodontal disease leads to bacterial dysbiosis, calculus deposits and periodontal pockets. It may be manifested by bleeding gingiva,[78] tooth mobility and the eventual tooth loss, halitosis, and the worsening of oral and dental esthetics. It all causes functional and social difficulties while biting, chewing and speaking, which eventually worsen OHRQoL[77,79–83] and systemic health.[77,78] By activating inflammatory pathways, periodontitis may influence wellbeing and health during pregnancy, and can lead to complications such as preeclampsia, which is one of the major causes of maternal and perinatal morbidity and mortality,[84] premature delivery, and low birth weight.[85,86] Lipopolysaccharide is one of the most virulent factors of the anaerobic bacterium *Porphyromonas gingivalis* that is present in periodontitis,[87] and it may affect gene expression and diverse cellular processes by increasing the levels of microRNA-155.[85,86] Mahendra et al. suggested that the levels of microRNA-155 could be a genetic diagnostic tool for the rapid identification of preeclampsia.[86]

Studies have shown that generalized forms of periodontitis have a greater impact on OHRQoL than localized[88] and more severe forms.[49,79,89] Oliveira et al. demonstrated that periodontitis had similar effects on OHRQoL to general diseases, such as end-stage renal disease.[89] Other periodontal diseases that negatively affect OHRQoL are gingivitis and gingival recession.[83,90] Most of the patients in this study suffered from chronic forms of periodontitis, which may progress gradually throughout the years. However, unless any exacerbation (e.g., a periodontal abscess) occurs, the patient may not observe any major changes. Of the respondents in this group, 55.3% were continuing treatment, which means that acute complaints had already been mostly treated. The results showed slight differences in the subscale 1 OHIP-14 scores among periodontal patients, but they were not statistically significant ($p = 0.054$).

Systemic diseases, especially those with a pro-inflammatory component (e.g., type 2 diabetes mellitus, cardiovascular diseases), are a risk factor for the initiation and progression of periodontitis.[67,70] Indeed, periodontitis has been declared the 6th most frequent complication of diabetes mellitus.[91] Periodontitis and systemic chronic diseases have the same fundamental risk factors,[78] including tobacco use, poor oral hygiene, and dietary and lifestyle behaviors.[67]

The basis of periodontal therapy is regular home care, and professional subgingival plaque and calculus removal, which is called non-surgical therapy.[92] There may be indications for the use of adjunctive measures to improve periodontal health, such as topical antimicrobial agents, antibiotics, antiseptics, or host-modulating drugs.[92,93] With regard to the latter, a recently conducted systematic review suggests that the topical or systemic administration of melatonin might be useful for the management of periodontitis.[93] Furthermore, non-surgical periodontal treatment improves OHRQoL by reducing pain, psychological discomfort and physical disability.[55,94]

Tooth loss is a serious impairment that causes functional problems while eating, and thus deterioration in OHRQoL.[95] Comparing studies conducted in the 1980s and 1990s with the current work, there is a positive trend showing a reduction of edentulism in the Danish population (17.7% vs. 3.4%).[96] However, these values remain much higher in developing countries, where dental healthcare is limited to emergency care.[70] Tooth loss may be a consequence of caries or a periodontal disease.[70] Therefore, access to dental healthcare, regular dental visits, and patient education about disease prophylaxis and their compliance are some of the factors that can reduce the risk of tooth loss.

Nowadays, and particularly following the coronavirus disease 2019 (COVID-19) pandemic, telemedicine is rapidly developing, enabling patients to keep in contact with healthcare workers. This allows the detection of the early symptoms of the disease or the worsening of the health condition.[97] Social media are widely used, especially by younger people, and they may prove advantageous to develop appropriate and valuable health content on such platforms, and thus to broaden patient knowledge about prophylaxis and the proper treatment of oral and general diseases.[98,99]

Oral mucosal diseases comprise many disorders, such as oral leukoplakia (OL), oral erythroplakia (OE), burning mouth syndrome (BMS), oral lichen planus (OLP), oral submucous fibrosis (OSF), xerostomia, candidiasis, Sjögren's syndrome (SS), recurrent aphthous stomatitis (RAS), and autoimmune bullous diseases. Some of them (OL, OE, OLP, OSF, and oral epithelial dysplasia) are considered as potentially premalignant oral epithelial lesions (PPOELs)[100] or oral potentially malignant disorders (OPMDs),[101] of which leukoplakia is the most frequently occurring.[70] The rate of their malignant transformation to oral squamous cell carcinoma (OSCC) varies depending on the type and site of the lesion, and it is the highest for OE, with an average of 26.3% (ranging from 14.3% to 50.0%).[102] It is important to emphasize that prevention, early detection and treatment may halt malignant transformation to OSCC.[100,103] The main risk factors for developing OPMDs and their malignant transformation are tobacco and alcohol use. Depending on the type of disease, its severity and course (active or inactive), the reported symptoms may be more painful for the patient,[39,104] may have a social impact[42] or may reduce the secretion of saliva, as observed in SS,[105] all of which eventually worsen OHRQoL.[39,41] The proper treatment of these complaints may decrease pain and anxiety, and

improve OHRQoL.[106,107] In this cross-sectional study, the OHRQoL of the group of patients with oral mucosal diseases was most influenced by their oral mucosal disease. In other patients, OHRQoL was affected to a greater degree by the condition of their teeth. This means that oral mucosal diseases are perceived by patients as much more serious and that they may affect their life in multiple ways.

In patients looking for restorative or prosthetic treatment, the use of dentures significantly worsened OHRQoL. In this study, almost half of the patients were using removable prostheses and 34.59% had only fixed dentures. The UDC is a specialized clinic in which most patients are treated within the National Healthcare Fund, which only refunds acrylic dentures. Nonetheless, prosthetic treatment improves OHRQoL regardless of the treatment used.[108] Fixed tooth-supported dentures are set on the teeth, which need appropriate preparation, so it is important to properly assess the condition of the teeth before prosthetic treatment to avoid complications and failures. A significant advantage of such an approach is the reduction of prosthesis extension and the preservation of bone volume. Removable dental prostheses are supported on crowns (e.g., cast partial dentures, overdentures[109]). They can be carefully cleaned outside the mouth and can have teeth added. This may be important for older people with decreased fine motor skills, or for periodontal patients, in whom the risk of tooth loss is greater.[110,111] With the use of removable dental prostheses, financial constraints may be overcome; the dentures may also be used as temporary ones.[111] Another treatment option are implant-supported fixed or removable prostheses, which expand the prosthetic treatment opportunities. A proper surgical technique and the presence of an implant in the bone may influence bone volume in the short and long term.[112] Before prosthetic treatment, all indications, contraindications and patient expectations need to be considered.

Yoshimoto et al. reported a strong association between OHRQoL and masticatory satisfaction (defined as the ability to eat comfortably) among individuals using removable partial dentures,[113] whereas Inoue et al. claimed that the quality of removable dentures (stability and esthetics) had a minimal effect on the OHIP score.[114] On the contrary, according to Kurosaki et al., only implant-supported fixed dentures improved OHRQoL 6 years after prosthetic treatment, and there was no significant improvement in patients wearing fixed or removable partial dentures.[115] Meanwhile, according to Ali et al., both tooth- and implant-supported fixed prostheses positively affected OHRQoL in the short and long term.[116]

In this cross-sectional study, there was a significant positive correlation between the number of missing teeth and impact on OHRQoL in relation to oral mucosa and dentures. This means that the greater the number of lost teeth, the greater the problems for the patients referred regarding their oral mucosal disease and denture use, and the greater the necessity for a dental visit.

Conclusions

To prevent the worsening of OHRQoL, the proper prophylaxis of caries and its complications (pain, tooth destruction and extraction) is very important. It delays any need for prosthetic treatment. Proper patient education, prophylaxis and treatment of oral mucosal diseases and periodontal diseases are crucial for the preservation of OHRQoL.

Ethics approval and consent to participate

The present research was approved by the Ethics Committee of the Jagiellonian University Medical College in Cracow, Poland (No. 122.6120.354.2016). Informed written consent was obtained from all the participants.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Original paper

Evaluation of rapid versus slow maxillary expansion in early adolescent patients with skeletal maxillary constriction using cone-beam computed tomography: A short-term follow-up randomized controlled trial

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):583–591

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Funding sources
University of Damascus Postgraduate Research Budget (ref. No. 86754287781DAN).

Conflict of interest
None declared

Acknowledgements
None declared

Received on September 12, 2020
Reviewed on January 1, 2021
Accepted on February 20, 2021

Published online on September 15, 2022

Abstract

Background. Maxillary expansion is one of the treatment options for the correction of the skeletal constriction of the upper jaw. However, evidence regarding the best treatment effects with the use of rapid vs. slow maxillary expansion in the early adolescence period (i.e., between the age of 12 and 16 years) is still lacking in the available literature.

Objectives. The aim of the present study was to investigate the effectiveness of rapid and slow maxillary expansion in treating posterior skeletal constriction, and to compare the 2 techniques in terms of skeletal and dentoalveolar changes by using cone-beam computed tomography (CBCT).

Material and methods. The sample consisted of 34 patients (15 males and 19 females) suffering from posterior skeletal constriction. They were randomly allocated either to the rapid maxillary expansion (RME) group (17 patients aged 13.76 ±0.32 years) or to the slow maxillary expansion (SME) group (17 patients aged 14.02 ±0.28 years). The skeletal and dental landmarks, and changes in the posterior dimensions were examined using CBCT radiographs at the beginning of treatment (T1) and at the end of the observation period (T2).

Results. There were no significant differences between the 2 groups in terms of skeletal and dental changes except the amount of change in the inter-premolar width at the root apex, which was greater in the SME group ($p = 0.007$), as well as the amount of change in the skeletal palatal width in the molar region, which was also greater in the SME group ($p = 0.008$).

Conclusions. Both maxillary expansion protocols were effective in treating posterior skeletal constriction. The average changes in the skeletal and dental widths were generally similar in both groups. Therefore, SME can be considered as an alternative to RME in patients with skeletal maxillary constriction in the early adolescence period.

Keywords: cone-beam computed tomography, maxilla, palatal expansion technique, constriction

Cite as
Rabah N, Al-Ibrahim HM, Hajeer MY, Ajaj MA. Evaluation of rapid versus slow maxillary expansion in early adolescent patients with skeletal maxillary constriction using cone-beam computed tomography: A short-term follow-up randomized controlled trial. *Dent Med Probl.* 2022;59(4):583–591. doi:10.17219/dmp/133513

DOI
10.17219/dmp/133513

Introduction

Maxillary constriction is a common orthodontic problem, which can be found at any age.[1] It appears clinically as maxillary constriction accompanied by the presence or absence of dental crowding.[1,2] Maxillary expansion is the first treatment option for this skeletal defect of the upper jaw.[1] There are many types of maxillary expansion, depending on the applied force and the number of expansion times: rapid maxillary expansion (RME); semi-rapid maxillary expansion (SRME); and slow maxillary expansion (SME).[1] Maxillary expansion consists in increasing the width of the jaw by opening the palatal suture.[1,2] In cases where palatal suture fusion is encountered, surgically-assisted rapid maxillary expansion (SARME) can be used, and this method is considered an appropriate alternative solution for adult patients.[3,4]

Rapid maxillary expansion is based on a major and intermittent force system that leads to the dentoalveolar tipping of the posterior teeth.[5] It has recently taken priority as a treatment option for the skeletal posterior cross-bite.[2] Nevertheless, numerous side effects have been reported for this procedure, such as pain, relapse, molar inclination, bone loss, gingival recession, and root absorption.[6] On the contrary, SME is associated with less resistance of the skeletal structures and better bone formation within the median palatal suture, thereby mitigating the side effects of RME.[6]

Both RME and SME are considered treatment options available to growing patients between the age of 9 and 12 years.[2] Some researchers have supported the use of RME in the early mixed-dentition period.[7,8] Several studies have been conducted to compare RME and SME in the late mixed-dentition period, and most of them have found that both types of expansion bring similar results.[2,9] On the other hand, the choice of the expansion protocol in older age is more difficult, taking into account midpalatal suture ossification.[2] The availability of modern computerized tomography systems, which provide high accuracy with minimum radiation exposure, has enabled a thorough analysis of the maxillofacial complex components, as well as precise linear and angular measurements.[2,10] Several studies have compared RME and SME in early childhood, i.e., between the age of 6 and 9 years.[9,11] Other studies have compared the 2 types of expansion in the late mixed-dentition period, i.e., at the age of 9–12 years.[5,12] After the radiological assessment of patients aged 9–12 years, Martina et al. found that RME was similar to SME with regard to skeletal and dental measurements.[5] Their results indicated the advantage of SME over RME, as the complications of RME could be avoided.[5] However, no previously published research has attempted to study the feasibility and effectiveness of RME in comparison with SME in the early adolescence period, i.e., the early permanent-dentition period.

Therefore, this trial aimed to compare the transverse skeletal and dental changes following RME and SME in early adolescent patients (i.e., between the age of 12 and 16 years) by using cone-beam computed tomography (CBCT) imaging.

Material and methods

Study design and registration

This study was a single-center randomized controlled trial with a two-arm parallel-group design, comparing RME and SME in early adolescent patients. Patients attending the Department of Orthodontics at the Dental School of the University of Damascus, Syria, between July 2017 and June 2018 were screened for inclusion. The study was approved by the institutional Research Ethics Committee at the University of Damascus (UDDS-2675-15,032,017/SRC-4771). The trial was retrospectively registered at ClinicalTrials.gov (ID: NCT03667508).

Sample size calculation

The sample size was determined using Minitab®, v. 17 (Minitab, State College, USA), assuming a 2-millimeter difference in the maxillary basal width between the 2 groups (RME and SME) as clinically significant. The variability of this measurement was about 2.2 mm in a previously published study.[5] Using the independent-samples *t* tests with a significance level of 5% and a power of 80%, 16 patients were required in each group. One patient was added to each group to avoid any potential attrition, bringing the total number in each group to 17 patients.

Patients' recruitment and eligibility criteria

After examining 97 patients attending the Department of Orthodontics, 45 patients met the inclusion criteria and the research project was explained to them. From among the 40 patients who agreed to participate in the study, 34 (15 males and 19 females) were randomly selected (Fig. 1).

Information sheets were given to all patients and informed consent forms were collected upon approval. The inclusion criteria were as follows: patients in the early permanent-dentition period; chronological age between 12 and 16 years; presence of a functional unilateral posterior cross-bite (with a functional shift) or a bilateral posterior cross-bite (without any functional shift); bilateral upper jaw constriction (symmetric constriction) assessed clinically, and then confirmed radiographically; dental and skeletal class I and II malocclusion; normal and mild vertical

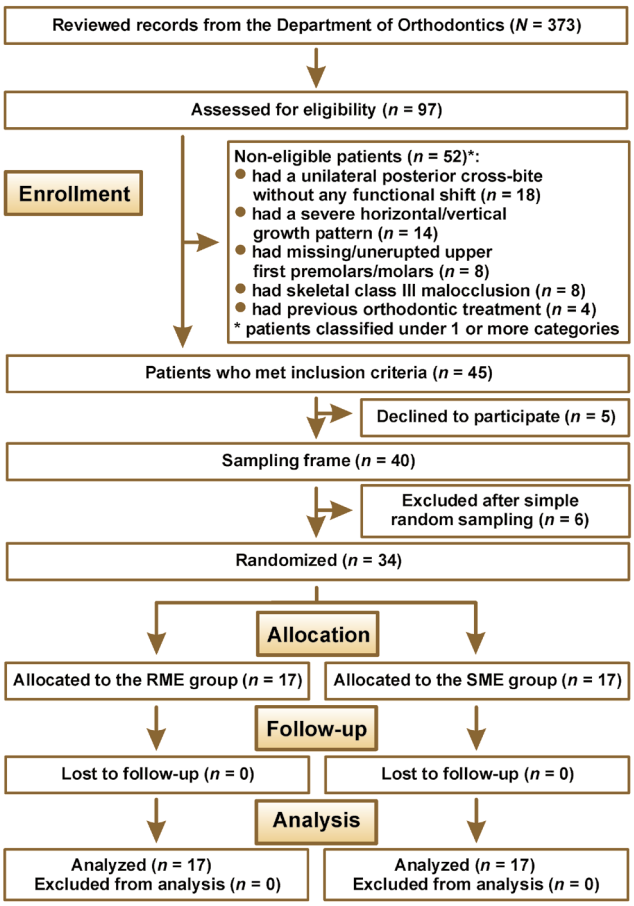

Fig. 1. Flow chart of patients' recruitment, follow-up and entry to data analysis
RME – rapid maxillary expansion; SME – slow maxillary expansion.

growth pattern; no general health problems; and good oral health. The exclusion criteria were as follows: presence of periodontal diseases; presence of general diseases, syndromes or cleft lip and palate; presence of a unilateral posterior cross-bite without any functional shift; severe horizontal/vertical growth pattern; missing/unerupted upper first premolars/molars; skeletal class III malocclusion; and previous orthodontic treatment.

Randomization, allocation concealment and blinding

The patients were distributed between the 2 groups using a list of random numbers generated by the Minitab software, with an allocation ratio of 1:1. The 34 patients were distributed randomly into 2 groups: the RME group (n = 17); and the SME group (n = 17). The allocation sequence was hidden by using opaque sealed envelopes. The blinding of patients and practitioners was not viable. Thus, blinding was used only for data analysis. The 1st group received RME, whereas the 2nd group received SME (Fig. 1). One of the academic staff members, not contributory to this study, was responsible for the generation of the random allocation sequence and the insertion of the participants into the 2 groups.

RME group and the activation protocol

The RME expander used in the current study was a modified Hyrax bonded rapid palatal expander with occlusal splints. Bonding was accomplished by using a conventional glass-ionomer cement (GIC) (Ketac™ Cem; 3M ESPE, Seefeld, Germany) on first premolars and first molars (Fig. 2A). The patient activated the expander twice daily (these 2 movements produced half of a full screw turn, equivalent to 0.4 mm),[13] until an overcorrection of maxillary constriction of approx. 2–3 mm was obtained.[14] The expander was left in its place for 3 months as a retention period,[15] and then, after removing the appliance, a CBCT image was taken.

SME group and the activation protocol

The SME expander used in the current study was a removable palatal expansion appliance consisting of posterior bite planes and a midline split incorporating 1 expansion screw (Fig. 2B). The patient activated the expander twice weekly,[13] until an overcorrection of maxillary constriction of approx. 2–3 mm was achieved.[14] The expander was left in its place for 1 month as a retention period,[5] and then, after removing the appliance, a CBCT image was taken.

There was no change in either group regarding the treatment procedures. The planned treatment protocol prior to the start of the trial was strictly followed until the end of the treatment follow-up.

CBCT image acquisition and analysis

To ensure the appropriate position of the patient's head, it was oriented in such a way that the Frankfurt plane was parallel to the horizon. The imaging system SCANORA® 3D (Soredex, Tuusula, Finland) was used (amperage: 12.5 mA; voltage: 90 kV; voxel size: 0.25 × 0.25 × 0.25 mm^3; mean scanning time: 20 s). Two CBCT images were taken

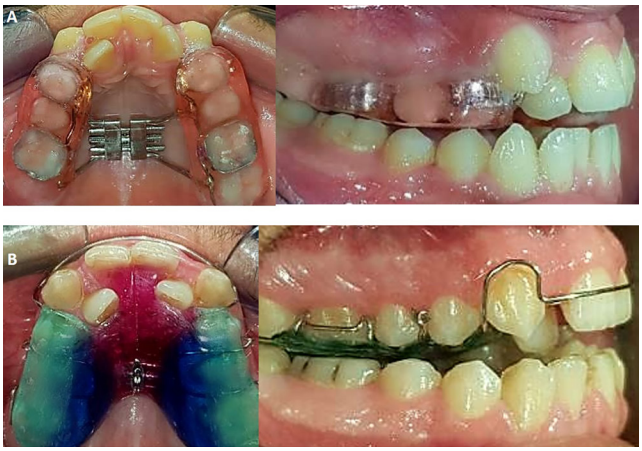

Fig. 2. Expansion appliances
A – bonded McNamara-type Hyrax; B – removable palatal expansion appliance.

at the following time points: before expansion (T1); and 3 months after expansion and the removal of the appliance in the RME group, and 1 month after expansion and the removal of the appliance in the SME group (T2). Eight landmarks were identified on CBCT images: 4 skeletal landmarks (right/left pterygoideous point and right/left piriform point); and 4 dental landmarks (right/left root apex and right/left cusp tip) (Table 1).[5] Four skeletal measurements were made: anterior palatal width; posterior palatal width; palatal width at premolars; and palatal width at molars (Table 1).[5,15] Six dentoalveolar measurements were made: inter-premolar width at the root apex; inter-premolar width at the cusp tip; inferred premolar tipping; molar width at the level of apices; molar width at the level of cusps; and inferred molar tipping (Table 1).[5] Figures 3 and 4 demonstrate the landmarks and measurements used. The definitions were derived from studies by Martina et al.[5] and Lin et al.[15] Both 'inferred' premolar and molar tipping measurements were given in millimeters (i.e., they were linear measurements), although they indirectly represented the amount of change in the buccolingual inclination of premolars and molars.[5]

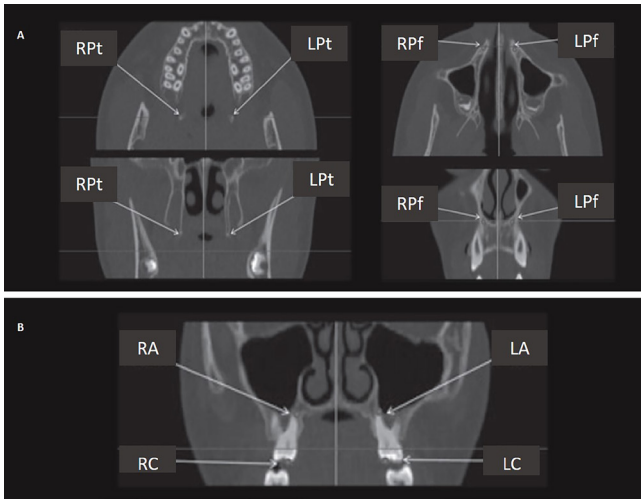

Fig. 3. Landmarks determined on cone-beam computed tomography (CBCT) images

A – skeletal landmarks: Pt – pterygoideous point (RPt – right side/LPt – left side); Pf – piriform point (RPf – right side/LPf – left side); B – dental landmarks: A – root apex (RA – right side/LA – left side); C – cusp tip (RC – right side/LC – left side).

Statistical analysis

Minitab, v.17, was used for data analysis. The normality of the distribution of each variable was checked using the Shapiro–Wilk test. Parametric tests were applied when the data was normally distributed; otherwise, non-parametric tests were employed. The two-sample *t* test or the non-parametric Mann–Whitney *U* test was used to detect significant differences between the 2 groups, whereas the paired-samples *t* tests or the Wilcoxon signed-rank tests were used to detect significant differences within each group.

Table 1. Landmarks and measurements determined on cone-beam computed tomography (CBCT) images

Category	Landmarks/measurements	Definition
Skeletal landmarks	pterygoideous point (Pt)	the most caudal point of the apex of the pterygoid process of the sphenoid*†
	piriform point (Pf)	the most lateral and caudal point of the nasal piriform aperture, at the boundary with the palatal cortex; this landmark was primarily identified in the coronal slices passing through the anterior edge of the nasopalatine foramen within the palatal cortex*†
Dental landmarks	root apex (A)	the apex of the palatal root of maxillary first premolar/molar*†
	cusp tip (C)	the mesio-palatal cusp tip of maxillary first molar/ the palatal cusp tip of maxillary first premolar*†
Skeletal measurements	anterior palatal width (Ant-W)	the anterior skeletal width in the region of the nasopalatine foramen (RPf–LPf)†
	posterior palatal width (Pos-W)	the posterior skeletal width in the region of the pterygoid processes of the sphenoid (RPt–LPt)†
	palatal width at premolars (HPW_P)	the skeletal width in the premolar region at the most inferior level of the hard palate (determined and measured in the coronal plane)‡
	palatal width at molars (HPW_M)	the skeletal width in the molar region at the most inferior level of the hard palate (determined and measured in the coronal plane)‡
Dentoalveolar measurements	inter-premolar width at the root apex (P–PW_apex)	measured between the apices of the palatal roots of maxillary first premolars (RA–LA)†
	inter-premolar width at the cusp tip (P–PW_cusp)	measured between the palatal cusp tips of maxillary first premolars (RC–LC)†
	inferred premolar tipping (P-tip)	the difference between RA–LA and RC–LC (measured in millimeters)†
	molar width at the level of apices (M–M_apex)	measured between the apices of the palatal roots of maxillary first molars (RA–LA)†
	molar width at the level of cusps (M–M_cusp)	measured between the mesio-palatal cusp tips of maxillary first molars (RC–LC)†
	inferred molar tipping (M-tip)	the difference between RA–LA and RC–LC (measured in millimeters)†

* for bilateral landmarks, R is added to the abbreviation to denote the right point and L is added to the abbreviation to denote the left point; † definitions taken from Martina R, Cioffi I, Farella M, et al. Transverse changes determined by rapid and slow maxillary expansion – a low-dose CT-based randomized controlled trial. *Orthod Craniofac Res.* 2012;15(3):159–168 ([5]); ‡ definitions taken from Lin L, Ahn HW, Kim SJ, Moon SC, Kim SH, Nelson G. Tooth-borne vs bone-borne rapid maxillary expanders in late adolescence. *Angle Orthod.* 2015;85(2):253–262 ([15]).

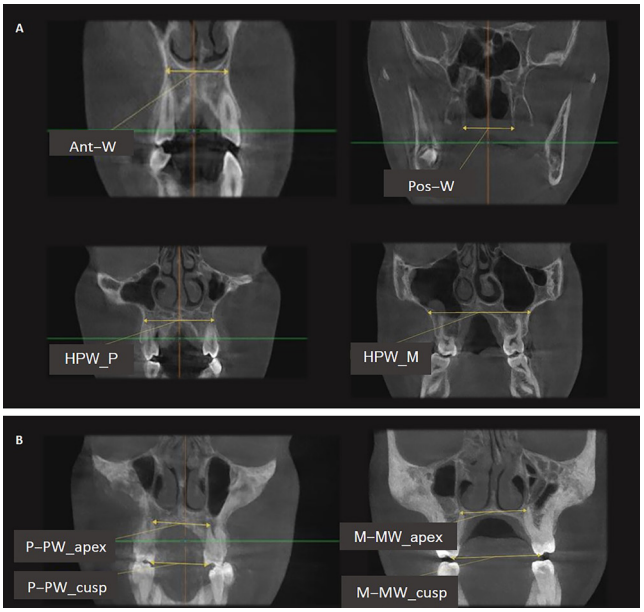

Fig. 4. Measurements determined on cone-beam computed tomography (CBCT) images

A – skeletal measurements: Ant-W – anterior palatal width; Pos-W – posterior palatal width; HPW_P – palatal width at premolars; HPW_M – palatal width at molars; B – dentoalveolar measurements: P–PW_apex – inter-premolar width at the root apex; P–PW_cusp – inter-premolar width at the cusp tip; M–MW_apex – molar width at the level of apices; M–MW_cusp – molar width at the level of cusps.

Error of the method

Ten CBCT images were randomly chosen from the gathered CBCT images using a list of random numbers generated by the Minitab software and they were re-measured at a 1-month interval by the same principal researcher (NR). The intraclass correlation coefficients (*ICCs*) were used to determine the reproducibility of the employed method, i.e., intra-observer reliability (or a random error), whereas the paired *t* tests were used to determine any systematic error.

Results

A total of 34 patients (15 males and 19 females) were enrolled in this trial. The RME group included 17 patients (8 males and 9 females; average age: 13.76 ±0.32 years), whereas the SME group also included 17 patients (7 males and 10 females; average age: 14.02 ±0.28 years), without a statistical difference between the 2 groups regarding gender distribution (p = 0.729). No patient withdrew from the study, and therefore the total number of patients who entered the data analysis stage, in which per-protocol analysis was performed, remained 34 (Fig. 1).

The descriptive statistics of the CBCT-based skeletal and dentoalveolar measurements at the beginning of treatment (T1) and at the end of the observation period (T2) in each group are presented in Table 2.

Changes in the skeletal widths

The anterior skeletal width of the maxilla increased in both groups similarly, without any significant differences between them (1.32 ±1.21 mm and 1.35 ±0.97 mm for the RME and SME groups, respectively; p = 0.926). The posterior skeletal width increased in both groups similarly, without any significant differences between them (0.49 ±0.76 mm and 0.01 ±2.49 mm for the RME and SME groups, respectively; p = 0.444). The skeletal width of the upper jaw in the premolar region increased in both groups similarly, without any significant differences between them (2.08 ±1.87 mm and 2.60 ±2.61 mm for the RME

Table 2. Descriptive statistics of the CBCT-based skeletal and dentoalveolar measurements at the beginning of treatment (T1) and at the end of the observation period (T2) in both groups

Variable	RME						SME					
	T1			T2			T1			T2		
	M ±*SD*	95% *CI*		*M* ±*SD*	95% *CI*		*M* ±*SD*	95% *CI*		*M* ±*SD*	95% *CI*	
		lower bound	upper bound		lower bound	upper bound		lower bound	upper bound		lower bound	upper bound
Ant-W	29.83 ±4.32	27.80	31.90	31.15 ±4.43	29.00	33.30	31.29 ±3.71	29.50	33.00	32.64 ±4.06	30.70	34.60
Pos-W	29.77 ±2.53	28.60	31.00	30.26 ±2.33	29.20	31.40	29.80 ±2.48	28.60	31.00	29.81 ±2.33	28.70	30.90
HPW_P	36.97 ±3.34	35.40	38.60	39.05 ±2.68	37.80	40.30	36.98 ±3.93	35.10	38.80	39.58 ±3.78	37.80	41.40
P–PW_apex	28.84 ±3.29	27.30	30.40	29.24 ±3.61	27.50	31.00	29.75 ±3.14	28.30	31.20	31.91 ±2.67	30.60	33.20
P–PW_cusp	27.47 ±2.73	26.20	28.80	31.59 ±2.51	30.40	32.80	26.99 ±2.73	25.70	28.0	32.12 ±2.90	30.70	33.50
P-tip	–1.37 ±4.55	–3.53	0.79	2.43 ±5.31	–0.09	4.95	–2.76 ±4.22	–4.77	–0.75	0.27 ±3.70	–1.49	2.03
HPW_M	59.91 ±3.75	58.10	61.70	60.45 ±3.72	58.70	62.20	60.74 ±4.68	58.50	6.00	62.07 ±5.11	59.60	64.50
M–MW_apex	29.94 ±4.12	28.00	31.90	31.20 ±4.23	29.20	33.20	30.61 ±2.65	29.30	31.90	32.18 ±3.05	30.70	33.60
M–MW_cusp	35.18 ±2.99	33.80	36.60	40.16 ±2.89	38.80	41.50	35.79 ±3.77	34.00	37.60	42.44 ±3.56	40.80	44.10
M-tip	5.24 ±3.42	3.61	6.87	8.96 ±4.28	6.93	11.00	5.18 ±3.91	3.32	7.04	10.32 ±3.94	8.45	12.20

M – mean; *SD* – standard deviation; *CI* – confidence interval.

and SME groups, respectively; p = 0.511). The skeletal width change of the upper jaw in the molar region at T2 was significantly greater in the SME group as compared to the RME group (1.33 ±1.03 mm and 0.54 ± 0.37 mm, respectively; p = 0.008) (Table 3).

Changes in the dental widths

The dental width change in the premolar region at the level of apices at T2 was significantly greater in the SME group as compared to the RME group (2.16 ±2.32 mm and 0.40 ±0.88 mm, respectively; p = 0.007). No statistically significant differences between the 2 groups were found in the premolar region at the level of cusps, and in the molar region at the levels of apices and cusps (p = 0.243, p = 0.335 and p = 0.062, respectively) (Table 3).

Changes in posterior teeth tipping

The inferred tipping of premolars increased in both groups similarly, without any significant differences between them (3.80 ±2.98 mm and 3.03 ±3.08 mm for the RME and SME groups, respectively; p = 0.461). The inferred tipping of molars increased in both groups similarly, without any significant differences between them (3.72 ±2.49 mm and 5.14 ±2.53 mm for the RME and SME groups, respectively; p = 0.108) (Table 3).

Discussion

The patients included in this study were in the early permanent-dentition period (12–16 years). This age group was chosen after reviewing the medical literature, which confirmed the possibility of the expansion of the median palatal suture in this age range.[16–18] Some authors have obtained successful outcomes using the conventional RME in post-adolescents and young adults up to 25 years old.[19,20] In a recent study by Jimenez-Valdivia et al., it was demonstrated that the chance of having an open midpalatal suture in patients aged 10–15 years, 16–20 years and 21–25 years was 70.8%, 21.2% and 17.0%, respectively.[20] This confirmed that the expansion of the palatal suture could be effectively performed during the early permanent-dentition period (12–16 years).

In the RME group, a modified Hyrax expander was used to take advantage of the presence of posterior acrylic bite planes that prevent or limit the lengthening of the posterior teeth.[21] In the SME group, a removable expander with smooth acrylic posterior bite planes was used; this appliance has been shown to be more comfortable and less painful than fixed appliances.[22,23]

All patients underwent CBCT imaging before expansion and after the retention period. The retention period was necessary to ensure enough time for the midpalatal suture to gain adequate remineralization, as well as to reduce the post-expansion relapse.[15]

In the current study, the posterior cross-bite was effectively treated, with significant increases in most transverse widths in both experimental groups. Transverse skeletal expansion was accomplished in both groups in approximately equal amounts. Resistance to expansion appeared in the region of the pterygoid processes, where the average amount of expansion was minimal (0.49 mm and 0.01 mm for RME and SME, respectively). This change was twice and a half smaller than that noticed in a study by Martina et al., who showed an average increase in the posterior width of 1.2 mm and 0.6 mm for RME and SME, respectively.[5] Differences between their findings and the present ones could be due to different age groups; in the former case, the participants were younger. While RME has been assumed to generate moderate stresses within the cranial base in children (7–11 years), other researchers have claimed that RME would probably create only

Table 3. Descriptive statistics of the changes observed in the CBCT-based measurements in both groups, following expansion and retention

Variable	RME				SME				*p*-value
	MD	*SD*	95% *CI* for difference		*MD*	*SD*	95% *CI* for difference		
			lower bound	upper bound			lower bound	upper bound	
Ant-W	1.32	1.21	0.74	1.90	1.35	0.97	0.88	1.81	0.926
Pos-W	0.49	0.76	0.12	0.85	0.01	2.49	–1.17	1.19	0.444
HPW_P	2.08	1.87	1.19	2.97	2.60	2.61	1.36	3.84	0.511
P–PW_apex	0.40	0.88	–0.00	0.82	2.16	2.32	1.05	3.25	0.007*
P–PW_cusp	4.12	2.06	3.15	5.11	5.13	2.77	3.80	6.44	0.243
P-tip	3.80	2.98	2.38	5.22	3.03	3.08	1.56	4.48	0.461
HPW_M	0.54	0.37	0.37	0.72	1.33	1.03	0.84	1.82	0.008*
M–MW_apex	1.26	0.73	0.91	1.61	1.57	1.09	1.05	2.09	0.335
M–MW_cusp	4.98	2.45	3.82	6.14	6.65	2.59	5.42	7.88	0.062
M-tip	3.72	2.49	2.54	4.90	5.14	2.53	3.94	6.34	0.108

MD – mean difference; * statistically significant (two-sample *t* test).

sprains in the pterygoid processes of the sphenoid bone in older age.[24–26]

Concerning the average increases in the skeletal widths at the premolar and molar levels, and in the anterior and posterior segments in the present study, there were not any significant differences between the experimental groups except for the transverse change at the level of molars, which was greater in the SME group as compared to the RME group (1.33 mm and 0.54 mm, respectively). Although this difference was statistically significant, it can be considered clinically negligible.

The average increases in the skeletal widths in the current study were 2–3 times smaller than those reported in studies by Martina et al.[5] and Lanteri et al.[27] The reason for such differences is probably the younger age of patients in these 2 studies, which could be associated with more efficient bone metabolism and a more active remodeling process.[28] In the current study, the mean changes in the skeletal widths increased gradually from the posterior to anterior regions, which indicated that expansion occurred along the midpalatal suture in a V-shaped pattern in both groups. It is in opposition to the homogenous pattern of expansion noticed in Martina et al.'s study.[5] The difference may be attributed to the different types of devices used. In the current work, the rapid maxillary expander contained acrylic parts that tightly rested on and around the posterior teeth at both the vestibular and palatal sides; besides, the slow maxillary expander included a palatal acrylic plate that had adequate tissue contact and was supported with posterior occlusal acrylic coverage. These acrylic parts may have ensured the delivery of satisfactory force on the teeth and the palate. In contrast, Martina et al. used a two-band palatal expander, which may have applied force on bone rather than on the teeth.[5] Another reason for this difference may be the older age of patients in the present study, which could be accompanied by resistance to expansion in the posterior region more than in the anterior region, giving V-shaped pattern expansion.[20,25]

For dental changes, increases in all dental widths at the level of molars and premolars were noticed, with no statically significant differences between the 2 groups except for the width between the apices of premolars. The mean width change in the premolar region at the level of apices was 0.40 mm in the RME group and 2.16 mm in the SME group. This change was 5.4 times greater in the SME group. This could be explained by a longer period of SME, which may have allowed adequate time for root movement in the buccolingual direction. These amounts of dental changes differed from those reported in 2 previous studies,[29,30] which could be due to variations in the average force applied, the type of device used and the patients' age in each study. Nevertheless, by comparing the mean amounts of dental expansion in the premolar region in the SME group, it was found that the mean increase in width at the level of cusps was 2.4 times greater than at the level of apices (5.13 mm and 2.16 mm, respectively), which meant that a buccal tipping of premolars occurred.

Buccal tipping was a common side effect of using expansion appliances. Both the RME and SME groups showed considerable changes in the tipping amounts. For upper first premolars, the average increase of tipping was a little smaller in the SME group, but the difference between the 2 groups was not statistically significant (3.80 mm and 3.03 mm for the RME and SME groups, respectively). At the same time, the mean values for the tipping changes of upper first molars were 3.72 mm in the RME group and 5.14 mm in the SME group, with no statistically significant difference between the 2 groups (p = 0.108). Similar results were found in studies by Garib et al.[29] and Lin et al.[15] In contrast, the values were lower in studies by Boysen et al.[31] and Erdinç et al.[32] These differences in dental tipping between the studies could be attributed to variations in the average force applied, the strength direction, the thickening of the alveolar bone around the roots, and the nature of the bone.

No critical harm was observed or documented in the current trial. In the RME group, patients experienced some pressure on the alveolar processes of the upper posterior teeth and in the nasal floor region during the active period of expansion, but it was well tolerated in general. In both groups, appliance fractures were found in 1 or more items of the expander during the treatment period in 4 patients (2 appliances in the RME group and 2 appliances in the SME group), which meant that the percentage of fractures was approx. 12% in each group. All fractured appliances were fixed within less than 24 h.

Limitations

Despite adherence to the calculated sample size, the number of patients was relatively small, and it is preferable to increase the number of patients in future research work to get more powerful statistical results. The current two-arm study compared RME with SME, and there was no an untreated control group. If a three-arm study design had been followed, we would have been able to compare the outcomes between the 3 groups by filtering out the growth effects and observing any possible spontaneous improvement of posterior skeletal maxillary constriction. Patients' responses, the levels of discomfort and pain, as well as quality of life should be assessed in future research work. This study did not assess the changes in the dimensions of the upper airways following maxillary expansion, and this aspect should be considered in future clinical trials. From a methodological perspective, the blinding of patients and care providers was not possible due to the nature of the interventions. This might be a source of detection bias. Since the current analysis of maxillary changes referred to a relatively short time, long-term follow-up periods to detect any post-retention relapse should be taken into account in future trials.

Generalization

The results of the current work could not be generalized to other kinds of expanders or the same types of expanders with different activation protocols. Therefore, more future clinical research with a larger number of patients and longer follow-up periods is required.

Conclusions

Slow maxillary expansion can be an effective alternative to RME in the early adolescence period (12–16 years). The average increases in the skeletal and dental widths were approximately similar in both groups except for skeletal expansion at the level of upper molars and dental expansion at the level of the apices of upper premolars, which were greater in the SME group. Furthermore, the buccal tipping of premolars and molars was observed as a side effect in both groups.

Trial registration

The trial was retrospectively registered at ClinicalTrials.gov (ID: NCT03667508).

Ethics approval and consent to participate

The study was approved by the institutional Research Ethics Committee at the University of Damascus, Syria (UDDS-2675-15,032,017/SRC-4771). Written informed consent was obtained from all participants.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Review

Complications post simple exodontia: A systematic review

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):593–601

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
The authors would like to thank the dental student center (DSC), which kindly supported the English edition of the present article.

Received on July 16, 2021
Reviewed on November 29, 2021
Accepted on December 6, 2021

Published online on December 14, 2022

Abstract

Exodontia procedures are not without complications, which are the dentist's responsibility to avoid by taking into account clinical, imaging, systemic, and operative factors, among others. The purpose of this systematic review is to determine and analyze the prevalence of complications post simple exodontia (CPES). The method used in this systematic review was adapted from the Cochrane Handbook and PRISMA statement. A systematic search was conducted in PubMed, Scopus and ScienceDirect using the search terms "Exodontia" AND "Complications". The search was conducted from the starting coverage date to January 31, 2020. The inclusion criteria were studies on simple exodontia, studies on CPES prevalence and human studies. Studies on complications after third molar exodontia, generalities in exodontia, narratives and systematics literature reviews, book chapters, and animal studies were excluded. A total of 1,446 articles were found in the first search using the search strategy (725 in PubMed, 96 in Scopus and 631 in ScienceDirect). After duplicates were removed, 948 articles were obtained. After reading the title and abstract, 9 articles were read in full. Finally, 3 articles were included in the review, with the most common complications being trismus, alveolitis, pain, dehiscence, infections, and retained roots. Trismus of the chewing muscles, alveolitis and retained roots were the most prevalent CPES, which were most likely related to the surgeon's experience, surgery duration and tissue trauma during surgery.

Keywords: exodontia, complication, systematic review, dentoalveolar surgery

Cite as
Herrera-Barraza V, Arroyo-Larrondo S, Fernández-Córdova M, Catricura-Cerna D, Garrido-Urrutia C, Ferrer-Valdivia N. Complications post simple exodontia: A systematic review. *Dent Med Probl.* 2022;59(4):593–601. doi:10.17219/dmp/144596

DOI
10.17219/dmp/144596

Introduction

Exodontia is a common procedure in dental practice; however, it is not without complications. Complications are defined in the literature as "unforeseen events that tend to elevate morbidity above expected" in a surgical procedure, and are usually related to age,[1,2] medical status[3] and harmful patient habits.[4] Complications can be classified as intraoperative and postoperative (post-exodontia),[5] when they occur during and after surgery, respectively. Regarding post-exodontia complications, a wide array is described and they can be classified into infectious, such as surgical wound infection, abscess and necrotizing fasciitis, and non-infectious, such as pain, hemorrhage, edema, alveolitis, paresthesia, communication with the maxillary sinus, temporomandibular disorder, trismus, tissue emphysema, and others.[5–8] These complications can range from mild to fatal[8]; therefore, great care to prevent the complications is essential. In this regard, the dentist can influence factors that affect a successful exodontia and decrease the risk of post-exodontia complications, such as accessibility, vision, patient positioning, correct surgical technique,[9] and complementary imaging examinations such as periapical radiography, orthopantomography,[10] and recently, radiation-free imaging techniques such as magnetic resonance and ultrasound imaging. The latter allows adequate three-dimensional visualization comparable to cone-beam computed tomography (CBCT) and an acceptable determination of the size of periapical lesions.[11,12] Exodontia of the third molar, as well as its complications, have been extensively studied in terms of diagnosis,[13] treatment[14,15] and prevention[16] because it is a highly complex procedure in which the tooth is often included or semi-included,[17] and the procedure requires more instruments and a longer operating time. Because of the above, the scientific literature refers to this type of exodontia as complex or surgical, as opposed to the exodontia of fully erupted teeth, which is referred to as simple or non-surgical exodontia.[9] Regarding the latter, there have been few studies focusing on the prevalence and analysis of complications post simple exodontia (CPES).

The goal of this systematic review was to investigate the reported prevalence of CPES.

Material and methods

Development of the protocol

The method used in this systematic review was adapted from the Cochrane Handbook for Systematics Reviews of Interventions[18] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[19] The following PICO question was used: What is the prevalence of complications post simple exodontia (CPES)? (Table 1).

Table 1. PICO criteria

PICO	Description
Population	patients with indication for exodontia
Intervention	simple exodontia
Control	patients without post-exodontia complications in relation to patients with post-exodontia complications
Outcomes	prevalence of post-exodontia complications

Search strategy

The following search terms were used in the PubMed, ScienceDirect and Scopus databases: "Exodontia" AND "Complication". The search was conducted from the starting coverage date to January 31, 2020.

Inclusion and exclusion criteria

The inclusion criteria for the articles analyzed in this study were studies on simple exodontia, studies on CPES prevalence and human studies. Studies on complications after third molar exodontia, generalities in exodontia, narratives and systematics literature reviews, book chapters, and animal studies were excluded.

Screening process

Two independent reviewers searched the databases, removed duplicated articles, read the titles and abstracts to exclude articles that were not relevant to the research topic, and finally read the full texts of the selected articles to ensure compliance with the inclusion criteria. Discrepancies between the 2 reviewers were resolved with the assistance of a 3rd team member.

Data extraction

Two reviewers independently extracted the following data from the included studies: author, year of publication, population studied, sociodemographic characteristics, academic level of the operator, number of simple exodontias performed during the study period, number of CPES, and prevalence of different types of CPES.

Evaluation of the methodological quality and the risk of bias

For this study, the criteria used by Burgos et al.[20] were modified. A score of 0–7 to indicated poor evaluation, 8–14 average evaluation and 15–21 good evaluation, as summarized in Table 2. The criteria proposed by Higgins et al.[21] were used to assess the risk of bias and are summarized in Table 3.

Table 2. Evaluation of the methodological quality of the analyzed studies

Description of the methodology	Baniwal et al., 2007[28]	Ventakeshwar et al., 2011[29]	Tong et al., 2014[30]
	qualification		
Objective	3	3	3
Design	3	3	3
Sample selection criteria	2	3	2
Characteristics of the study population	3	3	3
Characteristics of the applied reference standard	3	3	3
Characteristics of the diagnostic test under study	3	3	2
Sample size	3	3	3
Total	20	21	19

Table 3. Risk of bias

Study	Randomization (selection)	Allocation concealment (selection)	Blinding of participants (performance)	Blinding of assessors (detection)	Incomplete results data (wear)	Selective notification about results (notification)	Other sources of bias (other)
Baniwal et al., 2007[28]	low	low	low	low	low	unclear	high
Ventakeshwar et al., 2011[29]	low	low	low	low	high	low	low
Tong et al., 2014[30]	low	low	low	low	low	low	low

Table 4. Excluded articles

Study	Reason for exclusion
Simon and Matee, 2001[26]	does not specify complexity of the exodontia
Malden and Maidment, 2002[27]	describes a particular complication from third molar exodontia
Christiaens and Reychler, 2002[22]	describes exodontia of third molars
Blondeau and Daniel, 2007[23]	describes exodontia of third molars
Øyri et al., 2015[24]	describes exodontia of third molars
Momin et al., 2018[25]	describes exodontia of third molars

Results

Using the above search strategy, 1,446 articles were retrieved from 3 databases (725 from PubMed, 96 from Scopus and 631 from ScienceDirect). After duplicated articles were removed, 948 papers remained. After reading their titles and abstracts to determine their suitability for the study, 9 articles were read in their entirety to ensure compliance with the inclusion criteria. As a result, 6 articles were eliminated: 4 described exodontia of third molars,[22–25] 1 did not specify the complexity of exodontia[26] and 1 described a specific complication caused by third molar exodontia[27] (Table 4 show the details of excluded articles). Finally, 3 articles were included in this systematic review (Fig. 1).[28–30] The study groups in these 3 papers consisted of 22,084 patients in whom, who were treated with a total of 31,401 simple exodontia procedures in these 3 articles. Table 5 presents the details of these complications.

Methodological quality and the risk of bias

The 3 articles were of good methodological quality (Table 2 shows their quality from a quantitative view). The risk of bias is summarized in Table 3, which shows the characteristics of each study. In general, all 3 papers had a low level of bias, with all articles providing appropriate definitions of the inclusion and exclusion criteria used in the study.

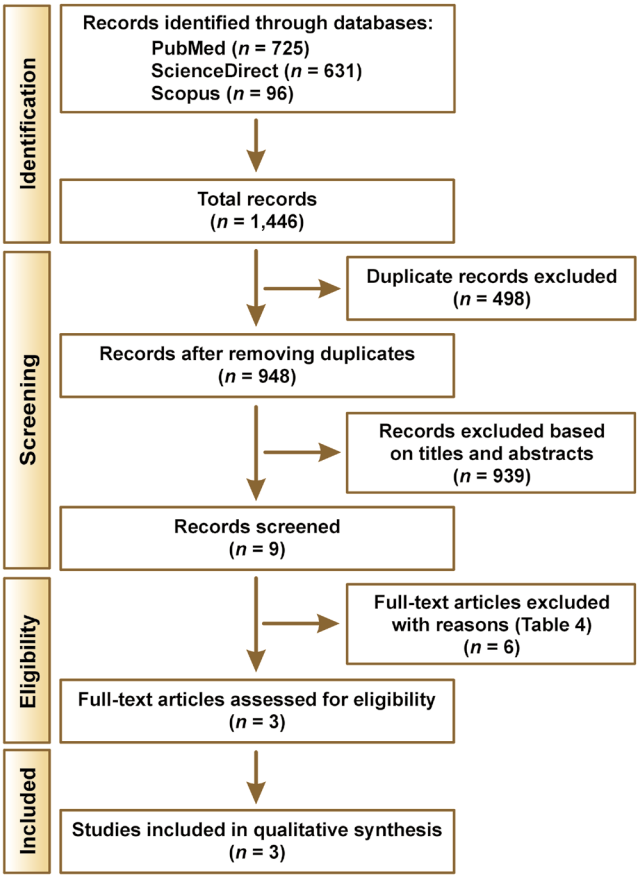

Fig. 1. Flow diagram of the study

Table 5. Characteristics of studies

Study	Study population	Sociodemographic characteristics	Academic level of the operator	Number of SESP	CPES n (%)	Prevalence of types of post-exodontia complications						
						A n (%)	H n (%)	T n (%)	P n (%)	I n (%)	RR n (%)	D n (%)
Baniwal et al., 2007[28]	patients treated by simple exodontia from March 2004 to March 2005 at B.P. Koirala Institute of Health Sciences, Mechi and Koshi zonal hospitals, Dharan, Nepal	6,639 patients, 37.12% men and 62.88% women, age range: 5–65 years, mean age NR	dental undergraduate students (4th and 5th year), interns and dentists	8,455	60 (0.70)	11 (0.13)	19 (0.22)	NR	NR	3 (0.03)	21 (0.25)	NR
Venkateshwar et al., 2011[29]	patients without systemic compromise, not pregnant or lactating, treated by simple exodontia between October 2007 and September 2010 in the Department of Oral and Maxillofacial Surgery at Padmashree Dr. D.Y. Patil Dental College and Hospital, Mumbai, India	14,975 patients, 56.5% men and 43.5% women, age range: 14–82 years, mean age: 41 years	dental undergraduate students and interns	22,330	8659 (38.77)	2618 (11.70)	289 (1.30)	4,023 (18.00)	864 (3.90)	86 (0.38)	NR	779 (3.48)
Tong et al., 2014[30]	patients treated by exodontia (simple and/or complex) from February 1 to June 30, 2012, at the Faculty of Dentistry of the University of Otago, Dunedin, New Zealand	454 patients, 48% men and 52% women, age range: 11–91 years, mean age: 45 ±19.3 years	dental undergraduate students (4th and 5th year) and dentists	412	57 (13.80)	32 (7.70)	0 (0.00)	23 (5.50)		2 (0.40)	NR	NR

NR – not reported; CPES – post-exodontia complications; A – alveolitis; H – hemorrhage; T – trismus; P – pain; I – infection; RR – retained roots; D – dehiscence; SESP – simple exodontia in the study period.

Synthesis of the results

Three of the included articles shared similar characteristics. Baniwal et al. aimed to analyze the prevalence of exodontia complications at tertiary and peripheral care centers at the Institute of Health Sciences in Kathmandu, Nepal, in 2007.[28] Exodontias were performed in peripheral centers by dentists and internal surgeons, and in tertiary centers by dentists, interns and 4th- and 5th-year students of dental school. Exodontias of impacted teeth were excluded. A total of 8,455 simple exodontias were performed in 6,639 patients, 37.12% of whom were male and 62.88% of whom were female, ranging in age from 5 to 65 years, under local anesthesia. Sixty complications and 37 CPES were reported to occur during and after the 7,152 exodontias performed in tertiary centers. In peripheral centers, there were 1,303 exodontias performed with 30 complications and 23 CPES. The CPES in the tertiary care center included 11 retained roots, 10 postoperative hemorrhages, 7 cases of alveolitis, 3 cases of osteomyelitis, 3 infections, and 1 hematoma, while the CPES in the peripheral centers included 10 retained roots, 9 postoperative hemorrhages and 4 cases of alveolitis. The rate of postoperative hemorrhage was statistically higher in peripheral centers than in tertiary care centers (p-value < 0.05).

The study by Venkateshwar et al. was performed in 2012 in Mumbai, India.[29] A total of 22,330 simple exodontias were performed on 14,975 patients, (8,464 being men and 6,511 women, age range: 14–82 years. Exodontias performed using a simple elevator and forceps were included in the study, but complex exodontias were not. All patients were injected with a maximum of 5 mL of 2% lidocaine hydrochloride anesthetic solution, given antibiotics (amoxicillin (250/500 mg) or amoxicillin (250 mg) and cloxacillin (250 mg)), as well as painkillers, and instructed how to care for their wounds during the postoperative period. The most common indications for exodontia were: periodontal disease (37.9%), caries (30.3%), orthodontic causes (14.8%), trauma (7.9%), defective endodontics (6.8%), a non-functional tooth (5.9%), iatrogenic causes (3.2%), and other causes (3.2%). Of the exodontias performed, 23% were of anterior maxillary teeth, 28% of posterior maxillary teeth, 16% of anterior mandibular teeth, and 33% of posterior mandibular teeth. The most common CPES were trismus in 4,023 patients (18%), alveolitis in 2,618 patients (11.7%) and pain in 86 patients (0.39%). There was a statistically significant difference (p-value < 0.05) between undergraduate and intern students in terms of exodontia complications, with undergraduate students having a higher incidence of complications. On the other hand, with regard to the time required to perform exodontia, the authors found significant differences (p-value < 0.05) in favor of a higher frequency of complications in exodontias performed in 30–60 min compared to exodontias performed in less than 30 min.

Finally, Tong et al. conducted a study at the Faculty of Dentistry of University of Otago in Dunedin, New Zealand, to determine the frequency and correlations of CPES.[30] In this study, approx. 1 out of every 11 teeth extracted were incisors or canines, nearly 1/3 were first or second premolars (29.6% of all teeth removed), and the first, second and third molars each accounted for approx. 20% of all teeth extracted (23.8%, 20.7% and 17.3%, respectively). More maxillary teeth than mandibular teeth were extracted (56.7% and 43.3%, respectively). A total of 412 simple exodontias were analyzed, with CPES occurring in 13.8% of cases, including 32 incidences of alveolitis (7.7%), 23 cases of pain and trismus (5.5%), and 2 infections (0.4%). Alveolitis was the most common complication, accounting for 56% of all complications. On the other hand, a statistically significant difference (p-value < 0.05) was found between the academic level of operators and the incidence of CPES, with 4th-year students (18.5%) having a higher incidence of complications compared to 5th-year students (11.0%) and graduated dentist (9.6%). The most common cause of alveolitis was exodontia of the first and second mandibular molars.

Discussion

The objective of this systematic review was to determine and analyze the prevalence of CPES described in the literature. The most common CPES in the study by Baniwal et al. were the retained roots.[28] Venkateshwar et al.[29] reported trismus to be the most common, and Tong et al.[30] reported alveolitis. However, the general literature describes alveolitis as the most studied complication post exodontia.[31]

Alveolitis was described by Blum as "postoperative pain at and around the exodontia site, which increases in severity at any time between the 1st and 3rd days after exodontia, accompanied by partial or total disintegration of the blood clot within the socket, with or without halitosis".[32] The average percentage reported is 3% in simple exodontia and increases to 30% in exodontias when third mandibular molars are included.[31,33] These values are similar to those found in this review (0.13–11.7%). Several factors have been linked to the occurrence of alveolitis, including flap design used in surgery,[34] menstrual cycle and/or use of oral contraceptives,[35,36] immediate irrigation of the alveoli with physiological serum post-exodontia,[37] use of painkillers,[38] smoking habits,[39] traumatic exodontia,[4] curettage of the socket,[40] use of antibiotics,[16,41,42] surgical time,[43] and operator experience.[39] Presurgical antibiotic prophylaxis[16,42] and postsurgical prescriptions of pharmacologic therapies[41] are described as possible preventive measures in alveolitis incidence. In this regard, Ramos et al. and Ren et al. determined in their respective systematic reviews[16,42] that prophylactic antibiotic use significantly reduces the incidence of alveolitis. However, due to the risk of bacterial resistance,[44] it is preferred to use post-exodontia chlorhexidine administration in any formulation, concentration or regimen, as it has been shown to reduce the incidence of alveolitis,[45] and reserve prophylactic antibiotic administration for patients with a medical history and local conditions that increase the risk of alveolitis. These factors may explain why trismus (and not alveolitis or other infectious complications) was more common in the study by Venkateshwar et al.,[29] in which antibiotics were given to all patients postoperatively.[16]

Trismus is defined differently by each author, but they all agree that it is a prolonged spasm of the mandibular elevator muscles that results in a limitation in buccal opening.[46] On the other hand, its etiology can be congenital, traumatic, neoplastic, neuromuscular, reactive, psychogenic, and drug-induced.[47] In relation to its traumatic etiology, scientific evidence has proposed muscle or join pain to be responsible for the muscle spasms that limit buccal opening.[48] Ernberg et al. suggested that a synergist co-contraction produced by the masseter and anterior belly of digastric muscles may cause a reduction in buccal opening.[49] Bodéré et al. showed an increase in the electromyographic activity of the masseter and temporal muscles in patients with myofascial pain, in which electromyographic activity increased bilaterally, even though the pain was unilateral.[50] Furthermore, the electromyographic activity of the temporal and masseter muscles, as well as the resting masseter reflex, were significantly higher in the groups of patients with pain compared to the group without pain. The authors concluded that an increase in electromyographic activity would likely stem from central nociceptive mechanisms. This supports the pain theory proposed by Fougeront et al., who suggested that electromyographic activity is reduced in the agonist muscles (in this case, mandibular elevators) during muscle function in situations that generate pain.[51] Lund et al. observed that muscle pain can result from the general protection of sore muscles during static and dynamic contractions, resulting in a characteristic "dysfunction" as a means of normal protective adaptation that is responsible for limiting buccal opening.[52] Regarding postoperative pain after exodontia, Lago-Mendez et al. demonstrated that patients undergoing more complex and time-consuming exodontias suffered a statistically significant higher degree of postoperative pain than those undergoing exodontia of less complexity and time.[53] Along the same research line, De Santana-Santos et al. showed that for patients undergoing mandibular third molar included exodontia, time was a statistically predictive factor of pain, swelling and trismus.[54] This correlates with the findings of a study by Venkateshwar et al., who found a higher prevalence of complications in simple exodontias lasting more than 30 min as compared to shorter procedures.[29]

In the present study, the prevalence of pain ranged from 3.9% to 5.5%. Al-Khateeb et al. discovered the prevalence of pain to be 81.8% on the first night following intervention, as well as a statistically significant higher prevalence

of pain in females between days 3 and 5 after exodontia.[55] On the other hand, these investigators discovered that teeth with chronic inflammation were associated with increased postoperative pain. There was also a significant correlation between the average pain intensity scores and previous dental injection pain. In contrast, Lago-Mendez et al. showed a statistically significant relationship between surgical difficulty and postoperative pain in a study of lower third molar exodontia, with the most extensive and difficult surgeries producing the most pain.[53] Finally, in a study that included third molar exodontia, Capuzzi et al. discovered that pain was statistically more intense in men than in women on the first and 3rd days.[56] Furthermore, patients treated by experienced surgeons reported less pain on the 1st and 3rd day following surgery than patients treated by inexperienced surgeons. There was also a direct correlation between age and pain, with younger patients reporting less pain than older ones. Given that 2 of the previous articles discuss exodontia of third molars, these findings partially match the data collected in this systematic review. Tong et al. reported a female sex predominance regarding the prevalence of pain, but it did not reach statistical significance. Meanwhile, no significant difference was found between pain prevalence and increased age; however, the authors commented on the importance of the surgeon's experience as patients treated by 4th- and 5th-year students had a higher prevalence of pain than those treated by dentists. These findings appear to indicate that experience allows for a better approach to surgical difficulty, resulting in a reduction in tissue trauma that causes pain.[30] However, Rakhshan et al. failed to find a relationship between clinical experience of the person performing exodontia and postoperative pain, so this issue should be viewed with caution.[57]

The literature describes dehiscence as the opening or rupture of a previously closed surgical incision site.[58] Its prevalence in lower third molar exodontia ranged from 0.5% to 33%,[59,60] while the prevalence found in this systematic review was 3.48%, which was only reported by Venkateshwar et al.[29] Factors such as technique, dentist dexterity, suture type, and type and design of the mucoperiosteal flap,[60–62] supported by the dentist's experience allows the surgeon to better address all intraoperative difficulties and avoid or reduce the likelihood of generating a dehiscence. This is consistent with the findings of the studies included in this systematic review, which showed a higher level of CPES in less experienced surgeons and students.[28–30]

The prevalence of postoperative infections varies between 0.8% and 42.6%,[63,64] and in this systematic review it was between 0.03% and 0.4%. This difference may be due to the fact that these studies were conducted on surgical exodontias, which involve increased tissue trauma and surgical time. Furthermore, in the study by Venkateshwar et al., the patients in which the analyzed exodontias were performed received a prescription for postoperative antibiotics, which could have decreased the prevalence of postoperative infections.[29] According to Jerjes et al., there is a statistically significant relationship between the dentist's experience and the incidence of postoperative infections, with oral and maxillofacial surgery residents being twice as likely as specialists to cause an infection.[65]

Retained roots are an intraoperative complication that occurs when a root fragment fractures and falls inside the socket during tooth avulsion. The dentist must decide whether to leave the root fragment inside the socket or attempt to excise it. If the fragment is left inside the socket, this could lead to a postoperative complication if the patient has painful symptoms or an infection. The most similar clinical situation is the intentional coronectomy of third molars with an anatomical position near the mandibular canal. Exodontias of these are considered to pose high risk of causing damage to the lower alveolar neurovascular structures. However, studies show that the likelihood of a complication from intentionally leaving a root in the socket is extremely low. Cosola et al. found that in 130 patients who underwent coronectomy with 4 years of follow-up, only 13 had root displacement but all were asymptomatic.[66] Nayyar et al. reported that the incidence of retained roots varied between 11% and 37%,[67] which is higher than the rate found in this systematic review. This difference is mainly because the prevalence described in the literature included studies in which the prevalence percentage was calculated based on orthopantomography[67,68] instead of exodontia. Retained roots tend to migrate from their position,[66–68] but they do not pose a long-term risk.[68,69] Factors such as pulp vitality, root stability in exodontia and complete wound closure promote root encapsulation.[67] This encapsulation facilitates the success of the maneuver and prevents dysesthesia.[70] This information should be carefully analyzed because in coronectomy the teeth are mostly without cavities or periodontal disease, unlike teeth in which unplanned root fracture occurs. The presence of these pathologies could affect the results other than those described in coronectomy studies.[71,72]

Hemorrhage had a prevalence ranging from 0.22% to 1.3% in this systematic review. The prevalence described in the literature is 0.1% in healthy patients and approx. 21.8% in anticoagulant-treated patients.[73] Factors such as multiple exodontias, increased prothrombin time, imbalance in hemostasis during surgery, high serum creatinine levels, and antibiotic prophylaxis are associated with postoperative hemorrhage in patients receiving oral antithrombotics.[74] Baniwal et al. proposed that hemorrhages were more prevalent in peripheral centers and that, according to the literature, are more frequent in patients with alveolitis and retained roots.[28] Identifying risk factors associated with hemorrhage and proactively controlling PT-INR in patients receiving antithrombotic therapy is essential.[74]

In terms of relationship between the experience of the dentist and CPES, Larsen et al. examined the surgical exodontias of 138 impacted third molars performed by experienced and inexperienced dentists. Alveolitis was

significantly more common in patients treated by an inexperienced surgeon. The experienced surgeons had 16 cases of alveolitis in 102 surgical sites compared to the 12 cases of alveolitis in 32 sites in the inexperienced surgeons group, indicating a statistically significant increase of more than 130% in the number of alveolitis cases in patients operated on by inexperienced surgeons.[39] Sisk et al. studied CPES in patients treated by academic oral surgeons and students.[75] They identified a difference between the prevalence of alveolitis among academic surgeons and students that was statistically significant for mandibular exodontia and total exodontia. The authors associated the lack of experience with greater surgical trauma in the student group, which would explain the difference between the 2 groups. Capuzzi et al. discovered similar results in their study.[56]

While the majority of the articles focused on third molar exodontia, findings reported in them are consistent with those found in this systematic review. For example, Baniwal et al. showed a low overall CPES prevalence of 0.47% (40) out of a total of 8,445.[28] Venkateshwar et al., on the other hand, discovered that complications occur more often in patients treated by undergraduate students than in treated by interns.[29] Furthermore, they discovered a significant difference in favor of a higher frequency of complications in exodontia performed in 30–60 min compared to exodontia performed in less than 30 min. Finally, Tong et al. suggested a relationship between CPES and the academic level of surgeons and found a statistically significant difference of more CPES in the least experienced group of 18.5%, 11% and 9.6% in 4th- and 5th-year students and dentists, respectively.[30]

However, in relation to the prevention of non-infectious post-exodontia complications, it has been shown that the use of kinesiotaping (KT) after impacted mandibular third molar exodontia significantly reduced swelling, pain and trismus.[6] In addition, it is associated with an improvement in the quality of life of the patients who received this therapy.[76,77] On the other hand, the use of platelet-rich plasma has also been associated with a significant decrease in pain and trismus.[78] In addition, the placement of an intraoral latex drainage system after exodontia of impacted mandibular third molars has been associated with a faster and less traumatic recovery.[79] Although, the mentioned studies were carried out in relation to exodontia of impacted third molars, it is prudent to consider these therapies in the case of extractions that are complicated and associated with prolonged surgical times.

Limitations

Few studies solely focused on simple exodontia as opposed to papers concerning third molar exodontia, which are far more prevalent than publications about simple exodontia. However, because there were few articles on simple exodontia, the findings had to be discussed in conjunction with studies on the surgical exodontia of third molars.

Conclusions

The most prevalent CPES in simple exodontia were retained roots described by Baniwal et al.,[28] trismus in the study by Venkateshwar et al.[29] and alveolitis in the paper by Tong et al.[30] These complications appear to be associated with the surgeon's experience, surgical time and tissue trauma during surgery. As a result, careful examination of each clinical case is required to compensate for the potential lack of experience of students and newly graduated dentists in the prevention of CPES.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Review

Place of placebo therapy in the treatment of burning mouth syndrome: A systematic review

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):603–616

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on June 26, 2022
Reviewed on July 17, 2022
Accepted on August 6, 2022

Published online on December 22, 2022

Abstract

Burning mouth syndrome (BMS) is defined as an idiopathic orofacial pain with intraoral burning or dysesthesia. This systematic review aimed to analyze the scientific literature with regard to the effectiveness of placebo therapy in patients with BMS. A literature search was conducted through the PubMed-indexed journals within MEDLINE®, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Trip databases from their inception to May 31, 2022. The search terms were defined by combining (medical subject headings (MeSH) terms OR keywords) "burning mouth syndrome" AND (MeSH terms OR keywords) "placebo". Methodological quality assessments were performed utilizing the Joanna Briggs Institute (JBI) Critical Appraisal tool to attribute scores from 1 to 11 to the selected studies. The literature search, study selection and data extraction were carried out by 2 authors. Disagreements between the authors were resolved by the 3rd author, if necessary. A total of 44 articles met the inclusion criteria. After assessing full-text articles for eligibility, 20 articles were excluded. Consequently, 24 articles were retained. A total of 21 studies included in this systematic review had a low score of bias. In 13 studies, a positive response to placebo was noted. Among them, 7 showed a placebo response indistinguishable from active treatment. These changes were more pronounced in patients receiving placebo therapy compared to active treatment in 1 study. Placebo therapy may occasionally be beneficial and ethically acceptable for patients with BMS. To get stronger evidence for the use of a placebo, future studies with standardized methodology and outcomes are required.

Keywords: pain, trigeminal, stomatodynia, placebo effect

Cite as
Khemiss M, Chaabouni D, Ben Khaled R, Ben Khélifa M. Place of placebo therapy in the treatment of burning mouth syndrome: A systematic review. *Dent Med Probl.* 2022;59(4):603–616. doi:10.17219/dmp/152646

DOI
10.17219/dmp/152646

Introduction

According to the International Classification of Orofacial Pain, burning mouth syndrome (BMS) is defined as "an idiopathic orofacial pain with intraoral burning or dysesthesia recurring daily for more than 2 h for over more than 3 months. It has no identifiable causative lesions, and it is manifested with and without somatosensory changes".[1] It has a prevalence of 0.1–3.9% and appears to be more frequent in females, especially in post-menopausal women between the age of 50 and 70 years.[2] Burning mouth syndrome is accompanied by normal clinical or laboratory findings.[3] Burning pain may affect multiple sites within the oral cavity, but most commonly affects the tongue.[4] Investigators have proven that this syndrome "may exist coincidentally with other oral conditions".[5] The use of the term "syndrome" is explained by the co-occurrence of BMS with other subjective symptoms.[6] Stomatodynia is the main indicator of this condition. It can be accompanied by other sensory disorders, such as xerostomia and complaints of altered taste with or without the presence of salivary hypofunction.[7] There is also no clear consensus on the exact etiopathogenesis of this syndrome. However, it is often considered idiopathic. Additionally, no definitive remedy is available and most of the treatment methods produce unsatisfactory results.[3] Given the complex etiopathogenesis of BMS, numerous therapeutic regimens have been proposed.[3] Treatment regimens should be adapted to each individual and a multidisciplinary approach is recommended.[8] In recent years, a number of therapeutic options have been developed by exploiting stem cells, opening up an important therapeutic possibility for this syndrome.[9,10] Treatments can consist of pharmacological agents (topical or systemic medications), cognitive behavioral therapy, and complementary or alternative medicinal therapies to soothe the patient's pain.[11] However, no therapeutic modality is considered the gold standard, and these treatments are not considered to be reliable and effective.[3] A placebo has thus been suggested as a solution for BMS.

A placebo is an "inert substance", usually a carbohydrate tablet or something that closely mimics the active treatment.[12] The term "placebo" has Latin origins. Etymologically, it means "I shall please".[13] It was first introduced into the medical field during the 18th century as a medicine responding to a patient's expectations without providing any real concrete outcomes.[13] Placebos have the potential to alleviate many medical conditions. The healing result of non-specific therapy increases a patient's belief in the placebo effect.[13]

Several systematic reviews have assessed the efficacy of various treatments for BMS,[11,14–23] but to the best of the authors' knowledge, only 1 study reviewed the placebo effect in the management of this syndrome.[24]

This study aimed to perform a systematic analysis of the literature regarding the effectiveness of placebo therapy in patients with BMS, evaluating short- and long-term outcomes.

Material and methods

Study design

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to ensure transparency and comprehensiveness.[25] The search protocol was specified in advance and registered with International Prospective Register of Systematic Reviews (PROSPERO, No. CRD42021231242).

Focused PICOS question

The criteria for including studies in this systematic review were determined according to the Participant–Intervention–Comparison–Outcome–Study (PICOS) design scheme (Table 1). Numerical scores were used to standardize the format of the questionnaires, such as mono-dimensional pain scores including a numeric rating scale (NRS), visual analog scale (VAS), face scale, present pain intensity (PPI), or multi-dimensional scores involving the McGill Pain Questionnaire (MPQ).

Search strategy

An electronic search was performed using 4 databases: the National Library of Medicine (MEDLINE®, PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Trip. The search terms used were a combination of (medical subject headings (MeSH) terms OR keywords) "burning mouth syndrome" AND (MeSH terms OR keywords) "placebo". No language or time restrictions were applied. The last electronic search was performed on May 31, 2022. It was enriched by hand searches and citation screenings. All reference lists

Table 1. Study inclusion criteria according to the PICOS design scheme

Criterion	Description
Types of studies (S)	randomized controlled trials, clinical controlled trials, blinded and controlled trials, clinical trials on non-pharmacological treatment dealing with the placebo effect in BMC
Participant characteristics (P)	patients of both sexes with BMC diagnosis
Intervention (I)	treatment with placebo
Comparison (C)	studies assessing current pharmacological treatment of BMC
Outcome (O)	immediate, short-term, long-term
Oral Pain	localization, surface, intensity

BMC – burning mouth syndrome.

of the selected full-text articles and related reviews were scanned for additional studies.

Screening and selection

Three reviewers (DC, RBK and MK) independently screened the titles and abstracts obtained during the 1st search. If a publication did not meet the inclusion criteria, it was excluded after agreement between all reviewers. Any disagreement between the 3 reviewers was resolved after a discussion. Full texts of the eligible articles were examined by the reviewers. When necessary, the original authors were contacted to obtain additional information.

Data extraction

Data extraction was independently conducted by 2 reviewers (DC and MK). Data extraction forms were subsequently compared between the researchers and a final form was obtained. The authors of eligible articles were contacted via e-mail for clarification in cases of doubt or missing data. In crossover studies, the 2 periods (before and after the crossover) were used.

Data recording

The design, sample size, intervention type, and control of each study were analyzed and summarized according to the Consolidated Standards of Reporting Trials (CONSORT) protocol:
– methods: study design, location/setting, recruitment period, and follow-up time;
– participants: inclusion and exclusion criteria, demographics and number of participants;
– intervention: details regarding the type of BMS treatments and types of placebo;
– outcome: pain.

Risk of bias in the included studies

Two reviewers (DC and MK) independently performed a quality assessment using the Joanna Briggs Institute (JBI) Critical Appraisal tool, specifically the checklist for randomized controlled trials (RCTs).[26] The checklist is a 13-item appraisal consisting of the following areas: (1) randomization component, (2) allocation concealment, (3) treatment group similarity at baseline, (4) blinding of participants, (5) blinding of personnel, (6) blinding of outcome assessors, (7) groups treated identically other than the intervention of interest, (8) follow-up, (9) intention to treat, (10) similar outcome measurements, (11) reliable method of outcome measurements, (12) statistical analysis, and (13) trial design. These items were scored as either "yes", "no", "unclear", or "not applicable". Two reviewers (DC and MK) independently evaluated the included studies with discrepancies handled through discussion. If discrepancies could not be resolved through discussion, the third reviewer (RBK) was involved to reach a consensus.

Three levels of bias were determined[26]:
– high risk of bias: "yes" scores below 49%;
– moderate risk of bias: "yes" scores between 50% and 69%;
– low risk of bias: "yes" scores higher than 70%.

Results

Search results

The search process yielded 89 articles, of which 12 were duplicates. Among the 77 remaining papers, 33 were excluded after a review of the title and abstract. After assessing 44 full-text articles for eligibility, 20 were excluded for other reasons.[27–46] Consequently, 24 articles were included in the review.[47–70] The search results are presented in Fig. 1.

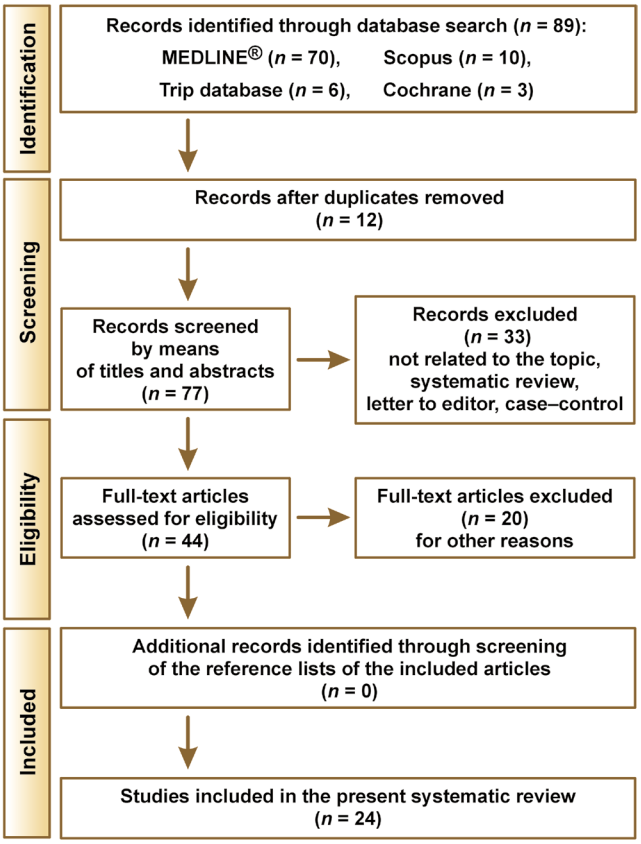

Fig. 1. Study selection flowchart

Study selection and characteristics

The retained studies were assessed for methodological quality (Table 2). A total of 21 studies included in this systematic review had a low score of bias.[47–59,62–69] Three studies had a moderate score of bias.[60,61,70] The final bias scores ranged from 53.8% to 100%.

Table 2. Quality scoring of the retained articles according to the Joanna Briggs Institute (JBI) Critical Appraisal checklist

Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	Score	Risk of bias
De Pedro et al.[52] 2020	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	11	low
Scardina et al.[66] 2020	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	12	low
Škrinjar et al.[64] 2020	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Zoric et al.[70] 2018	U	U	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	8	moderate
Varoni et al.[55] 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13	low
Valenzuela and Lopez-Jornet[53] 2017	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	11	low
Sugaya et al.[65] 2016	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Valenzuela et al.[49] 2016	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Palacios-Sánchez et al.[51] 2015	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	11	low
Cano-Carrillo et al.[67] 2014	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Heckmann et al.[68] 2006	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	11	low
Spanemberg et al.[54] 2012	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Rodríguez de Rivera Campillo et al.[69] 2010	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Cavalcanti and da Silveira[59] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	11	low
Carbone et al.[48] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Miziara et al.[58] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
López-Jornet et al. [50] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Sardella et al.[56] 2008	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Petruzzi et al.[47] 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13	low
Gremeau-Richard et al.[62] 2004	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Femiano et al.[60] 2004	N	U	U	N	N	N	Y	Y	Y	Y	Y	Y	Y	7	moderate
Femiano and Scully[61] 2002	Y	U	U	N	N	N	Y	Y	Y	Y	Y	Y	Y	8	moderate
Sardella et al.[57] 1999	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Tammiala-Salonen and Forssell[63] 1999	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	11	low

N – no; U – unclear; Y – yes.

Table 3 details the main characteristics and methodology points of the retained studies. The studies were published between 1999[57,63] and 2020.[52,64,66] They were conducted in Spain,[49,50,52,53,67,69] Croatia,[64] Serbia,[70] Italy,[48,55–57,60,61] Brazil,[54,58,59,65] Germany,[68] France,[62] and Finland.[63] Three studies failed to report where they were carried out.[47,51,66] The number of treated participants varied from 20[55,68] to 192,[60] with a wide range of ages, varying from 22[61] to 89[68] years. All BMS participants were appropriately defined as having chronic pain for more than 3, 4 or 6 months with normal oral mucosa.

Table 3. Main characteristics of the studies evaluating the placebo effect in burning mouth syndrome (BMS)

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
De Pedro et al.[52] 2020	Madrid, Spain	single-blind RCT	TG: 10, 2/8, 60.30 ±15.19[a] CG: 10, 2/8, 67.60 ±10.68[a]	2019	age >18 years diagnosis of BMS	hyposalivation or Sjögren's syndrome previous head and neck radiotherapy pregnant women patients with uncontrolled systemic diseases patients suffering from burning mouth symptoms secondary to local factors	laser treatment	silent/off laser therapy	5 weeks (4 months)	VAS MPQ
Scardina et al. [66] 2020	NR	double-blind RCT	40, 0/40, 62.06 ±3.1[a]	NR	diagnosis of BMS patients who had healthy mucosa	candidiasis, lichen planus, glossitis, periodontitis systemic pathologies smokers previous appearance of mycosis hypertension patients with daily pharmacological treatments	laser treatment	silent/off laser therapy	4 weeks (60 days)	VAS NRS
Škrinjar et al.[64] 2020	Zagreb, Croatia	double-blind RCT	TG: 12, 1/11, 61 (47–70)[b] CG: 11, 2/9, 62 (50–69)[b]	NR	burning >3 months normal appearance of the oral mucosa	diabetes serum iron and vitamin B deficiency previous head and neck radiotherapy patients with autoimmune diseases patients taking antidepressants, anxiolytics, anticonvulsants, and hormonal therapy	laser treatment	silent/off laser therapy	10 days (NR)	VAS
Zoric et al.[70] 2018	Belgrade, Serbia	RCT, crossover	TG: 50, 13/37, 67.4 ±8.8[a] CG: 50, 11/39, 62.2 ±13.8[a]	2014–2016	burning sensation in the oral cavity absence of any visible oral lesions symptoms duration ≥3 months	previous therapy with antidepressants previous treatment for BMS pregnant/breastfeeding women diagnosed neurodegenerative disorders previously diagnosed depression presence of local infection, allergic stomatitis xerostomia subjects with alterations in blood cell count, iron vitamin B12 and folic acid levels trigeminal neuropathic or atypical facial pain autoimmune diseases cancer, radiotherapy	fluoxetine	cellulose	6 months (NR)	VAS
Varoni et al.[55] 2018	Milan, Italy	triple-blind RCT, crossover	20, 4/16, 64.4 ±11.6[a]	2013–2015	age ≥18 years burning or stinging chronic oral pain pain ≥4 months normal oral mucosa	hyposalivation therapy with melatonin therapy with anticoagulants working at night pregnant/lactating women	active melatonin compresses	NR	8 weeks (NR)	VAS
Valenzuela and Lopez-Jornet[53] 2017	Murcia, Spain	RCT	44, 3/41, 65.5 ±10.6[a], 33–88[c]	NR	diagnosis of BMS patients with continuous burning/pain on a daily or almost daily basis during all/part of the day >6 months no local/systemic factors that could produce the same symptoms	history of head and neck malignancy radiation diabetes mellitus chronic thyroid disease Sjögren's syndrome fibromyalgia and rheumatoid arthritis anemia analgesic and/or anti-inflammatory medications pregnancy unwillingness to give consent to participate	laser treatment	silent/off laser therapy	4 weeks (NR)	VAS

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
Sugaya et al.[65] 2016	São Paulo, Brazil	double-blind RCT	23, 2/21, 59.7 (29–83)[b] TG: 13, 0/13, 57.3 (29–83)[b] CG: 10, 2/8, 62.7 (53–81)[b]	NR	patients meeting the diagnostic criteria for BMS	clinical alterations in the oral mucosa hyposalivation diabetes hypovitaminosis B anemia previous laser radiation previous malignant/benign head and neck neoplasia pregnant and breastfeeding women	laser treatment	silent/off laser therapy	2 weeks (90 days)	VAS
Valenzuela et al.[49] 2016	Murcia, Spain	double-blind RCT, crossover	TG: 31, 3/28, 65.8 ±10.6[a] CG: 26, 4/22, 67.2 ±12.6[a]	NR	diagnosis of BMS in accordance with the International Classification of Headache Disorders	oral lesion endocrine, immunological, nutritional, or infectious disorders patients with history of head and neck malignancy radiation therapy to the head and neck area poorly managed diabetes mellitus chronic thyroid disease Sjögren's syndrome	2% *Chamaemelum nobile* + water, hydroxyethyl, sorbitol, potassium sorbate, sodium metabisulfite, food coloring, chamomile aroma	water, hydroxyethyl, sorbitol, potassium sorbate, sodium metabisulfite, food coloring, chamomile aroma	4 weeks (NR)	VAS
Palacios-Sánchez et al.[51] 2015	NR	double-blind RCT	60, 5/55, 62.13 (36–86)[b]	NR	diagnosis of BMS age >18 years history of continuous oral burning pain >4 months	burning sensation related to local alterations alteration and uncontrolled systemic diseases patients treated with cisplatin, cyclophosphamide, gentamicin, and amikacin patients undergoing any type of BMS treatment	ALA	cellulose	2 months (NR)	VAS
Cano-Carrillo et al.[67] 2014	Murcia, Spain	double-blind RCT	60, 12/48, 63.3 ±12.9[a] TG: 30, 9/21, 61.7 ±11.6[a] CG: 30, 3/27, 64.9 ±14.1[a]	2011–2013	clinical history of continuous symptoms of oral burning/pain >6 months normal blood test findings non-smokers	patients with pain attributable to other conditions history of hypersensitivity or allergy to the materials used in the study known neurological disorders patients previously treated with antidepressants, anticonvulsants and psychotropic drugs previous psychological therapies no treatment for BMS in the last 2 weeks in the case of topical treatments or in the last 4 weeks in the case of systemic therapies	lycopene + virgin olive oil	water and dye	12 weeks (NR)	VAS
Heckmann et al.[68] 2006	Erlangen, Germany	double-blind RCT	TG: 10, 5/5, 67.5 (49–89)[b] CG: 10, 2/8, 65.4 (49–78)[b]	NR	idiopathic cases	general diseases human immunodeficiency virus infection vitamin B12 deficiency asthma narrow angle glaucoma sleep apnea syndrome general reduction of health condition Candida infection of the oral mucosa allergy toward dental materials or dentures or drugs used in this study severe diseases of the central nervous system psychiatric diseases radiation therapy pregnant/lactating women alcoholism	clonazepam	lactose monohydrate	9 weeks (NR)	VAS

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
Spanemberg et al.[54] 2012	São Lucas (Brazil)	double-blind RCT	TG: 30, 3/27, 63.6 ±9.61[a], 41–79[c] CG: 30, 4/26, 61.5 ±6.76[a], 46–73[c]	NR	age ≥40 years burning or pain in the oral mucosa ≥6 months clinically normal mucosa	individuals who were taking antidepressant, anxiolytic or anticonvulsant drugs previous chemo- and/or radiotherapy hyposalivation alterations in hemogram, serum levels of glucose, iron, folic acid, and vitamin B12	*Paullinia cupana* + *Trichilia catigua* + *Zingiber officinale* + *Ptychopetalum olacoides*	magnesium silicate	8 weeks (4 weeks)	VAS face scale
Rodríguez de Rivera Campillo et al.[69] 2010	Barcelona (Spain)	double-blind RCT	66, 2/64, 64.9 (48–85)[b]	2005–2006	oral burning no apparent oral lesions no treatment of the patients in the last month	oral mucosa disorders patients who did not attend the follow-up visits	clonazepam	lactose	6 months (NR)	VAS
Cavalcanti and da Silveira[59] 2009	São Paulo (Brazil)	double-blind RCT, crossover	31, 4/27, 63.1(36–78)[b]	2005–2007	history of oral burning pain ≥6 months absence of oral findings	local and/or systemic causes for oral burning	ALA	cellulose	30 days (NR)	VAS
Carbone et al.[48] 2009	Turin (Italy)	double-blind RCT	52, 9/43, 67.3 ±11.9[a]	2004–2006	previous untreated BMS presence of an isolated complaint of chronic pain in the oral mucosa with a normal clinical examination pain >4 months, continuous throughout all/part of the day, with no paroxysms and not following a nerve trajectory	diabetes that was not under effective pharmacological control patients with known abnormal neurological disorders individuals who were taking antidepressant, anticonvulsant or psychotropic drugs/ psychological therapy signs of parafunctional habits hypersensitivity to ALA hypersensitivity related to dental material contact	ALA + vitamins ALA	dicalcium phosphate, microcrystalline cellulose, hydroxypropyl methylcellulose, silicon dioxide, vegetable magnesium stearate, shellac/ stearic acid	8 weeks (2 months)	VAS MPQ
Miziara et al.[58] 2009	São Paulo (Brazil)	double-blind RCT	44, 15/29, 55 ±6.7[a]	2002–2007	patients with BMS no other symptoms of systemic disease patients who accepted to undergo a psychotherapy group session	patients with a doubtful diagnosis patients followed up for less than 3 months patients who did not agree with the treatment protocol	psychotherapy sessions	NR	3 months for psychotherapy (NR) 1 month for the placebo (NR)	MPQ PPI
López-Jornet et al.[50] 2009	Murcia (Spain)	double-blind RCT	60, 6/54, 64.4 ±11.6[a]	2004–2007	continuous oral burning or pain, daily or almost daily, during all/part of the day >6 months, independent of the nervous pathway and without paroxysms normal blood analysis	patients with pain attributable to other entities patients with problems with dentures, biochemical anomalies and a previous history of hypersensitivity or allergy to ALA pregnant/lactating women patients taking medication which interfered with the study medication	ALA	cellulose	8 weeks (NR)	VAS

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
Sardella et al.[56] 2008	Milan (Italy)	double-blind RCT	TG: 19, 1/18, 65.9 ±4.2[a] CG: 20, 3/17, 63.9 ±4.9[a]	2014–2016	history of oral burning pain ≥6 months	local/systemic condition causing an oral burning antidepressant, sedative, anticonvulsant, cardiovascular, hypoglycemic, immunosuppressant, anticoagulant drugs, diltiazem, tamoxifen, bronchodilator treatment	*Hypericum perforatum* extract	NR	12 weeks (NR)	VAS
Petruzzi et al.[47] 2004	NR (NR)	triple-blind RCT	50, 14/36 TG: 55.6 ±6[a] CG: 57.4 ±7[a]	NR	diagnosis of BMS patients never been treated for BMS	NR	capsaicin	NR	30 days (NR)	VAS
Gremeau-Richard et al.[62] 2004	Paris, Lyon, Bordeaux, Saint-Étienne, Clermont-Ferrand (France)	double-blind RCT	48, 4/44, 65 ±2.1[a]	NR	presence of an isolated complaint of chronic pain in the oral mucosa with a normal clinical examination continuous pain ≥4 months without paroxysms and not following a nerve trajectory	diabetes anemia patients with abnormal neurological conditions patients treated on a daily basis with antidepressant, anticonvulsant, or other psychotropic drugs/psychological therapy	clonazepam	NR	2 weeks (6 months)	NS
Femiano et al.[60] 2004	NR (Italy)	RCT	192, 88/104, 48 (24–67)[b]	1999	BMS diagnosis corrected whole blood folate and blood sugar assays	patients with a positive medical or drug history abnormal sialometry evidence of mucosal disease biochemical or hematological abnormalities	ALA + psychotherapy	cellulose	2 months (6 months)	VAS
Femiano and Scully[61] 2002	NR (Italy)	single-blind RCT	60, 18/42, 45 (22–68)[b]	NR	continuous burning discomfort ≥2 months no relevant drug or medical history	NR	ALA	cellulose	2 months (1 year)	VAS
Sardella et al.[57] 1999	Milan (Italy)	double-blind RCT	30, 4/26, 69 (54–85)[b]	1996–1998	diagnosis of "idiopathic" or "essential" BMS clinically normal oral mucosa absence of local or systemic diseases	nutritional and hematological deficiencies diabetes mellitus *Candida* infection, oral lichen planus, geographic tongue xerostomia denture design faults, parafunctional habits allergy to dental materials	benzydamine hydrochloride	HCl	4 weeks (NR)	VAS
Tammiala-Salonen and Forssell[63] 1999	Turku (Finland)	double-blind RCT	37, 0/37, 58.6 (39–71)[b]	1992–1996	daily or almost daily burning pain ≥6 months with moderate to severe intensity	NR	trazodone	NR	8 weeks (NR)	VAS MPQ

M – male; ; F – female; RCT – randomized controlled trial; TG – treatment group; CG – control group; ALA – alpha lipoic acid; HCl – hydrogen chloride; VAS – visual analog scale; MPQ – McGill Pain Questionnaire; NRS – numeric rating scale; PPI – present pain intensity; NS – numerical scale; [a] mean ± standard deviation (*M* ±*SD*); [b] median (minimum–maximum) (*Me* (min–max)); [c] min–max; NR – not reported.

Randomization was applied in 22 studies (Table 2).[47–59,61–69] All 24 studies were controlled clinical trials, involving 2 triple-blind studies (participant, caretaker and assessor),[47,55] 17 double-blind studies,[48–51,54,56–59,62–69] and 2 single-blind studies (participants).[52,61] Four of the clinical trials had a crossover design (Table 3).[49,55,59,70] All studies reported data on items 7 (i.e., groups treated identically other than the intervention of interest), 8 (i.e., follow-up), 9 (i.e., intention to treat), 10 (i.e., similar outcome measurements), 12 (i.e., statistical analysis), and 13 (i.e., trial design; Table 2). Twenty-two studies with a treatment duration between 10 days and 3 months were categorized as short-term assessments.[47–68] The remaining 2 studies performed long-term assessments of 6 months.[69,70] At the end of the intervention, follow-up was reported in 8 studies,[48,52,54,60–62,65,66] ranging between 1 month and 1 year (Table 3).

Visual analog scale was the primary assessment tool for measuring pain intensity. It was used in 22 studies.[47–57,59–61,63–70] Supplementary assessment tools, such as MPQ,[48,52,58,63] NRS,[66] PPI,[58] numerical scales,[62] and face scales[54] were also used to evaluate pain (Table 3). Secondary outcome assessments were performed to assess the quality of health, anxiety, depression, and quality of sleep using patient-reported questionnaires, including the 36-item short form survey,[52] oral health on quality of life,[49,52,53,67] Crown-Crisp Experimental Index,[58] Hamilton Depression Rating Scale,[70] Hamilton Anxiety Rating Scale,[53,55,56,67,70] Beck Depression Inventory,[51,63,68,70] psychometric Symptom Checklist-90-R,[52] Medical Outcomes Study Sleep Scale,[55] Epworth Sleepiness Scale,[55] xerostomia severity test,[49,53] salivary flow-rate,[68] taste test,[68] and smell test.[68] Quantitative assessments of pain intensity were performed in 17 studies.[48–50,52–56,59,62–64,66–70] Functional improvement was quantitatively assessed in 7 studies (Table 4).[47,51,57,58,60,61,65]

Placebo effects in burning mouth syndrome

Although the placebo was administered in the same way as the active treatment in all of the studies, its composition was noted in only 13 (54.2%) studies.[48–51,54,57,59–61,67–70] The most commonly used placebo was cellulose.[50,51,59–61,70] The placebo pill in one study contained cellulose as the primary ingredient and dicalcium phosphate, microcrystalline cellulose, hydroxypropyl methylcellulose, silicon dioxide, vegetable magnesium stearate, and shellac/stearic acid as secondary ingredients.[48] Other placebo formulations included ingredients such as water and dye,[67] lactose monohydrate,[68] magnesium silicate,[54] lactose,[69]

Table 4. Comparison of pain before and after placebo treatment

Author, year	Data	Baseline	End of the treatment	End of the follow-up	Treatment vs. placebo	Key findings
De Pedro et al.[52] 2020	VAS[a]	TG: 6.8 CG: 7.1	TG: 3.4* CG: 7.6	TG: 3.9† CG: 7.6	VAS for pain decreased significantly in the TG vs. the CG at the end of treatment and after 4-month follow-up	no placebo effect
Scardina et al.[66] 2020	NRS[a]	TG: 7 CG: 7	TG: 3* CG: 5*	TG: 3† CG: 7	clear improvement was seen on the NRS of the linear type in the 2 groups after 2 months, patients in CG showed a recurrence of burning sensation	placebo effect
Škrinjar et al.[64] 2020	VAS[b]	TG: 5.5 (4–9) CG: 5 (0–8)	TG: 4 (3–7) * CG: 3 (1.5–6.5)*	NR	VAS scores were significantly lower in both groups	placebo effect
Zoric et al.[70] 2018	VAS[c]	TG: 7.5 ±1.7 CG: 7.2 ±1.7	TG: 3.5 ±2.5* CG: 3.9 ±2.8*	NR	good efficacy of the medication in treating BMS compared to placebo	possible placebo effect
Varoni et al.[55] 2018	ΔVAS[c]	TG: 0.6 ±0.5	CG: 1.2 ±0.4	NR	melatonin and placebo have comparable efficacy in reducing pain caused by BMS lack of difference can be attributed to the effect of placebo on BMS patients	possible placebo effect
Valenzuela and Lopez-Jornet[53] 2017	VAS[c]	TG: 7.56 ±1.5 TG': 8.38 ±1.7 CG: 7.83 ±1.3	TG: 6.38 ±1.6* TG': 7.06 ±1.8* CG: 7.65 ±1.2	NR	VAS scores obtained from the 2 groups treated with laser were significantly lower than scores for placebo group	no placebo effect
Sugaya et al.[65] 2016	*n*	TG: 6 of the 13 patients reported complete remission of symptoms in all sites affected by the burning sensation at the last control checkpoint. CG: 4 of the 10 patients reported total remission of symptoms in all affected sites at the end of the control period.			laser protocol used to treat this group of BMS patients produced benefits similar to those of the placebo group	possible placebo effect
Valenzuela et al.[49] 2016	VAS[c]	TG: 7.4 ±1.5 CG: 6.9 ±1.8	TG: 6.7 ±1.4 CG: 6.2 ±1.9	NR	no significant differences were found between the groups	no placebo effect
Palacios-Sánchez et al.[51] 2015	%	TG: improvement 64%, worsened 0%, no change 36% CG: improvement 27.5%, worsened 17.2%, no change 55.2%		NR	$p < 0.05$	no placebo effect

Author, year	Data	Baseline	End of the treatment	End of the follow-up	Treatment vs. placebo	Key findings
Cano-Carrillo et al.[67] 2014	VAS[b]	TG (pain): 9 (5–10) CG (pain): 9 (6–10) TG (burning): 5 (1–10) CG (burning): 5 (2–10)	TG (pain): 6 (3–10) * CG (pain): 6 (2–10) * TG (burning): 4 (1–8)* CG (burning): 4 (1–8) *	NR	no significant differences were found between the groups	placebo effect
Heckmann et al.[68] 2006	VAS[c]	TG: 7.4 ±2.4 CG: 6.0 ±2.2	TG: 3.9 ±2.9* CG: 4.6 ±2.4*	TG: 4.5 ±2.4† CG: 4.5 ±1.8†	changes were much more pronounced in patients receiving clonazepam compared to placebo	possible placebo effect
Spanemberg et al.[54] 2012	VAS[c]	TG: 6.87 ±2.16 CG: 7.17 ±2.0	TG: 3.33 ±2.56* CG: 5.47 ±2.76*	TG: 3.33 ±2.49† CG: 5.73 ±2.71†	improvement in TG was significantly greater than that of CG after 4 and 8 weeks of herbal compound use reduction in symptoms was still evident after 12 weeks	possible placebo effect
Rodríguez de Rivera Campillo et al.[69] 2010	VAS[c]	TG: 7.7 ±1.5 CG: 7.6 ±1.6	TG: 3.0 ±1.3* CG: 4.4 ±1.0*	NR	clonazepam showed a significant improvement compared to placebo	possible placebo effect
Cavalcanti and da Silveira[59] 2009	VAS[d]	TG: 64.2 TG (after placebo): 47.8 CG: 53.4 CG (after placebo): 78.9	TG: 44.2* TG (after placebo): 41.8 CG: 38.4* CG (after placebo): 52.0*	NR	reduction on symptoms after oral administration of ALA did not have statistical significance compared to the results obtained after oral administration of placebo	placebo effect
Carbone et al.[48] 2009	VAS[c]	TG: 6.89 ±2.42 TG′: 6.50 ±2.59 CG: 6.65 ±2.41	TG: 5.94 ±2.73* TG′: 4.71 ±3.10* CG: 5.05 ±3.39*	TG: 5.11 ±3.98† TG′: 4.50 ±3.39† CG: 5.40 ±3.05†	no significant difference between the TG and CG	placebo effect
Miziara et al.[58] 2009	*n* (%)	TG: improvement 17 (70.8%), no change 7 (29.2%) CG: improvement 8 (40.0%), no change 12 (60.0%)		NR	difference in the results between the 2 groups	no placebo effect
López-Jornet et al.[50] 2009	VAS[c]	TG: 6.3 ±2.8 CG: 6.6 ±2.5	TG: 4.0 ±2.7 CG: 2.8 ±2.5	NR	no significant differences between the 2 groups	no placebo effect
Sardella et al.[56] 2008	VAS[b]	TG: 6.8 (3–10) CG: 7.45 (2–10)	TG: 4.5 (0–10) CG: 6.2 (0–10)	NR	no statistically significant differences were observed in the VAS scores between active treatment and placebo	no placebo effect
Petruzzi et al.[47] 2004	VAS (%)	TG: 8–10 (60%), 4–7 (32%), 0–3 (8%) CG: 8–10 (52%), 4–7 (28%), 0–3 (20%)	TG: 8–10 (4%), 4–7 (12%), 0–3 (84%)* CG: 8–10 (52%), 4–7 (24%), 0–3 (24%)	NR	differences between TG and CG were not mentioned	no placebo effect
Gremeau-Richard et al.[62] 2004	VAS[c]	TG: 6 ±0.3 CG: 6.2 ±0.4	TG: 3.5 ±0.7* CG: 5.5 ±0.4	NR	differences between active treatment and placebo were significant	no placebo effect
Femiano et al.[60] 2004	*n* (%)	TG: worsening 7 (15%), unchanged 22 (46%), improvement 19 (40%) TG′: worsening 2 (4%), unchanged 7 (15%), improvement 39 (81%) TG″: worsening 1 (2%), unchanged 4 (8%), improvement 43 (90%) CG: worsening 18 (37%), unchanged 24 (50%), improvement 6 (13%)		NR	differences between TG and CG were significant	no placebo effect
Femiano and Scully[61] 2002	*n* (%)	TG: worsening 0 (0%), unchanged 1 (3%), improvement 29 (97%) CG: worsening 6 (20%), unchanged 12 (40%), improvement 12 (40%)		NR	statistically significant symptomatic improvement with alpha-lipoic acid (97%) used over 2 months compared to placebo (40%)	possible placebo effect
Sardella et al.[57] 1999	*n* (%)	TG: worsening 0 (0%), unchanged 9 (90%), improvement 1 (10%) CG: worsening 0 (0%), unchanged 8 (80%), improvement 2 (20%)		NR	oral rinses seemed to be no more effective than a placebo solution in the symptomatic relief of essential BMS	no placebo effect
Tammiala-Salonen and Forssell[63] 1999	VAS[a] MPQ[a]	TG: 59.2 CG: 46.6 TG: 8.2 CG: 7.5	TG: 46.6* CG: 34.3* TG: NR CG: NR	NR	VAS: no significant differences between the groups in terms of treatment effects	placebo effect

[a] *M*; [b] *Me* (min–max); [c] *M* ±*SD*; [d] *Me*; NR – not reported; * $p < 0.05$ (end of the treatment vs. baseline); † $p < 0.05$ (end of the follow-up vs. baseline).

and hydrogen chloride (HCl).[57] Valenzuela et al.[49] applied water, hydroxyethyl, sorbitol, potassium sorbate, sodium metabisulfite, food coloring, and chamomile aroma as a gel. Three studies confirmed that the placebo matched the treatment arm with respect to shape, taste, smell, and color.[47,69,70] In 8 other trials, the authors mentioned that the placebo was identical-looking to the treatment.[48,49,51,54,59,61,62,67] Silent/off laser therapy in contact with the mucosa was applied as a treatment in 5 studies (Table 3).[52,53,64–66]

In 13 studies, a positive response to the placebo was noted.[48,54,55,59,61,63–70] Moreover, in 7 of these studies,[48,59,63–67] the placebo response was statistically indistinguishable from the active treatment (Table 4). These changes were more pronounced in patients receiving a placebo compared to alpha lipoic acid (ALA) when the treatment was administered after the placebo during a crossover trial.[59] Carbone et al.[48] found that pain significantly decreased in the placebo group at the end of 4 months of follow-ups compared to the treatment group. However, in one study, patients treated with silent/off laser therapy had a recurrence of the burning sensation.[66]

Discussion

Our systematic review included 24 RCTs investigating the placebo effect in BMS. Randomized controlled trials are widely considered the most rigorous method for evaluating treatment efficacy or preventive interventions.[71] In fact, 87.5% of the included studies had a low risk of bias. It is known that systematic reviews can be affected by bias at the level of individual studies.[72] For this reason, an assessment of the validity of these studies was a crucial step when conducting this systematic review.[73] If bias is ignored, the true effect of the intervention may be overestimated or underestimated.[72] The main result in 7 of the studies was that treatment with a placebo produces a response that may be as large as the response to active drugs.[48,59,63–67] In 6 RCTs, the placebo arm showed a positive response but was less pronounced than in patients receiving active treatment.[54,55,61,68–70]

Burning mouth syndrome is one of the most difficult conditions facing oral health care professionals due to its variation in clinical manifestations.[3] Disagreements arise with regard to whether this condition should be considered a disease, disorder or syndrome. However, no sufficient data is available to justify any modification in taxonomy.[7] Burning mouth syndrome has a negative impact on a patient's life since it is always accompanied by pain.[5] Pain levels were the principal outcome in the patients of the included studies. They were evaluated using many assessment tools. Visual analog scale, which is a unidimensional measurement for pain intensity was most commonly used, especially in diverse adult populations.[74] McGill Pain Questionnaire was used in a few studies not only to describe the pain intensity but also the sensory, affective and evaluative aspects of pain. It is a multi-dimensional questionnaire designed to measure pain and its qualities in adults with chronic pain.[74]

There is no consensus on how to treat BMS.[3] Consequently, treatment modalities based on a patient's symptomatology often lead to unsatisfactory results. A recent systematic review[11] concluded that the effectiveness of both pharmacological and non-pharmacological treatments remains low. The latter should be tried first to manage BMS due to their low side effect profiles. It is important to mention that the key to treatment success depends on the following number of issues that must be solved: correct diagnosis, confirmation of diagnosis, patient's acceptance, patient's understanding of the likely clinical course, patient's participation in the elaboration of a treatment strategy, compliance, positive feedback during treatment, and ongoing interest of the clinicians.[75] Building trust and reassurance with patients is essential in the management of BMS.[3] Moreover, affected individuals should have a realistic understanding of the probability of being cured. The impact on a patient's attitude often results in long-term beneficial effects. The practitioner should meticulously investigate the patient's family, medical, dental, and personal history. He should also carefully interpret the data obtained from various physical and laboratory tests. In cases of underlying local, systemic or psychological factors, treating or eliminating these factors is crucial in the therapeutic process.[3]

A placebo can be of great use in reducing the burning and associated symptoms in patients with BMS. Placebo analgesia "is recognized as a positive response to the administration of a substance known to be inert and to have no analgesic action".[76] However, it is strongly thought to be a potent painkiller by the patient.[76] Current clinical pharmacologic research relies on the superiority of treatment over placebo.[76] It has been confirmed that the overall response to treatment is the result of the specific effect of the treatment and the effect of the context in which the treatment is given. Placebo interventions are designed to stimulate a therapeutic context, affecting the patient's brain, body and behavior.[77] This systematic review revealed that a placebo may be effective in reducing pain caused by BMS.[48,59,63–67] In addition, these studies reported a short-term assessment of the placebo effect. The reduction in symptoms was still evident 2 months after the end of the intervention.[48] Many mechanisms are involved in producing the placebo effect, such as expectations, conditioning, learning, motivation, memory, somatic focus, reward, anxiety reduction, and meaning.[77] Recent advances in placebo research and neuroimaging have shown that the placebo effect is a real neurobiological phenomenon. Placebo analgesia is regulated, at least in part, by endogenous opioid mechanisms and results in the active inhibition of nociceptive activity.[78] Nevertheless, no placebo effect was observed in 11 studies, and an improvement in the test group

was significantly greater than that in the placebo group in 6 RCTs.[54,55,61,68–70] Thus, it is not inherent that patients with BMS will feel better in response to the treatment with a placebo, particularly in the case of subjective outcomes, such as pain. Greene et al.[76] suggested that a third "no treatment" waitlist control group should be included in future RCTs. It would allow differentiation between the natural course of symptoms and a genuine placebo effect. However, whenever treatment is withheld, ethical questions arise. The use of placebo controls in RCTs is ethically acceptable in 4 conditions: "(i) when there is no proven effective treatment for the condition under study; (ii) when withholding treatment poses negligible risks to participants; (iii) when there are compelling methodological reasons for using placebo, and withholding treatment does not pose a risk of serious harm to participants; and more controversially, (iv) when there are compelling methodological reasons for using placebo, and the research is intended to develop interventions that can be implemented in the population from which trial participants are taken, and the trial does not require participants to forgo treatment they would otherwise receive".[71] The methodological reasons are important to ensure the ethical use of placebo controls in these last 2 controversial conditions.[71] In addition, a no-treatment waitlist control group in which patients eventually receive active drugs raises ethical questions similar to those connected with the use of placebo arms in RCTs. In both cases, an institutional review board would need to weigh the potential benefit of the scientific knowledge to be gained against the potential harm that could be derived from withholding active treatment. In case of disorders such as BMS, for which there is no standard of care, the inclusion of a no-treatment waitlist control group may be ethically acceptable.[24] Nevertheless, close attention should be paid to ensure that basic ethical principles are respected when placebo therapy is prescribed.[79]

Limitations

The present systematic review has some limitations. The first limitation concerns the sample size which differs between included studies. The second limitation is related to the duration of therapy. Patients were followed up for a short period of time, whereas the pain occurring in BMS is chronic. Future studies should last more than 3 months. The third limitation concerns the definition of clinically significant outcome. Although VAS was used in almost all the studies, this tool was applied in different ways. The 4th limitation is related to the placebo control which varied depending on the treatment used (laser therapy, for example). The 5th limitation concerns the definition of BMS, which is still lacking.[3] It is worth noting that there is an urgent need to give an exact and universally accepted definition of this syndrome. Despite these limitations, the magnitude of the placebo response in BMS appears to be quite robust.[24] Future RCTs investigating BMS would benefit from larger sample sizes, adequate follow-up periods and the use of a standard placebo. With respect to reporting data, we suggest that in future studies all available data should be reported, particularly VAS data, so that comparisons will be simpler.

Conclusions

Placebo therapy can sometimes be beneficial and ethically acceptable. The placebo effect found in this systematic review represents a significant challenge for future RCTs evaluating therapies for BMS. To obtain stronger evidence for placebo use, such trials should follow a standard protocol. An adequately long follow-up period must be established to discern if the treatment is more effective than a placebo.

Highlights

- Key finding: Placebo may be effective in reducing pain caused by BMS.
- Clinical implication: Placebo can be used as a treatment for BMS in some cases, especially since there is no gold standard treatment for this syndrome.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Review

Facial paralysis after intraoral anesthetic injection: A systematic review

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

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):617–627

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
The authors thank Constanza Castillo for modifying and editing the scheme of the deflection of the needle when entering the pterygomandibular space, using the inferior alveolar nerve block (INAB) technique.

Received on April 28, 2021
Reviewed on June 10, 2021
Accepted on June 14, 2021

Published online on December 30, 2022

Abstract

Many complications can occur after the injection of local intraoral anesthetics (ILIA) before dental intervention. Facial paralysis (FP) is one of these complications. The purpose of this study was to systematically analyze the association between ILIA and FP. A systematic review was carried out taking into account the methodology of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA statement. The search strategy used "Palsy AND Facial" and "Paralysis AND Facial" as search terms. The ScienceDirect, PubMed and Scopus databases were searched using the "dentistry journal" filter. The inclusion criteria included studies describing FP after or during ILIA that were published in dental journals. The CAse REports (CARE) checklist was applied in evaluating the methodological quality of case reports. A total of 2,462 articles (algorithm) were identified. After reviewing titles and abstracts, 18 articles were deemed relevant taking into account the objectives of this study. Only 13 of them, after reading the full text, met the inclusion criteria and were analyzed. Case reports on 18 cases of FP were analyzed, 12 of which described the early development of FP (onset within 24 h) and 6 the late development (onset after 24 h). Acceptable compliance with CARE guidelines was observed in the included studies . Early FP CRs presented the effect of the administered anesthetic on the facial nerve, and the vascular effect of the vasoconstrictor included in the anesthetic formula, while more recent FP CRs focused on the reactivation of herpes simplex virus type 1 (HSV-1), human herpesvirus 6 (HHV-6) or varicella-zoster virus (VZV).

Keywords: local anesthetics, systematic review, anesthesia, Bell's palsy, facial paralysis

Cite as
Ferrer-Valdivia N, Fernández-Córdova M, Herrera-Barraza V, Araya JE. Facial paralysis after intraoral anesthetic injection: A systematic review. *Dent Med Probl.* 2022;59(4):617–627. doi:10.17219/dmp/138910

DOI
10.17219/dmp/138910

Introduction

The scientific literature describes a wide range of clinical complications following the injection of local intraoral anesthetics (ILIA), which can be divided into 2 groups: systemic and local complications. Allergic reactions, toxicity and methemoglobinemia, among others, are listed in the systemic group, whereas ocular complications, trismus of the masticatory muscles, pain, infection, paresthesia, and facial paralysis (FP) constitute the local group.[1] In FP, the patient is unable to move the muscles of expression of the affected side, causing insufficiency in the labial functions and ocular closure, which impairs the quality of life of the patients and their relatives.[2] Among known types of FP, idiopathic facial paralysis (IFP), also known as Bell's palsy, has been studied most intensively. It has the same characteristics as FP, but its onset is sudden, without a clear etiological factor.[3] Recently, Zhang et al. summarized the possible clinical etiologies of IFP, including viral infection, ischemia, immune inflammation, exposure to cold, and various anatomical conditions of the facial nerve.[4] However, there is little information from a dental point of view on how intraoral anesthesia techniques or used anesthetic can cause FP.[5] The objective of this study was to analyze the association between ILIA and FP by means of a systematic review of scientific dental literature.

Material and methods

The method used was adapted from the Cochrane Handbook for Systematic Reviews of Interventions[6] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for systematic reviews.[7]

The following question was used for the organization of this study: Is there scientific evidence of FP after ILIA in dental care? This allowed the descriptions of the Population (P), Intervention (I), Comparison (C), and Outcomes (O) to be obtained (the PICO framework).

1. Population: Adult patients without baseline central or peripheral nervous system disorders.
2. Intervention: ILIA.
3. Comparison: There was no comparison since there are hardly any records regarding ILIA without complications.
4. Outcome: FP subsequent to ILIA.

Search strategy

In the search strategy, the following terms: "Palsy AND Facial" and "Paralysis AND Facial" were used to search the ScienceDirect, PubMed and Scopus databases. A restriction date of August 2019 and a search filter "only dental journals" was used to find studies whose aim was to understand the association of FP with ILIA and treatment of FP after ILIA.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) studies that report FP attributable to ILIA in dental care; 2) case report (CR) studies; 3) studies published in dental journals; and 4) studies on humans.

The following publications were excluded: 1) studies of FP following orthognathic surgery; 2) studies of FP following parotid gland removal; 3) studies of FP caused by condylar process fracture treatment; 4) studies of FP due to factors other than ILIA; 5) book chapters; and 6) animal studies.

Screening process

Two independent reviewers searched the databases, removed duplicate articles from the list of papers they created, read titles and abstracts to identify papers not relevant to the research topic, and finally read full texts of selected articles to verify compliance with the inclusion criteria. Differences between the 2 reviewers were resolved by a 3rd team member.

Data extraction

Two reviewers independently collected the following data from the analyzed studies: authors, year of publication, type of study, number of cases reported, sex and age of patients, time of onset of FP, FP classification, anesthetic used, anesthetic technique, affected side, dental treatment performed, treatment provided for FP, degree of recovery, and recovery time.

Assessment of methodological quality

For the evaluation of the methodological quality of the case CRs, the CAse REports (CARE) checklist (https://www.care-statement.org/checklist) was used.[8] Although this checklist was designed as a guide for the elaboration of CRs, the lack of guidelines for assessing the methodological quality of this type of study makes the use of CARE necessary. A quantitative analysis was performed, in which each affirmative question from CARE checklist was assigned 1 point, while each negative answer was assigned a value of 0. In addition, 3 levels of methodological quality were established according to the total sum of points for a given study: poor (0–15), acceptable (15–22) and excellent (23–30). We required at least a value of 50% (15 points) or greater of the total possible score for a study to be classified as acceptable, and more than 70% (22 points) positive responses to be classified as excellent. The papers were also quantitatively analyzed according to the topics that make up CARE guidelines: Title/Keywords, Abstract, Introduction, Patient Information, Clinical Findings, Timeline, Diagnostic Evaluation, Therapeutic Intervention, Follow-up and Outcomes, Dis-

cussion, Patient Perspective, and Informed Consent. Finally, a qualitative analysis using the CARE checklist was performed.

Results

A total of a total of 3,301 articles were identified in the 3 searched databases: 985 in PubMed, 1,379 in ScienceDirect and 937 in Scopus. This number was reduced to 2,462 after the elimination of duplicate articles. Subsequently, the titles and abstracts were read to assess whether the papers were relevant to the study subject. Eighteen articles were selected and completely read to verify compliance with the inclusion criteria.

Five articles did not meet the selection criteria and were eliminated for the following reasons: 1) FP occurred immediately after an inappropriate surgical procedure (air blast performed with a triple syringe to visualize the surgical bed)[9]; 2) case report without information required for analysis[10]; 3) a retrospective study that analyzed the reactivation of varicella-zoster virus (VZV) in delayed FP after dental treatment and orofacial surgery in patients who presented with FP 20 days after dental treatment.[11]; 4) FP attributed to endodontic treatment of lower right molar[12]; and 5) intervention was performed under general anesthesia[13] (Table 1). Finally, 13 articles (Fig. 1) were included in this systematic review, with a total of 18 cases analyzed (Table 2).[14–26]

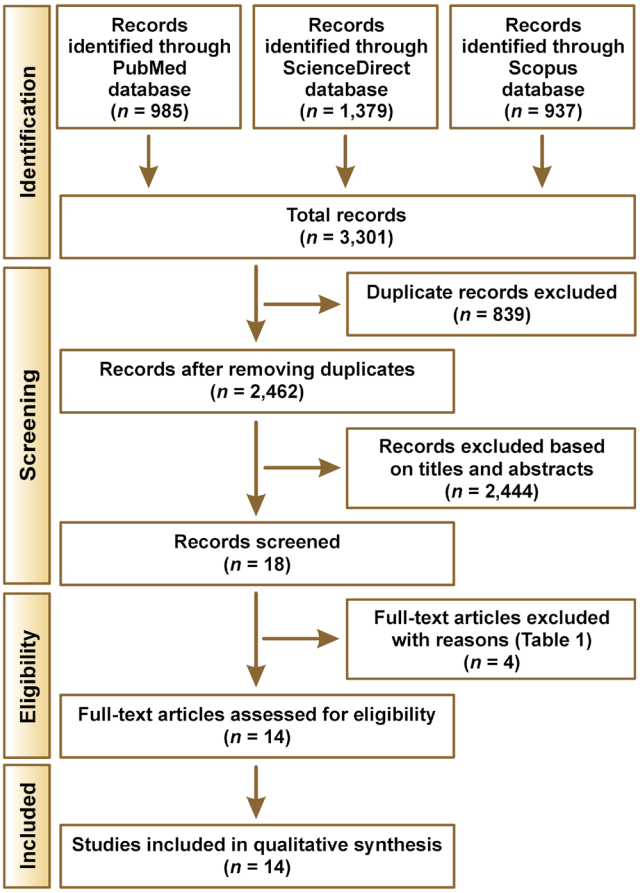

Fig. 1. Flowchart of the selection studies

Generic analysis of the studies

Of the 13 articles included in this review, 9 were CRs,[14–18,20,21,24,25] 3 CRs and literature reviews,[19,22,23] and 1 a CR in a form of a letter to the editor.[26] One study reported 4 cases,[15] 2 studies reported 2 cases each[19,21] and 10 studies reported 1 case each.[14,16–18,20,22–26] In the 18 cases analyzed, the sex distribution of the treated patients was as follows: in 9 cases, the patients were women,[15,22–26] in 7 cases men[16–21] and in 1 case there was no information on sex.[14] In relation to the age of the treated patients, 17 cases reported this data[15–26] and 1 case did not.[14] The mean age of treated patients was 34.25 years with a minimum age of 16 years and a maximum age of 62 years.

In relation to the anesthetic technique used in analyzed cases, it was observed that the truncal technique of an inferior alveolar nerve block (IANB) was employed in 11 cases,[14–25] while in 4 cases, other types of IANB technique were chosen: with infiltration of anesthetic on the buccal nerve,[21] with infiltration of anesthetic at the level of the upper central incisor on the same side,[19] with infiltration of vestibular anesthesia at the level of the upper third molar,[26] and with infiltration of vestibular anesthesia in relation to the first upper premolar law.[25] In 2 cases, the anesthetic technique used was not reported.[18,21] In relation to the type of anesthesia used, it was observed that lidocaine was chosen in 9 cases,[14–17,19,20,22] articaine in 5,[21,24–26] mepivacaine in 1,[23] and in 2 cases, the used anesthetic was not reported.[18,21] The sides being anesthetized were

Table 1. Excluded studies

Study	Reason for exclusion
Burke and Adams, 1987[9]	Facial paralysis (FP) occurred after the application of a burst of compressed air to visualize surgical area.
Stoy and Gregg, 1951[10]	Case report without information required for analysis.
Furuta et al., 2000[11]	A retrospective study that analyzed the reactivation of varicella-zoster virus (VZV) in delayed FP after dental treatment and orofacial surgery in patients who presented with FP 20 days after dental treatment.
Demetoglu et al., 2016[12]	Facial paralysis occurred after endodontic treatment of the first right lower molar, then exodontia of this tooth was performed and the paralysis disappeared.
Bobbitt et al., 2000[13]	Intervention was performed under general anesthesia.

Table 2. Characteristics of included studies

Study	Study type	Number of cases reported	Sex	Age [years]	Anesthetic and vasoconstrictor	Anesthesia technique	Affected side	Dental treatment performed	Time of onset of FP	FP classification	Recovery (total, partial or no recovery)	Recovery time [days]
Tiwari and Keane 1970[14]	case report	1	not reported	not reported	lidocaine adrenalin	IANB	left	dental surgery (accomplished)	night after the treatment	early	total	38
Gray 1978[15]	case report	4	F	44	lidocaine not reported	IANB	left	dental surgery (accomplished)	3 min after anesthesia application	early	total	1 (2 h)
			F	29	lidocaine not reported	IANB	left	dental surgery (accomplished)	3 min after anesthesia application	early	total	1 (7 h)
			F	16	lidocaine not reported	IANB	left	dental surgery (accomplished)	2 min after anesthesia application	early	total	1 (1.5 h)
Weinberg et al. 1985[16]	case report	1	M	50	lidocaine adrenalin	IANB	left	lower canine endodontic treatment (not accomplished)	11 min after anesthesia application	early (right side)	total (right side)	1 (55 min)
Ling 1985[17]	case report	1	M	22	lidocaine epinephrine	IANB	left	impacted lower third molar surgical exodontia impacted (accomplished)	20 days after treatment	late	total	30
Shuaib and Lee 1990[18]	case report	1	M	26	not reported	not reported	right	lower third molar exodontia (accomplished)	within 24 h after treatment	early	total	44
Miles 1992[19]	case report and review	2	M	26	lidocaine adrenalin	IANB and infiltration to superior alveolar nerve	right	dental surgery (first lower right molar and upper central incisor) (accomplished)	4 days after treatment	late	total	30
Shenkman et al. 1996[20]	case report	1	M	34	lidocaine epinephrine	IANB	right	dental surgery (amalgam) (accomplished)	20 min after treatment	early	without recovery	not applicable
Tazi et al. 2003[21]	case report	2	M	40	articaine epinephrine	IANB and infiltration to buccal nerve	right	lower third molar exodontia (accomplished)	20 days after treatment	late	total	150
			M	42	not reported	not reported	right	upper first molar exodontia (accomplished)	24 h after treatment	late	partial	31
Vasconcelos et al. 2006[22]	case report and review	1	F	21	lidocaine epinephrine	IANB	right	lower third molar exodontia (accomplished)	morning after treatment	early	total	90
Chevalier et al. 2010[23]	case report and review	1	F	34	mepivacaine without vasoconstrictor	IANB	left	lower second molar pulpotomy (accomplished)	2 h after treatment	early	total	365
Tzermpos et al. 2012[24]	case report	1	F	20	articaine adrenalin	IANB	left	dental surgery (lower first molar) (accomplished)	24 h after treatment	late	total	60
Ilea et al. 2014[25]	case report	2	F	62	articaine adrenalin	IANB	left	lower first molar pulpectomy (not accomplished)	2 min after anesthesia application	early	total	1
			F	59	articaine adrenalin	IANB and infiltration to middle superior alveolar nerve	right	vestibular drainage at the level of the first premolar (accomplished)	on the day after treatment	early	total	21
Zhang et al. 2016[26]	case report letter to editor	1	F	23	articaine not reported	IANB and infiltration to posterior superior alveolar nerve	right	upper third molar exodontia (not accomplished)	immediately after anesthesia application	early	total	1 (2 h)

FP – facial paralysis; IANB – inferior alveolar nerve block; F – female; M – male.

8 right and 9 left, and the affected sides were 8 right and 9 left, resulting in 17 reports of FP on the same anesthetized side (ipsilateral side), and a single report on the other side (contralateral side).[14–26] Furthermore, out of the 17 reported cases, 12 displayed early FP within 24 h[14–16,18,20,22,23,25,26] and the remaining 5 late FP.[17,19,21,24] Only 9 patients received some type of treatment of FP,[14,17,18,20–24] such as corticosteroids in 5 reports,[14,17,18,21,24] nonsteroidal anti-inflammatory analgesics (NSAIDs) in 1,[20] NSAIDs with an antibiotic (amoxicillin) and vitamin B complex in 1,[25] and vitamin B, cytidine and uridine complexes in 1.[22] Finally, it was observed that 15 patients achieved full recovery, 1 partial recovery and 1 no recovery. The mean recovery time from FP was 54.1 days, with a minimum and maximum time of 45 min and 365 days, respectively. The cases in which the recovery time was shorter than 7 h were approximated as 1 day to calculate the mean time in days. Detailed characteristics of each included study and case are presented in Table 2.

Analysis of the methodological quality of the included studies

According to the CARE guidelines and the criteria described in the Materials and methods section, the methodological quality of the CRs included in this review was generally acceptable, with a mean value of 15.5 (52%). In the analysis of the CRs on a case-by-case basis, 12 scored 50% or more of positive answers and were classified as acceptable, and 5 failed to exceed 50% and thus were classified as poor. No case in any paper scored more than 70% of positive responses, and thus none of the cases were classified as having excellent quality. However, when analyzing the methodological quality in relation to the publication year, 5 of 6 cases described in articles published before 1990 had a very low percentage of positive responses (37%, 27%, 23%, 23%, and 47%). This score improved over time, as all analyzed articles published after that date had a score of 50% or more.

Methodological quality analysis in terms of individual topics that make up CARE guidelines yielded the following percentages of positive responses: Title/Keywords – 56%, Abstract – 57%, Introduction – 71%, Patient Information – 57%, Clinical Findings – 88%, Timeline – 82%, Diagnostic Assessment – 34%, Therapeutic Intervention – 57%, Follow-up and Outcomes – 25%, Discussion – 79%, Patient Perspective – 0%, and Informed Consent – 12%.

During the analysis of affirmative answer percentages using the CARE guidelines, the 4 questions that obtained the highest percentages were "Discussion of the relevant medical literature with references" – 100% and "The scientific rationale for any conclusions (including assessment of possible causes)" – 100% (both from the Discussion topic), "Did the patient give informed consent? Please provide if requested" (from the Informed Consent topic) – 100%, and "Introduction: What is unique about this case and what does it add to the scientific literature?" (from the Abstract topic) – 94%. On the other hand, the 4 questions that obtained the lowest percentages were and "Intervention adherence and tolerability (How was this assessed?)" – 6% and "Adverse and unanticipated events" (both from Follow-up and Outcomes topic) – 0%, "Prognosis (such as staging in oncology) where applicable" (from the Diagnostic Assessment topic) – 0%, and "The patient should share their perspective in one to two paragraphs on the treatment(s) they received" (from the Patient Perspective topic) – 0%. The details of the methodological quality analysis are presented in Table 3, and all the questions constituting the CARE guidelines are listed in Table 4.

Discussion

Facial paralysis following ILIA can be classified as early or late, with early cases occurring within the first 24 h, and late cases beginning later than 24 h after ILIA. On the other hand, the length of anesthetic action of lidocaine, mepivacaine and articaine on soft tissues varies from 3 to 5 h,[27] so late FP cannot be caused by the local anesthetic affecting the facial nerve. Possible causes of FP as a consequence of ILIA described in the analyzed studies include: 1) direct effect of the anesthetic solution on branches of the facial nerve, 2) viral reactivation and 3) the vasoconstrictive effect on sympathetic fibers that affects the facial nerve. If the first proposed cause is true, it would mean that the anesthetic solution is deposited directly into the parotid region (PR), which the facial nerve passes after leaving the stylomastoid foramen.[28] Given that the anesthetic does not have the capacity to pass through the fascia that delineates the PR,[29] the anesthetic would need to be deposited near a terminal branch of the facial nerve.

It should be noted that in most of the intraoral anesthesia techniques used in dentistry, anatomical injection sites away from the PR and terminal motor branches of the facial nerve are routinely chosen. However, IANB is the riskiest technique in relation to the possibility of depositing anesthetic in the PR as the anesthetic inoculation site is the pterygomandibular space (PS), which is located close to the PR. The articles included in this systematic review reported that 13 of the 18 FP cases occurred in patients where the IANB technique was used, and only in 5 FP cases, a different or no anesthetic technique was described. Furthermore, among the 13 reported FP cases in which IANB technique was chosen, 9 had early onset, which supports the explanation that the anesthetic is the cause of FP and may have been deposited in the PR in those cases.

One of the possible factors causing anesthetic deposition in the PR could be the deflection of the needle as it passes through the soft tissues until it reaches the anesthetic inoculation area. A deviation of the needle from the expected insertion path can occur. This phenomenon has been studied in needles used in dentistry for performing

Table 3. Characteristics of the selected studies

Topic	Tiwariand Keane 1970[14]	Gray 1978 (a)[15]	Gray 1978 (b)[15]	Gray 1978 (c)[15]	Weinberg et al. 1985[16]	Ling 1985[17]	Shuaib and Lee 1990[18]	Miles 1992 (a)[19]	Shenkman et al. 1996[20]	Tazi et al. 2003 (a)[21]	Tazi et al. 2003 (b)[21]	Vasconcelos et al. 2006[22]	Chevalier et al. 2010[23]	Tzermpos et al., 2012[24]	Ilea et al. 2014 (a)[25]	Ilea et al. 2014 (b)[25]	Zhang et al. 2015[26]	Percentage of positive responses for each question [%]	Percentage of positive responses for each topic [%]
Title	0	1	1	1	0	0	0	1	1	1	1	1	1	0	1	1	1	71	56
Keywords	0	0	0	0	1	0	0	1	1	0	0	1	0	1	1	1	0	41	
Abstract	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	94	57
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	88	
	1	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	29	
	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	18	
Introduction	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	71	71
Patient Information	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	88	57
	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	77	
	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	0	0	18	
	0	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	1	47	
Clinical Findings	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	88	88
Timeline	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	82	82
Diagnostic Assessment	1	0	0	0	1	1	1	0	1	0	0	1	1	0	1	1	1	59	34
	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	41	
	0	0	0	0	1	0	0	1	1	0	0	1	0	1	0	0	1	35	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Therapeutic Intervention	1	0	0	0	1	1	1	1	0	1	1	1	1	1	1	1	0	71	57
	1	0	0	0	1	1	0	1	0	1	1	1	1	1	1	1	0	65	
	0	0	0	0	0	1	0	1	0	0	0	0	1	1	1	1	0	35	
Follow-up and Outcomes	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	1	0	24	25
	1	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	71	
	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	6	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Discussion	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	18	79
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100	
Patient Perspective	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Informed Consent	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	12	12
Total number of positive responses for each case	11	8	7	7	14	17	16	15	17	18	18	21	21	18	18	18	19	1.5	–
Methodological quality of each study	P	P	P	P	P	A	A	A	A	A	A	A	A	A	A	A	A	A	
Percentage of positive responses for each case [%]	37	27	23	23	47	57	53	50	57	60	60	7	70	60	60	60	63	52	

A – acceptable; P – poor; 0 – negative answer; 1 – positive answer.

ILIA, with a maximum deviation of 8.4 mm and 5.2 mm from the expected insertion path in the studies reported by Jeske and Boshart[30] and Hochman and Friedman,[31] respectively. On the other hand, it has also been shown that the bevel of the needle influences the deviation of the needle as it passes through the tissues, generating a deviation to the opposite side to the one on which it is located.[32–35] It could mean a deviation of the needle towards

Table 4. CAse REports (CARE) checklist questions

Topic	Check list item description
Title	1. The words "case report" should be in the title along with the area of focus.
Keywords	2. Two to five key words that identify areas covered in this case report.
Abstract	3. (a) Introduction. What is unique about this case? What does it add to the medical literature?
	3. (b) The main symptoms of the patient and the important clinical findings.
	3. (c) The main diagnoses, therapeutics interventions, and outcomes.
	3. (d) Conclusion: What are the main "take-away" lessons from this case?
Introduction	4. One or two paragraphs summarizing why this case is unique with references.
Patient Information	5. (a) De-identified demographic information and other patient specific information.
	5. (b) Main concerns and symptoms of the patient.
	5. (c) Medical, family, and psychosocial history including relevant genetic information (also see timeline).
	5. (d) Relevant past interventions and their outcomes.
Clinical Findings	6. Describe the relevant physical examination (PE) and other significant clinical findings.
Timeline	7. Important information from the patient's history organized as a timeline.
Diagnostic Assessment	8. (a) Diagnostic methods (such as PE, laboratory testing, imaging, surveys).
	8. (b) Diagnostic challenges (such as access, financial, or cultural).
	8. (c) Diagnostic reasoning including other diagnoses considered.
	8. (d) Prognostic characteristics (such as staging in oncology) where applicable.
Therapeutic Intervention	9. (a) Types of intervention (such as pharmacologic, surgical, preventive, self-care).
	9. (b) Administration of intervention (such as dosage, strength, duration).
	9. (c) Changes in intervention (with rationale).
Follow-up and Outcomes	10. (a) Clinician and patient-assessed outcomes (when appropriate).
	10. (b) Important follow-up diagnostic and other test results.
	10. (c) Intervention adherence and tolerability (How was this assessed?).
	10. (d) Adverse and unanticipated events.
Discussion	11. (a) Discussion of the strengths and limitations in your approach to this case.
	11. (b) Discussion of the relevant medical literature.
	11. (c) The rationale for conclusions (including assessment of possible causes).
	11. (d) The primary "take-away" lessons of this case report.
Patient Perspective	12. When appropriate, the patient should share their perspective on the treatments they received.
Informed Consent	13. Did the patient give informed consent? Please provide if requested.

the posterior part of the PS when performing an IANB. In this technique, the bevel of the needle should be oriented laterally (internal surface of the ramus of the mandible), which increases the possibility of the needle having a medial and posterior deviation when approaching the PR (Fig. 2).

In relation to the possibility of anesthetic injections into the PR, Petersen showed in 1971 that improper application of the IANB technique could cause anesthetic to be deposited in the PR, resulting in an early FP.[36] The steps required to achieve success in the IANB technique are well documented.[27] The essential thing for the dentist is to feel that the needle is in contact with the internal surface of the mandibular ramus, which confirms the PS location, and that the needle is not on the other side. Gay Escoda and Berini Aytés emphasized the importance of this needle–bone contact, specifying that this is the only sure way to prevent injecting the anesthetic into other anatomical areas close to the PS.[37] Thus, the most probable cause of IFP could be explained by the aberrant penetration of the anesthetic solution into the retromandibular space or the fascia of the parotid gland when anesthetizing the inferior alveolar nerve if the needle penetrates beyond the posterior edge of the mandibular ramus.[38–40]

However, the etiology of late FP is not well defined. Several possible factors have been proposed, such as respiratory infection, immunosuppression, stress, fever, menstruation, sun exposure, exposure to cold, dental procedures, and a result of the reactivation of the herpes virus.[21,40,41] Herpes viruses are ubiquitous pathogens that infect humans and other animal species. In the human herpesviridae family, 8 different species are recognized, including herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), VZV, Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), HHV-7, and HHV-8.[42–46] The reactivation of these viruses cause recurrent infections and trigger cell lysis and multiple symptoms with clinical manifestations.[45–47]

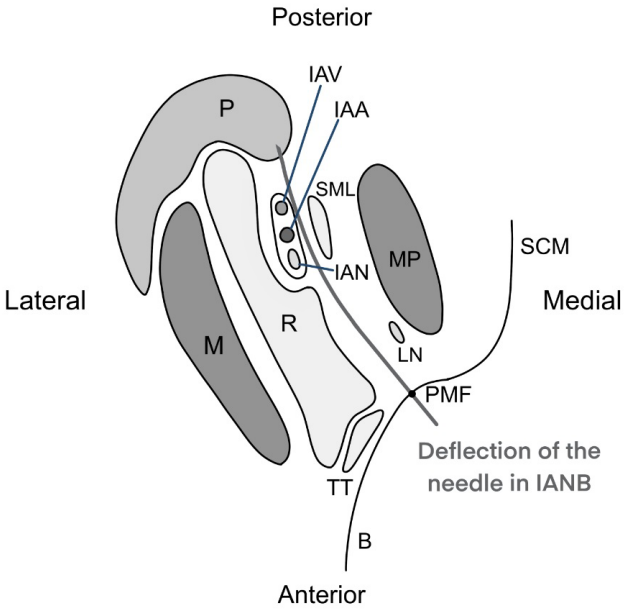

Fig. 2. Schematic representation of needle deflection during IANB in transversal section of the right ramus of mandible (image modified from the article by Khoury et al.[56])

B – buccinator; IAA – inferior alveolar artery; IAN – inferior alveolar nerve; IAV – inferior alveolar vein; LN – lingual nerve; SML – sphenomandibular ligament; M – masseter; MP – medial pterygoid muscle; P – parotid gland; PMF – pterygomandibular fold; R – ramus of mandible; SCM – superior constrictor muscle; TT – tendon temporal muscle; gray line from PMF to P – deflection of the needle in IANB.

The mechanisms related to understanding how viral reactivation triggers FP are not entirely clear, but if anatomical communication is established, this could explain such reactivation to some extent. Herpes simplex virus type 1 is predisposed to a latency period within the neuronal soma of the neurons present in the trigeminal ganglion,[48] which innervates the tongue and gums through the lingual nerve, which in turn is in close contact with the nerve of the tympanic cord (branch of the facial nerve) that carries the parasympathetic innervation to the submandibular and sublingual glands, as well as transmits sensory information from the anterior two-thirds of the tongue.[28] These anatomical and physiological connections allow the local anesthetic injected near the entrance of the mandibular duct during IANB to cause a temperature change due to the vasoconstrictor present in the dental cartridge syringe. This causes the reactivation of the HSV-1 located in the trigeminal ganglion, the VZV located in the facial nerve ganglion or trigeminal ganglion, or the HHV-6 located in the salivary glands in patients infected with these dormant viruses, as it has been shown that these viruses are thermogenic.[49] Gaudin et al. studied 16 patients presenting with FP after a dental intervention, 14 of whom had prodromal symptoms consistent with the manifestation of viral reactivation (lingual tinnitus, dysgeusia, facial numbness, and postauricular pain).[50] Two patients were diagnosed with Ramsay Hunt syndrome (headache, earache and FP). Among the 16 patients analyzed, the IANB technique was used in 8 and was ipsilateral in all patients with FP in relation to the anesthetized side.[50] Furuta et al. studied 8 patients undergoing dental treatment or oral surgery that presented with FP using serological tests and polymerase chain reaction (PCR).[11] The VZV was detected using polymerase chain reaction (PCR) in the saliva of 6 patients and HSV-1 was detected in the saliva of the remaining 2. Similarly, Turriziani et al. evaluated the viral presence in saliva samples from 95 patients who presented with IFP within 48 h of onset, and the following results were observed: HHV-6 was detected in 63% of patients, HSV-1 in 13% and VZV in 3%.[51] There were also animal studies: Fujiwara et al. injected Wistar rats with HSV-1, causing FP in them after 3–5 days.[52]

Finally, the last explanation presented in the literature for FP after ILIA is the activation of sympathetic fibers that surround the stylomastoid artery, causing ischemia in the facial nerve and subsequent FP. Scientific evidence supporting this idea is based on studies on experimental animals that had a vasoconstrictor injected directly into the facial nerve duct, causing FP.[53] Unfortunately, there are no animal studies or clinical trials that analyzed the feasibility of generating this effect through the ILIA.

Only 9 patients received some type of treatment of FP[14,17,18,20,22–25]: 5 were administered corticosteroids,[14,17,18,20,24] 1 was given NSAIDs),[20] 1 received NSAIDs with an antibiotic (amoxicillin) and vitamin B complex,[25] and 1 got vitamin B, cytidine and uridine complexes.[22] (all details are presented in Table 5). The scientific literature reports mainly the administration of corticosteroids, antivirals, or a combination of both. Madhok et al. in their systematic review of corticosteroid treatment for FP found that 17% of patients treated with corticosteroids achieved an incomplete recovery after 6 months of treatment compared to 28% of patients who did not receive treatment.[54] On the other hand, the use of antivirals compared to placebos had a nonsignificant detrimental effect on the recovery from FP. In addition, treatment with the combination of corticosteroids and antivirals showed no benefits compared to treatment with corticosteroids alone.[55] However, these therapies have been described for patients suffering from IFP in which the etiology is not known, different from the scenario identified by dentists, because the patient manifests early or late FP depending on the case. In this regard, the dentist has the advantage of knowing that the etiology of early FP is probably due to the direct condition of the facial nerve caused by anesthesia or due to the effect exerted by the vasoconstrictor on the stylomastoid artery, and they treat this type of FP with the administration of corticosteroids, while it is recommended to treat patients with late FP with a combination of corticosteroids and antivirals due to the possibility of viral reactivation. There are also other means of patient care available, such as the use of artificial tears and eye patches to prevent resection and lesions of the globe and conjunctiva, and the use of artificial saliva to prevent oral dryness and the development of periodontal diseases and caries.

Table 5. Facial paralysis treatment

Study	Facial paralysis treatment
Tiwari and Keane, 1970[14]	5 mg of prednisolone 4 times a day orally, facial muscle exercises, protection of the left eye with dark glasses during the day and a patch at night, mouthwash after meals
Gray, 1978[15]	not reported in all 3 cases
Weinberg et al., 1985[16]	not reported
Ling, 1985[17]	4 mg of triamcinolone 4 times a day orally for 10 days, with gradual dose reduction
Shuaib and Lee, 1990[18]	prednisone, dosage not reported
Miles, 1992[19]	without treatment in both cases
Shenkman et al., 1996[20]	acetylsalicylic acid, dosage not reported
Tazi et al., 2003[21]	prednisone 1 mg/kg for 5 days
Vasconcelos et al., 2006[22]	vitamin B complex and cytidine and uridine complex both twice a day
Tzermpos et al., 2012[24]	20 mg of prednisone 3 times a day during the 1st week, 20 mg 2 times a day during the 2nd week, 20 mg once a day during the 3rd week, and 10 mg once a day during the 4th week and indication of eye lubricant
Ilea et al., 2014[25]	no treatment (kept under observation)
Zhang et al., 2015[26]	without treatment

Limitations

There are some limitations to this study. First, there are few studies reporting FP cases following ILIA, and there may be many undocumented cases, making it difficult to show the true prevalence. Secondly, as far as methodological quality is concerned, no studies attained an excellent level, and there may be a lack of importance for the total understanding of FP following the ILIA.

Conclusions

The FP following ILIA has a low prevalence. Early FP CRs presented the effect of the administered anesthetic on the facial nerve, and the vascular effect of the vasoconstrictor included in the anesthetic formula, while more recent FP CRs focused on the reactivation of HSV-1, HHV-6 or VZV. Furthermore, there seems to be a relationship between the anesthetic technique used and the risk of FP, with special attention paid in this regard to the IANB technique due to the anatomical proximity of the puncture site to the PR and the anatomical space through which the motor branches of the facial nerve pass through to innervate the muscles of facial expression. Close following of the consecutive steps of the IANB technique are essential to prevent FP because contact of the needle with the bone is perceived as the only way to verify that the anesthetic is being deposited in the PS and not in the PR or another anatomical space. However, ensuring the contact of the needle with the bone tissue can prevent the appearance of only early FP, but not late FP. The knowledge about appropriate pharmacological therapy is important in treating late FP. In addition, it seems prudent not to associate IFP or Bell's palsy with FP that occurs after a dental intervention, because unlike the former, there is a possible causative factor of the FP and it is not entirely idiopathic. Furthermore, a scarce but acceptable level of evidence was observed in the present study regarding the relationship between ILIA and FP. Finally, all ILIAs are safe to use in dental practice and must be properly selected depending on the anatomical area to be blocked. However, general dentists and specialists should be updated on the management and treatment of FP after ILIA. Regarding treatment, based on what is described in the literature, we suggest corticosteroids if the FP is early, and a combination of antiviral drugs with corticosteroids in late FP.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable

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Review

Aldehyde dehydrogenase 1: Its key role in cell physiology and oral carcinogenesis

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

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):629–635

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on February 3, 2021
Reviewed on November 29, 2021
Accepted on December 6, 2021

Published online on December 30, 2022

Abstract

Aldehyde dehydrogenase (ALDH), an aldehyde-metabolizing enzyme, is a cytosolic antioxidant. It performs many important physiological catalytic and non-catalytic functions in mammalian cells. Apart from physiological functions, like the biosynthesis of vital molecules, this NAD(P)+ substrate-dependent enzyme superfamily is primarily involved in catalyzing the oxidation of highly reactive exogenous and endogenous aldehydes to their respective carboxylic acids. Among ALDH isoenzymes, ALDH1 has gained much attention as a prominent stem cell marker, as it is associated with the maintenance of stemness and the differentiation of normal stem cells, in addition to involvement in oncogenic functions, like cell proliferation, anti-apoptosis and the reduction of oxidative stress in cancer stem cells (CSCs). In this context, the authors review the physiological functions of ALDH1 in normal cells, normal stem cells and CSCs, along with the discussion of the putative role of ALDH1 in oral carcinogenesis by commenting on its expression in normal oral mucosa cells, oral potentially malignant disorders (OPMDs), like leukoplakia and dysplastic lesions, and oral squamous cell carcinoma (OSCC).

Keywords: carcinogenesis, stem cells, oral squamous cell carcinoma, aldehyde dehydrogenase 1

Cite as
Swain N, Thakur M, Pathak J, Patel S, Hosalkar R. Aldehyde dehydrogenase 1: Its key role in cell physiology and oral carcinogenesis. *Dent Med Probl.* 2022;59(4):629–635. doi:10.17219/dmp/144575

DOI
10.17219/dmp/144575

Introduction

Aldehyde dehydrogenases (ALDHs) are one of the 3 aldehyde-metabolizing enzyme groups found in virtually all mammalian cellular compartments, the other 2 groups being aldehyde oxidases and aldo-keto reductases.[1] The ALDH NAD(P)$^+$ substrate-dependent enzyme superfamily catalyzes the oxidation reactions of highly reactive exogenous and endogenous aldehydes to their respective carboxylic acids. In addition to their role in aldehyde oxidation, ALDHs also have their share in other, non-catalytic physiological functions, like the biosynthesis of vital molecules, i.e., retinoic acid (RA), folate, gamma-aminobutyric acid, and betaine, binding to endobiotics and xenobiotics, and the absorption of ultraviolet (UV) radiation and its involvement in osmoregulation in humans.[2] In humans, the ALDH superfamily is currently comprised of 11 families (ALDH1, ALDH2, ALDH3, ALDH4, ALDH5, ALDH6, ALDH7, ALDH8, ALDH9, ALDH16, and ALDH18) and 4 subfamilies, which comprise 19 functional genes.[3] Among these, the class 1 ALDH gene in humans is found on chromosome 9, spans about 53 kb and is comprised of 13 exons that are separated by 12 introns. *ALDH1* encodes 501 amino acids, including the chain initiation Met. The 5' upstream region of *ALDH1* contains 2 glucocorticoid response elements, which suggests that *ALDH1* may be influenced by hormones.[4] There are further 6 genes in human ALDH1 family: *ALDH1A1*; *ALDH1A2*; *ALDH1A3*; *ALDH1B1*; *ALDH1L1*; and *ALDH1L2*. Primarily, ALDH1 proteins are localized in cytosol in various tissues, except ALDH1B1, which has a mitochondrial localization.[5] The constitutive expression of ALDH1 in the tissues of mammals and the multifaceted physiological role of ALDH1 highlights its diagnostic, therapeutic and prognostic importance. In this review, we describe the role of ALDH1 in normal cells, normal stem cells and cancer stem cells (CSCs) in detail.

ALDH1 in cellular physiology

Retinoic acid metabolism

Retinoic acid and its metabolites are important in embryological development, morphogenesis and the regulation of gene expression. The ALDH1 family includes ALDH1A1, ALDH1A2, ALDH1A3, ALDH1A7, and ALDH1A8, which are primarily involved in the catalysis of retinal to RA. Consequently, RA then enters the nucleus, where it induces c-MYC and cyclin D1 transcription, which promotes resistance to apoptosis and increases cell proliferation, especially in cells with estrogen receptors. However, RA can also cause differentiation and apoptosis through the transcription of the retinoic acid receptor beta (RARβ). When the endogenous concentration of RA is low, exogenous RA can activate the ALDH1A1 promoter to enhance the production of RA.[6]

Acetaldehyde metabolism

Ethanol, a common by-product of carbohydrate metabolism, is metabolized to acetaldehyde by several enzymes, such as catalase, alcohol dehydrogenase (ADH) and cytochrome P4502E1. The reactive oxygen species (ROS) generated by acetaldehyde contribute to oxidative stress, which promotes the formation of DNA and protein adducts. The ALDH1A1 enzyme is involved in acetaldehyde metabolism – acetaldehyde is subsequently metabolized to acetate by ALDH2 – and hence ALDH1A1 acts as part of the cellular anti-oxidative defense system.[7]

Oxidative stress

Reactive aldehydes are detrimental to humans. They may be generated when endobiotic and xenobiotic compounds such as alcohols, amino acids, neurotransmitters, and environmental pollutants (e.g., food additives, motor vehicle exhaust, cigarette smoking, pesticides) are metabolized. Reactive aldehydes are strongly electrophilic, long-lasting compounds that readily form macromolecule adducts on proteins, RNA and DNA. Such modifications lead to DNA damage, enzyme inactivation, cell death, and carcinogenesis. The expression of ALDHs is generally upregulated in response to the oxidative stress induced by aldehydes. ALDH1, specifically ALDH1A1, along with ALDH2 catalyze the reactive aldehydes generated as a result of alcohol toxicity. These reactive aldehydes comprise, among others, 4-hydroxy-2 nonenal (4-HNE) as well as malondialdehyde (MDA), which are ALDH1B1 substrates. In addition to alcohol-induced oxidative stress, ALDHs, specifically ALDH1A1 along with ALDH3A1, are involved in detoxifying the reactive aldehydes produced by UV radiation by inhibiting the formation of 4-HNE and MDA.

ALDH1 in stem cells

Normal stem cells

Increased ALDH activity has been associated with stemness, owing to the consistent expression of ALDHs in the stem cells of several tissues. Aldehyde dehydrogenases have also been implicated in the functioning of stem cells, including expansion, self-protection and differentiation. Retinoic acid metabolism also contributes to the retinoid signaling pathway, and thereby plays an important role in maintaining stemness in stem cells.[7] The protection conferred by ALDHs in stem cells can be attributed to the detoxifying capabilities of the enzymes, mainly against various exogenous and endogenous aldehydes. In addition to aldehydes, ALDH1 also confers protection against various cytotoxic drugs, like cyclophosphamide and 4-hydroperoxycyclophosphamide (4-HC). In vitro experiments in both murine and human experimental models show that ALDH1 inhibition through inhibitors such as N,N-diethyl-

aminobenzaldehyde (DEAB) results in the expansion and differentiation of hematopoietic stem cells (HSCs) by delaying the G0/G1 transition, which results in a large number of HSCs remaining in the G0 phase.[8,9] Almost all tissues have a stem cell population. In bone marrow, among the population of stem cells, there are cells of high ALDH activity. Hematopoietic progenitors and neural stem cells usually express high levels of ALDH activity ($ALDH^{hi}$ cells). Besides, stem cells from adipose tissue, being multipotent mesodermal cells, also embrace a $ALDH^{hi}$ cell population.[10] Amongst all ALDH isoenzymes, ALDH1A1 seems to be expressed predominantly in the aforementioned stem cell populations. Reportedly, ALDH1A1 significantly contributes to the maintenance of stem cell populations by restricting cell proliferation through the irreversible conversion of 10-formyltetrahydrofolate (10-FTHF) into tetrahydrofolate (THF).[10] As ALDH1 activity in normal stem cells differs from tissue to tissue, Deng et al. classified tissues into 3 types according to the level of ALDH1 expression: 1. tissues with no expression or limited expression, such as lung and breast; 2. tissues with a weaker expression as compared to others, such as gastric epithelium and colon; and 3. tissues that have a greater expression level, such as liver and pancreas.[11]

Cancer stem cells

Analogous to normal stem cells, the functional contribution of ALDH1 in CSCs mainly revolves around RA metabolism. In the classical pathway, ALDH metabolizes RA to products like 13-cis-retinoic acid (13-cis-RA), all-trans-retinoic acid (ATRA) and 9-cis-retinoic acid (9-cis-RA), which bind to retinoic acid receptor alpha (RARα) prior to entering the nucleus. In order to induce the expression of downstream target RARβ, RA binds to RARα and X retinoid receptor (RXR) dimers. This eventually results in cell differentiation as well as growth inhibition. In contrast to this, and through non-classical pathways, RA can induce anti-apoptosis, anti-differentiation and proliferative activity by activating the phosphoinositide 3-kinase (PI3K) signaling pathway and reducing the activity of protein kinase C. In addition, in cells with estrogen receptor alpha (ERα) and peroxisome proliferator-activated receptors beta/delta (PPARβ/δ), RA can form heterodimers with these receptors to upregulate pro-survival genes.[6,9]

Apart from RA metabolism, ALDH plays a significant protective role by reducing the level of ROS production and oxidative stress in CSCs, which thus prevents their apoptosis. Oncogenic pathways, like Notch-DLL4, MUC1-C, ERK, and Wnt/β-catenin, either upregulate ALDH1 transcription or increase its activity in CSCs (Fig. 1).[6,12] Regardless of whether oxidative stress is of endogenous (aerobic metabolism) or exogenous (due to chemotherapeutic or radiotherapeutic agents) origin, ALDH can reduce the ROS level in CSCs. Cancer stem cells are an important contributor to drug resistance in cancer treatment. Cumulative evidence of the strong association of chemotherapeutic drug resistance with ALDH1 expression in CSCs indicates the potential role of ALDH1 in molecular targeted therapies for several cancers. Various mechanisms have been suggested for describing the protective role of ALDH1 against these cytotoxic drugs, such as the oxidation of the aldehyde group to carboxylic acid and ultimately the transformation of the drugs into non-toxic forms, and the induction of RA-mediated signaling pathway.[6]

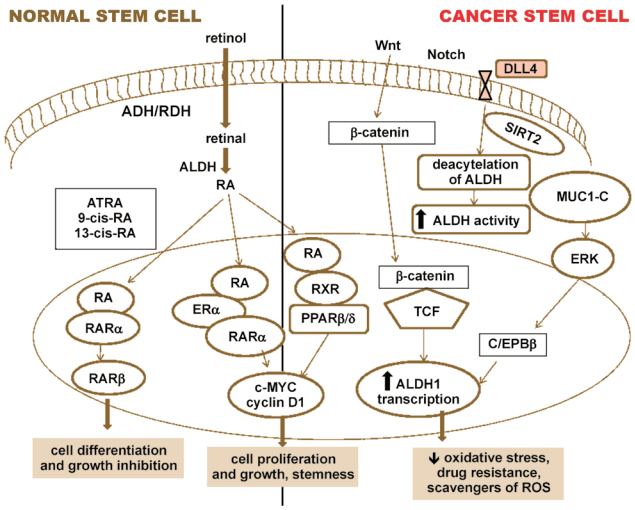

Fig. 1. Potential role of aldehyde dehydrogenase 1 (ALDH1) in normal and cancer stem cells

ALD – alcohol dehydrogenase; ALDH – aldehyde dehydrogenase; ATRA – all-trans-retinoic acid; ERα – estrogen receptor alpha; PPARβ/δ – peroxisome proliferator-activated receptors beta/delta; RA – retinoic acid; RARα – retinoic acid receptor alpha; RARβ – retinoic acid receptor beta; RDH – retinol dehydrogenase; ROS – reactive oxygen species; RXR – X retinoid receptor; TCF – T-cell factor.

With this knowledge regarding the physiological and pathological role of ALDH1 at the cellular level, we attempted to revisit its putative role in oral carcinogenesis by observing its expression in various premalignant and malignant lesions of oral cavity.

Methodology

Eligibility criteria

In the present study, we considered P (Population) as human samples of oral potentially malignant disorders (OPMDs) and oral cancer; I (Intervention) – immunohistochemical staining for ALDH1; C (Comparison) – normal oral mucosa; and O (Outcome) – the expression of ALDH1 in OPMDs and oral cancer.

Research question

Is there a difference in the expression of ALDH1 in the samples of OPMDs and oral cancer as compared to normal oral mucosa based on immunohistochemical staining?

Search strategy

An electronic search of the PubMed, Google Scholar and Scopus databases was performed up to October 2021, using a combination of keywords: "aldehyde dehydrogenase 1", "ALDH1" with "oral premalignant/precancerous lesion", "oral premalignant/precancerous condition", "oral potentially malignant disorders", "oral leukoplakia", "oral erythroplakia", "oral lichen planus", "oral epithelial dysplasia", "oral submucous fibrosis", "actinic cheilitis", "dyskeratosis congenita", "keratoacanthoma", "verrucous hyperplasia", "verrucous carcinoma", "proliferative verrucous leukoplakia", "smokeless tobacco keratosis", "discoid lupus erythematosus", "cheilitis glandularis", "xeroderma pigmentosum", "oral cancer", "oral squamous cell carcinoma", and AND/OR boolean operators. Only full texts of original research articles published in the English language, pertaining to the expression of ALDH1 in OPMDs and oral cancer were included for the review. Review articles and abstracts were excluded.

Study selection process

The retrieved records were reviewed systematically by 2 independent reviewers and any disagreement was resolved by mutual consensus. Initially, the titles were reviewed and irrelevant records were excluded. The abstracts of the selected records were evaluated based on the inclusion and exclusion criteria. In cases of insufficient abstracts, the full-text articles were analyzed for relevance to the topic. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were consulted while conducting the review. The flowchart for article selection is shown in Fig. 2.

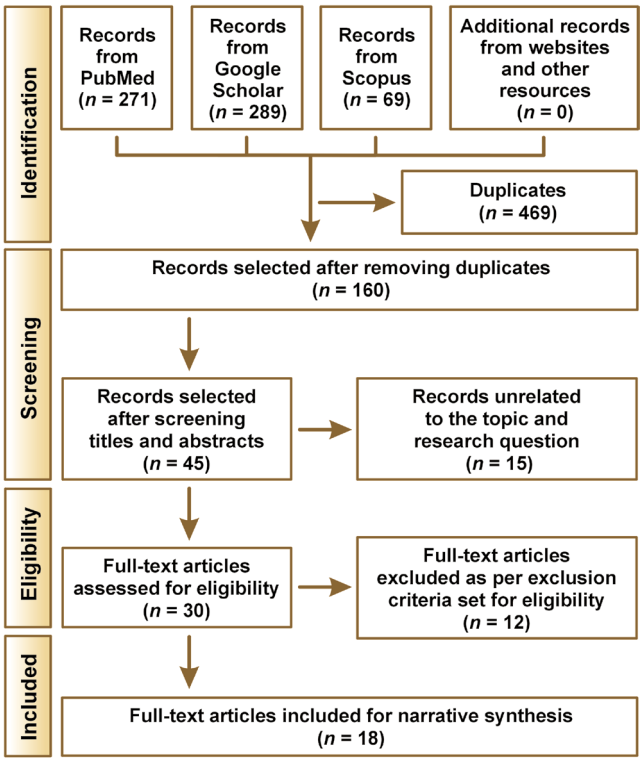

Fig. 2. Flowchart for the selection of articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Table 1. Details of the conducted clinical studies on the aldehyde dehydrogenase 1 (ALDH1) immunoexpression in oral potentially malignant disorders (OPMDs)

Authors, year	Details of the sample	Expression pattern of ALDH1
Habiba et al. 2017[14]	oral leukoplakia (n = 79)	positive expression in 48% of cases 50% and 73% of UT and MT cases exhibit expression, respectively (a 3.02-fold increase in risk)
Feng et al. 2013[17]	oral erythroplakia (n = 34)	positive expression in 55.9% of cases 29.4% and 82.4% of UT and MT cases exhibit expression, respectively (an 11.20-fold increase in risk)
Feng et al. 2020[18]		ALDH1 immunoreactivity increased in the multiple transformed group as compared to UT cases, supporting the field cancerization theory
Custódio et al. 2018[19]	actinic cheilitis (n = 43)	positive expression in 51.1% of cases
Liu et al. 2013[20]	oral leukoplakia (n = 141)	positive expression in 38.3% of cases 26.9% and 70.3% of UT and MT cases exhibit expression, respectively (a 4.17-fold increase in risk)
Xu et al. 2013[21]	oral lichen planus (n = 101)	positive expression in 34.6% of cases 30.3% and 66.7% of UT and MT cases exhibit expression, respectively (a 6.71-fold increase in risk)
Mansourian et al. 2017[22]	oral lichen planus (n = 30) (immunoabsorbent assay of unstimulated saliva)	the mean level of ALDH1 was higher in non-reticular oral lichen planus than in the reticular types
Rao et al. 2020[23]	oral epithelial dysplasia (n = 40)	positive expression in 35% of cases 25% and 10% cases showed low and high expression, respectively
Abdulmajeed et al. 2013[24]	oral epithelial dysplasia (n = 61)	increased expression in severe dysplasia as compared to those with minimal dysplasia
Marangon et al. 2019[31]	verrucous carcinoma (n = 7)	negative expression in all cases, suggestive of the indolent behavior of the lesion

UT – untransformed; MT – malignant transformed.

Results

All the selected studies (n = 18) were systematically analyzed. Table 1 presents the list of clinical studies focused on the expression of ALDH1 in OPMDs. Out of all the evaluated studies (n = 10), only 4 recorded the follow-up of patients and observed the association between the expression of ALDH1 and the risk of malignant transformation in OPMDs (a 3–11-fold increase in risk). The overall ALDH1 positivity was reported in 35–56% of all cases of OPMDs, while no expression was observed for verrucous carcinoma. The clinical studies depicted in Table 2 show a wide range (13.5–70%) in the positive expression of ALDH1 in the tumor cells of (oral squamous cell carcinoma) OSCC patients. A positive association between the ALDH1 expression and the prognostic parameters (the lymph node status and angiolymphatic invasion) and the overall survival outcome in OSCC patients was identified in 1 study.

Discussion

Expression in normal mucosa

A few researchers have attempted to examine the ALDH1 expression in normal or normal-like oral mucosa, only to observe negative immunoreactivity.[8,13–15] An in-depth study conducted by Kato et al. revealed a differential expression pattern of ALDH isoenzymes in human palatal mucosa.[16] According to their study, the expression of ALDH1A1 was absent throughout the epithelium; the expression of ALDH1A1 and ALDH1A3 cytoplasmic protein and mRNA was confined to the upper suprabasal layer. However, the signals of *ALDH1A3* mRNA in the basal and parabasal cell layers were observed without any protein expression. This discrepancy could be a result of inadequate translation into protein, the inhibition of translation initiation or post-transcriptional dysregulation.[16]

Table 2. Details of the conducted clinical studies on the aldehyde dehydrogenase 1 (ALDH1) immunoexpression in oral squamous cell carcinoma (OSCC)

Authors, year	Details of the sample	Expression pattern of ALDH1	Inference
Michifuri et al. 2012[15]	OSCC (n = 80)	positive expression in 50% of cases	ALDH1 expression was positively correlated with lymph node metastasis
Custódio et al. 2018[19]	LSCC (n = 20)	positive expression in 55% of cases	ALDH1 expression was positively correlated with carcinogenesis in the lip
Rao et al. 2020[23]	OSCC (n = 40)	positive expression in 70% of cases 5% and 65% cases showed low and high expression, respectively	ALDH1 reactivity was correlated with higher chances of lymph node metastasis and lower survival rates of patients
Abdulmajeed et al. 2013[24]	OSCC (n = 127)	overexpression of ALDH1 in OSCC as compared to the dysplastic or normal counterpart	disorganized distribution of ALDH1 expression in cancerous tissue as compared to dysplastic tissue
Juvencio de Freitas Filho et al. 2021[25]	oral cancer (n = 56)	positive expression in 25.4% of cases	increased ALDH1 immunoreactivity was correlated with a higher grade of oral malignancy the basaloid variant showed the highest ALDH1 expression (56.3%)
Huang et al. 2014[26]	TSCC (n = 66)	positive expression in 63.6% of total cases weak and strong positive expression in 36.4% and 27.2% of cases, respectively	the cancer sphere-formation ability of ALDH1 observed when co-expressed with other stem cell markers, like SOX2
Tamatani et al. 2018[27]	OSCC (n = 70)	positive expression in 25.7% of cases	ALDH1 was significantly associated with histological differentiation, invasion mode and lymph node metastasis, and hence observed as a prognostic factor for disease-free survival
Wu et al. 2017[28]	OSCC (n = 78)	higher expression observed	higher expression of ALDH1 was not significantly associated with the clinicopathogologic status of patients
Ortiz et al. 2018[29]	OSCC (n = 50)	positive expression in 46% of cases	ALDH1 high immunoexpression was positively associated with angiolymphatic invasion by tumor cells
Qian et al. 2014[30]	OSCC (n = 2) OPSCC (n = 65)	negative expression in OSCC positive expression in 49% of OPSCC cases	ALDH1A1 was an independent prognostic factor for survival
Marangon et al. 2019[31]	OSCC (n = 163)	positive expression in 47.24% of cases	ALDH1 expression was higher in the tumor budding area than in the area outside budding, especially in tumors with high-intensity tumor budding
Prudente de Moraes et al. 2017[32]	OSCC (n = 52)	positive expression in 13.5% of cases	the 5-year survival outcome was found to be lower in ALDH1-positive cases

LSCC – lip squamous cell carcinoma; TSCC – tongue squamous cell carcinoma; OPSCC – oropharyngeal squamous cell carcinoma.

Expression in OPMDs

Due to being a potent antioxidant enzyme and having a consistent association with the pathophysiology and clinical outcomes of various human carcinomas, the role of ALDH1 in OPMDs has fascinated many researchers. The details of the studies are described in Table 1.[14,17–24] All the studies performed an immunohistochemical analysis of ALDH1 in the biopsied tissue samples; only 1 study used an immunoabsorbent assay of unstimulated saliva. Increased ALDH1 expression and the severity of dysplasia were found to be positively correlated. Irrespective of the nature of the study and the sample, the observations of all studies implicate ALDH1 in oral carcinogenesis as well as its prognostic significance in the risk assessment for malignant transformation in OPMDs.

Expression in oral cancer

The studies not only targeted the ALDH1 expression in OSCCs, but also focused on the correlation of the ALDH1 expression with the co-expression of other stem cell markers, like Bmi-1, CD44, OCT4, ABCG2, and SOX2 (Table 2).[15,19,23–32] The overexpression of ALDH1, with or without the co-expression of other stem cell markers, was observed to be negatively associated with clinical outcomes and prognosis in OSCC patients. These observations could be explained by the contribution of ALDH1 as a potent antioxidant enzyme in protecting CSCs from oxidative damage from endogenous aldehydes, and chemotherapeutic and radiotherapeutic agents. In addition, ALDH1 also helps to maintain the stemness of CSCs through RA metabolism, which explains the mechanism of drug resistance in ALDH1^{hi} stem cell population-containing cancers. With the co-expression of other stem cell markers, ALDH1 was found to significantly contribute to the formation of foci and spheres as well as invasion and migration, which thus resulted in more aggressive tumor cells responsible for a poor clinical outcome in cancer patients.

Conclusions

Apart from its vital role in cell physiology, cumulative evidence shows that high levels of ALDH1 expression is associated with a greater degree of stemness in CSCs, and suggests that molecular therapies that target ALDH1 may be promising anticancer therapies. Aldehyde dehydrogenase 1 was found to be a prognostic indicator for aggressiveness, survival and drug resistance in oral cancer. Furthermore, in OPMDs, the co-expression of ALDH1 with other stem cell markers could be used to assess the risk of malignant transformation, thus adding benefit to the prevention of oral cancer.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Review

Management of transverse root fractures in dental trauma

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):637–645

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on November 9, 2021
Reviewed on December 27, 2021
Accepted on January 16, 2022

Published online on December 20, 2022

Abstract

The management of complex dental trauma can be modulated according to the emergencies that may arise over time. Clinical management of transverse root fractures may require different therapies based on situations, such as delay and error in the treatment of an avulsion trauma associated with apical third root fracture, patient's poor compliance, or external and internal root resorption. The primary aim of this article was to review studies regarding root fractures in the permanent dentition and root fracture management. The secondary aim was to present the inflammatory reaction and the complications (i.e., infections) that may occur if the International Association for Dental Traumatology (IADT) guidelines are not followed. In addition, a scenario is devised in which endodontic surgery, despite the baseline patient's conditions and negative prognosis, can help to inhibit the inflammatory root resorption and allow the preservation of soft and hard tissues within a long follow-up from the injury, for the purpose of demonstrating the next possible implant-prosthetic rehabilitation.

Keywords: dental trauma, avulsion, root fracture, apicoectomy, scanning electron microscopy

Cite as
Marasca B, Ndokaj A, Duś-Ilnicka I, et al. Management of transverse root fractures in dental trauma. *Dent Med Probl.* 2022;59(4):637–645. doi:10.17219/dmp/145895

DOI
10.17219/dmp/145895

Introduction

Avulsion of a permanent tooth occurs in 0.5–3% of all tooth injuries. It is most common in young permanent dentition and it mainly affects the maxillary central incisors.[1] Tooth avulsion injuries are common in childhood and adolescence as a result of accidental falls, road accidents and shocks in sports.[2] Numerous studies have shown that tooth avulsion is one of the most serious tooth injuries and, compared with other types of dental injuries, its long-time prognosis is highly dependent on the actions taken immediately after the trauma. In most situations, replantation is the treatment of choice, but this cannot always be performed immediately. Moreover, the prognosis of a tooth injury depends mainly on the management of the dental trauma and is closely related to the complexity of the injury itself.

Dental avulsion management must adhere to the international guidelines.[3] Timeliness of the procedure, preservation of the tooth on a physiologic storage medium, adherence to the date of root canal treatment and proper splinting are of fundamental importance to prevent inflammatory root resorption and ankylosis caused by infection of root canal system and by damage and loss of viability of periodontal ligament (PDL) cells.[4]

The complexity of a tooth trauma depends on the simultaneous presence of multiple lesions on the same tooth element, such as a tooth avulsion associated with a root or crown fracture, or the presence of a bone wall fracture. Transverse root fractures may occur as a concurrent injury with crown fracture, concussion, subluxation, lateral luxation, extrusion, or avulsion of the coronal fragment. The most common concurrent injuries are concussion and subluxation. Unfortunately, studies reporting the incidence of the various dental injuries have not reported how often these concurrent injuries co-occur with root fractures.[5,6] Additionally, these injuries almost always occur at a young age due to the greater liveliness of children.[7]

The trauma is often connected not only to the teeth but also to the jaw and, more specifically, to the temporomandibular joint (TMJ). The traumas to the TMJ can cause temporomandibular disorders that may last for a long time along with occlusion modification, pain and facial asymmetry.[8,9] Orofacial traumas can be clinically less evident and cause only enamel loss, but over a long time they can cause hypersensitivity of the tooth or loss of pulp vitality.[10,11] To prevent dental or TMJ trauma in certain risk categories, such as subjects who practice extreme sports or patients with high risk factor, the use of a mouth guard is recommended.[12]

Patients with increased overjet, amelogenesis problems, syndromic patients, as well as neurological (epilepsy) or psychiatric patients commonly suffer from dental trauma. For example, syndromic patients are at high risk of severe malocclusions, dental malformations and poor oral hygiene due to the lack of collaboration[13] that can cause destructive caries which lowers tooth resistance.[14–18]

In cases of trauma, it is essential to inform patients and their caregivers about the therapeutic protocols and follow-up periods. Nowadays, information can easily be distributed via the Internet and telemedicine.[19–21]

The complexity of dental avulsion cases requires an appropriate multidisciplinary therapeutic approach, which must consider periodontal, orthodontic, surgical, and prosthetic issues. A long-term prognosis, entailing the need to face various clinical scenarios (e.g., tooth ankylosis, loss of bone support, implant rehabilitation in adulthood) should also be taken into account.[22,23] In most cases, the replantation of the tooth and its preservation over time help to protect the alveolar bone around the site of the trauma and may offer significant long-term advantages in preparation for definitive implant-prosthetic treatment.[24]

The primary aim of this article is to review the literature regarding root fractures in the permanent dentition and their management. The secondary aim is to present the complications that may occur if the international guidelines are not followed.

Material and methods

A narrative literature overview to discuss the management of dental root fractures was carried out. Case definitions and classifications, diagnostic considerations, and the clinical protocol of the emergency management and inflammatory reaction were reviewed and analyzed.

Root fractures

Epidemiology and classification

Dental root fracture involves the dentin, cementum and pulp. The fractures can be vertical or transverse.[1,5] Vertical fracture usually requires tooth extraction and prosthetic rehabilitation. Transverse root fracture can be oblique with varying orientations and is classified as: i) fracture of the apical third of the root; ii) fracture of the middle third of the root; iii) fracture of the coronal third of the root that can be: a) subcrestal; or b) supracrestal.

Physiological responses and healing

According to Andreasen et al.,[1] the existing physiological responses of the tooth and its associated tissues to root fractures are as follows:

– healing with hard dental tissue interposition;
– healing with connective tissue interposition;
– healing with bone and connective tissue interposition; and
– no healing with inflammatory granulation tissue interposition in the fracture line, as a result of pulp necrosis and infection of the pulp space in the coronal fragment.

The pulp and PDL cells are stimulated only in the first case, and in 0.5–7% of cases almost complete restitutio ad integrum is achieved.[1] The infection of the canal system and necrosis of the apical and coronal fragments of the tooth are the reasons for the lack of healing in 22% of teeth with root fractures.[6]

Emergency management

Emergency management depends on the displacement of the coronal fragment and the level of the root fracture.[6]

Lateral luxation or extrusion of the coronal fragment require repositioning back into the sockets. If the avulsion of the coronal fragment has occurred, it should be managed as a tooth avulsion.[6]

The management of root fractures in the apical and middle thirds, as well as those that are subcrestal in the coronal third of the root, require the same conservative protocol. However, supracrestal fractures in the coronal third are managed differently.[6]

Clinical protocol

Repositioning and splinting

If the coronal fragment is displaced, it should be repositioned, and a splinting should be applied. Splints should be made by stainless steel wire bonded with composite resin to the labial surface of the affected tooth and to 1 or 2 teeth on either side of the affected tooth. Splints should restrict the movement of the coronal fragment. Rigid stabilization offers the best conditions for healing and, if present, a splint also stabilizes the fracture of alveolar bone. The recommended duration of the splint use is from 4 weeks up to 4 months.[6]

Root canal treatment

Since the prognosis for pulp recovery is favorable, root canal treatment should not be initiated at the emergency appointment. The clinical approach is to "wait and see". Moreover, maintaining the pulp vitality allows for the possibility of healing with hard dental tissue interposition.[6]

Antibiotic therapy

Antibiotics are not indicated unless the coronal fragment has been avulsed.[6]

Follow-up

Regular follow-up is essential and should be performed at 4-week intervals while the teeth are splinted, and then at 3-month intervals for the first year.[6]

Management of the inflammatory reaction and complications on an infectious basis

Clinical cases may present with varying degrees of complexity that may not always be diagnosed in the time frame indicated in the International Association for Dental Traumatology (IADT) guidelines. In fact, if the guidelines are not followed, infectious complications may occur, which often require a more complex clinical strategy, such as the removal of broken apices due to the lack of improvement or endodontic surgical resection.

Complications of infection

On some occasions, patients are diagnosed only after a significant amount of time has passed since the injury. The vast majority of these are patients of developmental age (i.e., adolescents or young adults). In such situations, it is not possible to follow the management protocols included in the IADT guidelines. Dental trauma and its incorrect management can lead to consequences with a major impact on dental esthetics and oral health-related quality of life. Dental trauma may involve the 2 maxillary central incisors and a fracture of the apical third of the roots, fracture of the alveolar process on the palate or buccal side, or a complete tooth avulsion of the coronal fragment.

Infections may occur if the international guidelines for the treatment of root fractures are not followed, in particular, if the teeth are dry stored after the avulsion, and then are reimplanted and splinted using a fixed orthodontic splint, as well as if the patient does not undergo endodontic treatment to remove the splint. The most frequent infections are repeated abscess episodes that affect the teeth involved in the trauma. The results of clinical examination show spontaneous pain and dull sound of the involved teeth upon percussion, light teeth extrusion, poor oral hygiene and mobility evaluated based on Miller's classification. In such cases, routine radiological examinations (intraoral X-ray images) are prescribed.

The radiological aspect of no healing is shown in Fig. 1. No healing occurs if the pulp of the coronal fragment becomes necrotic and infected, with interposition of granulation tissue that extends into the adjacent bone and evidence of radiolucency extending laterally. Figure 1 also shows external inflammatory resorption in the apical third of the root and signs of bone periapical radiolucency.

Cone beam computed tomography (CBCT) may often be required as a follow-up to assess the involvement of surrounding tissues, the amount of external and internal root resorption on the involved teeth, the anatomy of the root fracture of the apical third, and displacement of the coronal segment. Figures 2 and 3 illustrate CBCT parasagittal images that confirm the results of the intraoral radiographs. The diastasis between the coronal and apical fragments of #11 appear to be more evident on the fracture line and

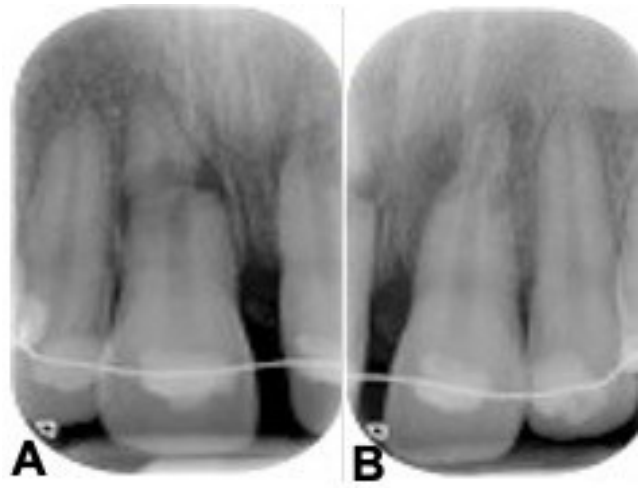

Fig. 1. Dental trauma left untreated for a period of 4 months after the injury

A – avulsion trauma managed with the coexisting fracture of the apical third of the root of tooth #11 at 4 months after the injury; B – treated tooth #21 when inflammatory external and internal root resorption was already visible and progressive.

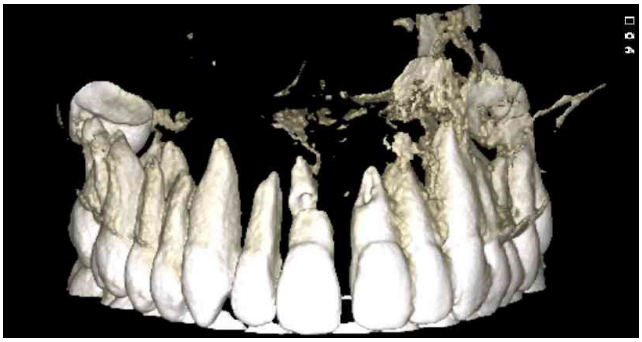

Fig. 2. Three-dimensional (3D) reconstruction of the upper arch by using cone beam computed tomography (CBCT)

Tooth #21 shows external inflammatory resorption and tooth #11 the fracture of the apical third of the root. Additionally, tooth #11 shows a gap between the root and the crown portion.

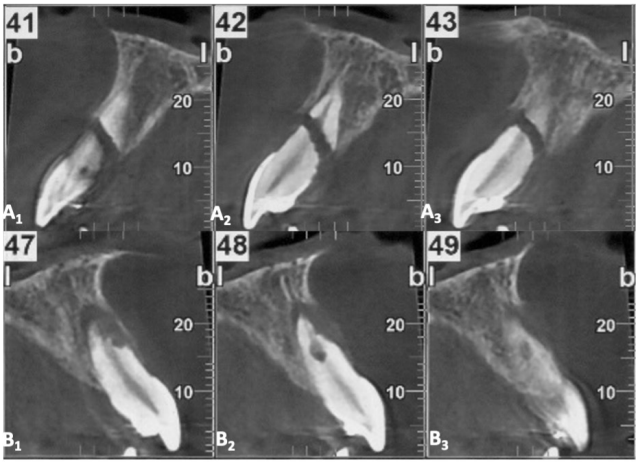

Fig. 3. Series of the parasagittal images from CBCT of the 2 central incisors at 4 months after the injury

upper row – tooth #11; lower row – tooth #21.

the presence of a "new apical foramen" is highlighted. In addition, areas of external inflammatory resorption on the apical fragment are evident and the fracture line appears jagged. The images relating to #21 appear suggestive for external inflammatory resorption, particularly on the vestibular side, which is the site of concomitant bone inflammation in the parasagittal image #48. Internal pulp resorption can also be observed at the apical third of the root.

Endodontic surgical resection in cases of persistent infections

The inflammatory reaction that results in no healing is caused by the infection of the root canal system. In cases of root fracture, the infection occurs at the fracture site rather than in the periapical tissues. The coronal fragment has a "new apical foramen," which is now situated at the fracture line rather than at the apical end of the root. Root canal therapy of the coronal fragment can be initiated and calcium hydroxide intracanal medication can be administered. If symptoms persist (i.e., abscess episodes and/or mucous fistula), an apicoectomy can be performed. Figure 4 shows the fractured apical root fragment being removed and retrograde closure of the new root apex,[25] which in one case is at the apicectomy level #11 and in the other at the root fracture line #21.[26,27]

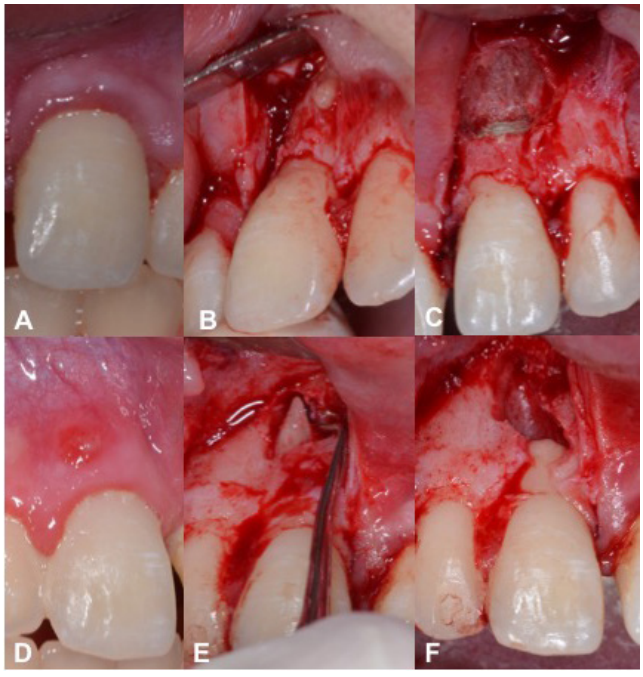

Fig. 4. A, B, C – interceptive therapeutic treatment (apicoectomy) performed on tooth #21 due to the persistence of apical infection. Apicoectomy was performed when inflammatory resorption was already present, trying to block the resorption and promote the healing of the periodontal ligament (PDL) and the adjacent bone tissue. The operation consisted in removing at least 3 mm of the root apex of tooth #21, and in each case, it involved the entire area affected by internal and external inflammatory resorption; D, E, F – apicoectomy performed on tooth #11 due to the presence of a mucous fistula after 8 months of calcium hydroxide intracanal medication of the coronal fragment, and the lack of healing between the apical and coronal parts of the broken tooth. The treatment consisted in removing the broken apical third and straightening the neo apex, followed by the retrograde obturation of the apical opening with mineral trioxide aggregate (MTA) for both tooth elements. The fractured apical root fragment was removed,and both apices were analyzed by means of scanning electron microscopy (SEM)

Inflammatory root resorption and its effects on the morphology of dental hard tissue

Resorption following infection may affect both the coronal and apical fragments. Additionally, involved root surfaces include the outer surfaces and it is not uncommon to for internal resorption to occur. Scanning electron microscopy (SEM) is an important technological aid for the analysis of the surface of the roots that are removed during endodontic surgery. Scanning electron microscopy enables the analysis of root morphology and the description of anatomy after resorption. The images presented in this review were captured with a SEM Hitachi Model S2460N (Hitachi, Tokyo, Japan) microscope with an acceleration voltage of 20 kV beam, and current of approx. 70 μA. The images present the SEM analysis of the surfaces of the fractured apical portion of #21 and the excised apical portion of #11. Interestingly, the area of the fracture of the apical fragment shows a geometric organization with vertical faults. As demonstrated earlier, fracture resistance is influenced by several factors, such as density, the diameter and the degree of obliteration depending on the patient's age, presence of dentinal tubules and dentin microcomposition, which displays lower fracture resistance in deeper layers.[28,29]

Figures 5 and 6 show the root apexes of 2 excised fragments. On the root surface of tooth #21 (without root fracture), clear external resorption areas are visible even at lower magnification (×40); the same areas of resorption are less visible on the surface of tooth #11 at a higher magnification (×110). This indicates that the degree of external resorption was higher for #21 than #11.

The areas of resorption of tooth #11, that presented with the fracture of the third apical portion of the root, are more limited and shallower than those observed on the root surface of tooth #21, which has been completely avulsed, where the resorption was more aggressive and the lesions appeared to be diffuse, destroying the root surface (Fig. 7,8).

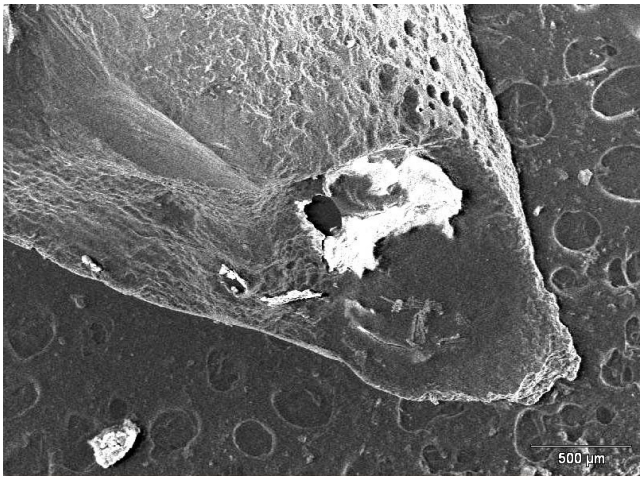

Fig. 5. SEM image of the apex of tooth #21 at ×40 magnification

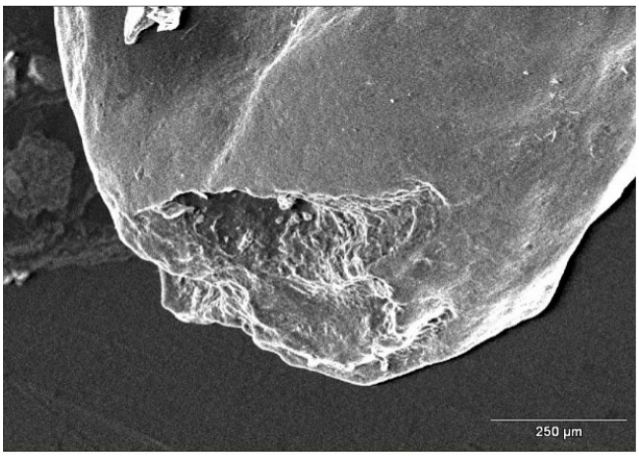

Fig. 6. SEM image of the apex of tooth #11 at ×110 magnification

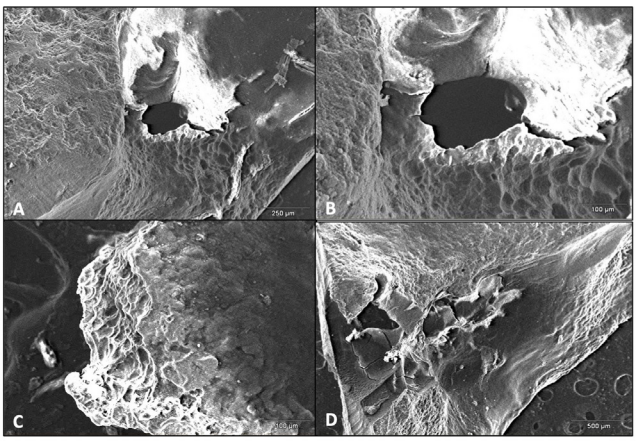

Fig. 7. SEM images showing the areas of external inflammatory resorption at different magnification on the root surface of tooth #21

A – ×90; B – ×200; C – ×60; D – ×45.

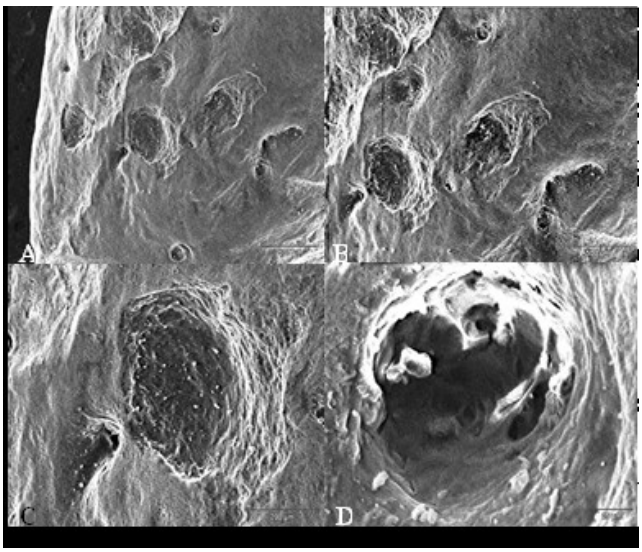

Fig. 8. SEM images showing the areas of external inflammatory resorption at different magnification on the root surface of tooth #11

A – ×45; B – ×60; C – ×80; D – ×700.

Figures 9 and 10 show the surface of the 2 removed apical fragments of tooth #21 and #11, respectively. Interestingly, the surface of the fracture that is visible on the apical root fragment removed during the apicoectomy of #11 is characterised by the presence of regular steps, reflecting a repetitive pattern.

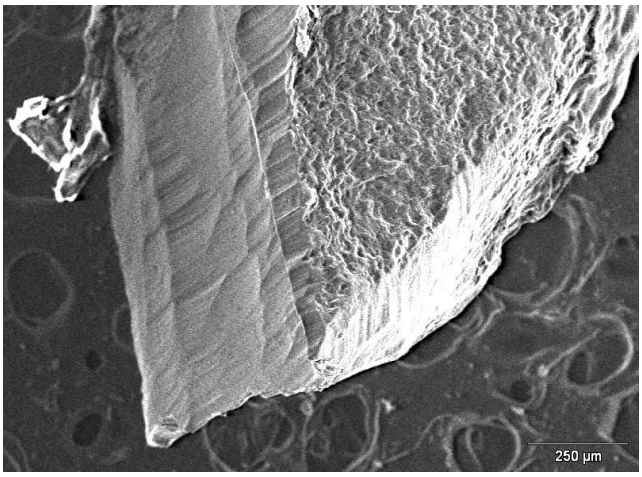

Fig. 9. SEM image showing the border between the milled surface during apicoectomy, visible on the left side, and the root wall, on the right side, of tooth #21 (magnification ×80)

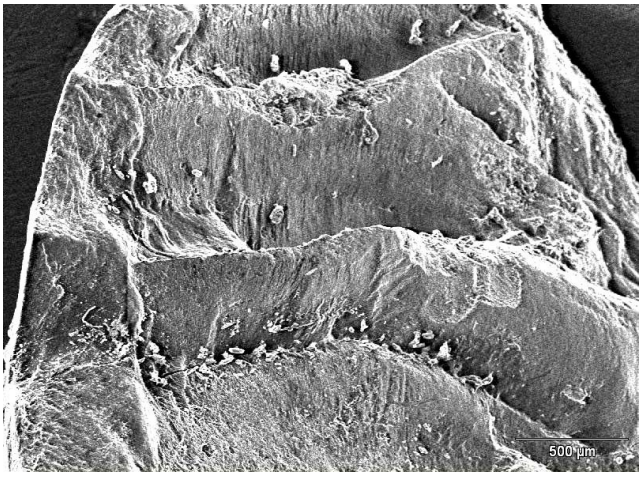

Fig. 10. SEM image showing the fracture surface of tooth #11, visible on the removed apical root fragment. The fracture surface is grooved, with regular organization forming successive steps (magnification ×45)

Micrographs are taken and energy dispersive spectroscopy (EDS) analysis is performed in the step regions in order to provide further information on fracture modality. Chemical analysis (microanalysis) with SEM can be performed by measuring the energy distribution and X-ray intensity generated by an electron beam on the sample using the EDS. This enables to identify and quantify the chemical elements in a given surface. The analysis indicates the percentage changes in the composition of phosphorus (P) and calcium (Ca) along the selected line, respectively, on the horizontal side (Fig. 11) and on the vertical side (Fig. 12) of one of the steps visible on the fracture surface. The point analysis, carried out at 7 measuring points selected along the tested lines, also confirms the stability of the P and Ca percentages. The analysis of microanalytical maps of the element distribution clearly emphasizes the heterogeneity in the transition areas between the horizontal and vertical parts.

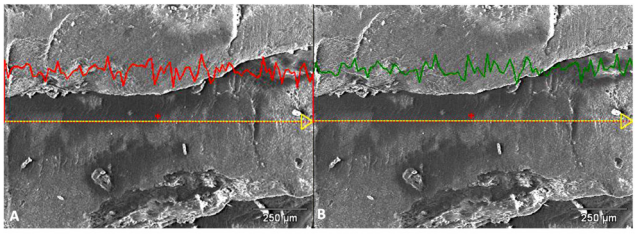

Fig. 11. Elemental analysis performed on the horizontal side of the step visible on the fracture surface of the apical fragment of tooth #11. The analysis of the energy dispersive spectroscopy (EDS) line shows phosphorus (P) changes along the lines in red (A) and changes in calcium (Ca) marked in green (B)

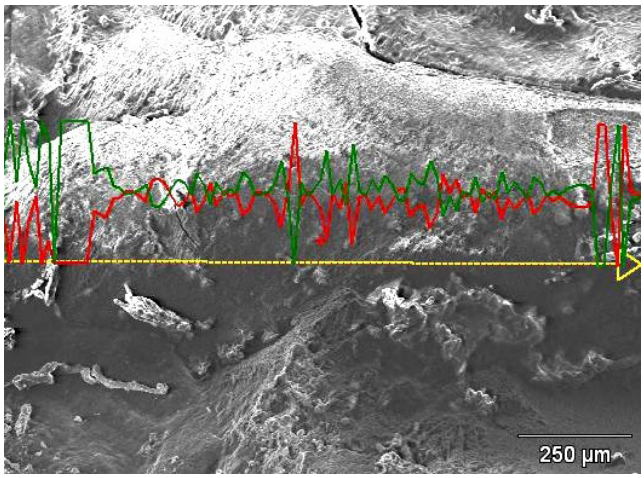

Fig. 12. In-line EDS analysis performed on the vertical surface of the step

Follow-up management

Follow-up should be performed at 4-week intervals while the teeth are splinted, and then at 3-month intervals for the first year. If no adverse clinical findings are evident, the annual visits should be arranged for the subsequent 5 years. Then, the tooth should be reassessed every 3–5 years. Follow-up visits are necessary to monitor pulp vitality, PDL cells vitality, periodontal status, and optimal oral hygiene maintenance through percussion, palpation, mobility tests, and periapical radiographs.[30] Pulp vitality must be assessed at every follow-up visit using cold and electric tests.[31]

Periodontal ligament cells need to be monitored to ensure that they remain healthy. They are assessed with periapical radiographs, percussion, palpation, and mobility tests. Periodontal probing is recommended in all cases with coronal third root fractures and when an apicectomy has been performed.[25] Patients must maintain excellent oral hygiene to avoid bacterial contamination of the root canal system.[32]

Figures 13 and 14 show periapical radiographs at 6 months after the 1st (Fig. 13) and 2nd apicoectomy (Fig. 14A) and at 24 (Fig. 14B) and 30 months (Fig. 14C) after the trauma, with complete remission of clinical and radiographic symptoms.[33]

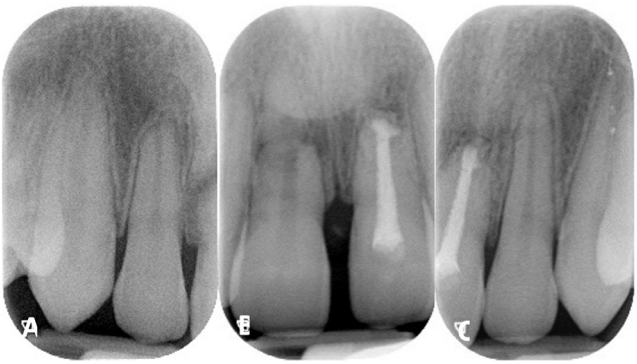

Fig. 13. Radiographs at 6 months after the apicoectomy of the upper central teeth (A–C)

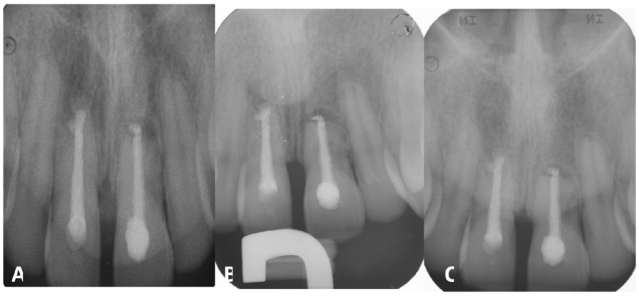

Fig. 14. Radiographs at 6 months after the apicoectomy of tooth #11 and at 18 months after the trauma (A), at 24 months after the trauma (B) and at 30 months after the trauma (C). Apicoectomy allowed the drastic decontamination of the periapical canal system and stopped the root resorption phenomenon

Discussion

The complexity of dental trauma results from several co-occurring elements that contribute to an increase in risk factors and a reduction in the long-term prognosis of the involved dental elements. The simultaneous presence of avulsion, apical third root fracture, non-compliance with the treatments according to the guidelines and, consequently, the early appearance of clinical signs of infection and inflammation define a complex clinical picture. Managing complex injuries requires a holistic approach that involves different dental professionals at different time points to guarantee the functionality and aesthetics of trauma areas.[6,34–36]

This paper focused on the management of transverse root fractures in dental trauma. Epidemiology and classification of transverse root fractures, as well as the physiological responses to healing, emergency management and clinical protocols were presented. Injury management often involves clinical situations that are far from approved guidelines and protocols. Indeed, it may be necessary to treat a patient with dental trauma and a concomitant fracture outside the recommended and guideline-prescribed times and procedures..

Maintaining optimal oral hygiene is essential and should be checked at all follow-up visits. In the case of apicectomy or root fractures, the new root is shorter and the plaque must be constantly controlled. Plaque formation within the gingival sulcus is a long-term risk factor that can lead to the penetration of bacteria along the periodontium and infection of the root canal system. In order to avoid possible infections, it is extremely important to maintain optimal oral hygiene conditions in the first phase of healing and during the splinting period. This can be achieved through the topical application of concentrates of *Camellia sinensis* and ozonated olive oil, which are effective in controlling the clinical indexes of periodontal disease and gingivitis.[37–39] The reduction of pain and maximum compliance with the necessary therapies can be achieved through the use of a holistic medicine approach, as recently demonstrated using photobiomodulation, kinesiology taping, and the use of lactoferrin to implement bone regeneration processes.[40–43]

On the other hand, the irreversibility of infectious phenomena, such as inflammatory resorption, despite endodontic treatment undertaken even a long time after the injury, emphasizes the importance of obtaining sterility of the root canal system as soon as possible. Sterility is essential to avoid triggering progressive inflammatory resorption or ankylosis, and the lack of healing between the apical and coronal fragments in cases of root fractures.[44–47] The latter clinical scenario suggests a necessary modulation of therapeutic choices towards interventions to guarantee the durability of the teeth involved in the trauma within the oral cavity.

Conclusions

Teeth with transverse root fractures present a favorable long-term prognosis if the fracture is subcrestal and localized in the apical and middle third of the root. Providing the best conditions for healing, repositioning and stabilization of the fragment is very important. However, when a transverse root fracture is accompanied by other injuries, such as the avulsion of the coronal fragment, the degree of treatment difficulty increases and the long-term prognosis decreases. In different clinical scenarios, healing response was suboptimal and patients had pulp necrosis, delayed treatment due to a lack of compliance and infectious complications. Difficult cases can be managed with root canal treatment and recommendations exist for these surgical therapeutic solutions that allow for the longest maintenance of the teeth. The choice of the therapeutic solutions can impact future implant-prosthetic rehabilitation by preserving soft and hard tissues.

Ethics approval and consent to participate

Informed consent was obtained from both the caregivers and the patient.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Review

Advantages of ultrasound guidance for TMJ arthrocentesis and intra-articular injection: A narrative review

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

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):647–656

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on December 2, 2021
Reviewed on February 15, 2022
Accepted on February 20, 2022

Published online on December 30, 2022

Abstract

Ultrasound (US) is a widely available, low-cost, non-invasive, and safe medical imaging method that enables real-time observation. Ultrasound offers several advantages for dentomaxillofacial images, such as portability, the possibility of dynamic and repeated examinations, patient comfort, and availability. It is a useful tool for recognizing the temporomandibular joint (TMJ) structures and their involvement during the course of different pathological processes, such as articular disk displacement, joint effusion and cortical erosion. In addition to its diagnostic use, US has been proposed as an auxiliary tool in minimally invasive procedures for arthrogenic temporomandibular disorders (TMD) to achieve an accurate puncture, recognize joint spaces and reduce surgical trauma. While US is widely used for large joints to visualize internal structures and guide the injection, this technique has only recently gained popularity for the TMJ procedures. Hence, the literature on this topic is scarce.

The present review describes the potential advantages and the clinical technique of US guidance for TMJ arthrocentesis and intra-articular injection (IAI).

Keywords: ultrasonography, temporomandibular joint disorders, arthrocentesis, interventional ultrasonography

Cite as
De Nordenflycht D, Tesch RdS. Advantages of ultrasound guidance for TMJ arthrocentesis and intra-articular injection: A narrative review. *Dent Med Probl.* 2022;59(4):647–656. doi:10.17219/dmp/146820

DOI
10.17219/dmp/146820

Introduction

Temporomandibular disorders (TMD) encompass a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joints (TMJs), masticatory muscles and associated tissues.[1] Temporomandibular disorders have been categorized into myogenous (masticatory muscular problems) and arthrogenous (problems with the TMJ components), the latter including internal derangements, arthralgia, osteoarthritis, and osteoarthrosis, which can be manifested by TMJ pain, TMJ noises during jaw function, jaw deviation, and functional limitation.[2]

Temporomandibular disorders are a significant public health problem affecting approx. 5–12% of the general population, and they are the second most common musculoskeletal condition (after lower back pain).[3] Temporomandibular disorders have been identified as the main cause of non-dental orofacial pain, with the most common symptoms being pain aggravated by mandibular function, limited mouth opening and joint sounds (described as "clicking", "popping" and "crepitus").[1] Orofacial pain affects patients' social functioning, and physical and psychological well-being. Likewise, the chronic nature of the pain substantially reduces quality of life,[4] probably due to the anxiety, stress, depression, physical and social disability, impaired work capacity, decreased productivity, social costs, and reduced economic income, which underscores the need for medical attention.[5]

General therapeutic goals for TMD involve restoring function, reducing pain, improving quality of life, and reducing the need for future treatment. However, since pain is an individual experience and each patient is exposed to different risk factors, each case should receive a customized therapeutic approach. Additionally, the structural damage may present different degrees of progression, and therefore a therapeutic goal may be different for each patient.[6] The management of TMD consists of a combination of medical-behavioral strategies, including non-invasive ones (i.e., patient education, relaxation techniques, coping strategies, home self-care programs, biobehavioral therapy, physical therapy, pharmacotherapy, and orthopedic therapy with occlusal appliances), and minimally invasive and open surgical procedures. In the majority of cases (75–90%), which are either joint or muscular TMD, positive results can be obtained from conservative and reversible interventions,[7] but in patients refractory to conservative treatment and/or where anatomical-structural disorders are a substantial source of pain and limitation, minimally invasive procedures can be considered.[8] Recent literature suggests that arthrocentesis, followed by the intra-articular injection (IAI) of different therapeutic agents, may be effectively used to treat arthrogenous TMD.[2] During these procedures, needle insertion is traditionally performed based on anatomical landmarks (the blind technique), with a potential risk of damage to the surrounding structures. To improve the precision of the procedure and reduce potential surgical damage, US has recently been suggested as an aid to guide punctures during arthrocentesis and IAIs.

The aim of the present review is to describe the potential advantages and the clinical technique of US guidance for TMJ arthrocentesis and IAIs.

Methodology

An electronic search of the medical literature was performed on July 30, 2021 and revised on January 25, 2022. The search was carried out in the PubMed, Scopus and Google Scholar databases, using controlled vocabulary. The authors used both MeSh (Medical Subject Headings) terms and free-text keywords for searching relevant articles. The keywords used were: "temporomandibular joint disorders"; "arthrocentesis"; "injection"; "ultrasound"; and "ultrasonography". The search strategy was adapted for each database. The search was limited to articles in peer-reviewed journals that were written in the English language. The process was repeated across all databases to ensure that no relevant articles were lost during the identification phase.

Studies conducted on patients (or cadavers) that received TMJ injections and/or arthrocentesis guided by US were considered for inclusion. Studies on humans of both genders without age limitation were taken into consideration. Studies included clinical trials (randomized and non-randomized), prospective and retrospective observational studies, case reports, case series, cadaveric studies, and technical notes, without restriction on the publication date. Only articles available as full texts that presented the descriptors in their title, abstract or main text were included. Narrative reviews, in vitro studies, duplicates between databases, and studies not reporting relevant data were excluded. No limits were applied with regard to the publication status. After verifying the availability of articles, the titles and abstracts of all the records obtained through the literature search were screened, and the full texts of the records meeting the inclusion criteria were retrieved for examination. After screening, the bibliography of the included studies and review articles on the subject were hand-searched for any missed references. All the reported outcomes and methods were identified, and they were recorded in a standardized data extraction sheet formulated in Microsoft Excel with information about: authors; the year of publication; the study design; the condition to be treated (a TMD diagnosis); the number of case subjects; the technique; the joint space (upper or lower); the US transducer; the drug injected; the number of control subjects; the route of US scanning; and the main results.

Results

Search results

The flowchart for article selection is shown in Fig. 1. After the removal of duplicate articles, a total of 141 records were identified, and then screened based on title and abstract. After the inclusion/exclusion criteria were applied, 13 articles were full-text reviewed and 3 additional records were identified through the manual search of the reference lists from the retrieved articles, and were added for a total of 16 articles. Among the selected articles, 4 were randomized clinical trials (RCTs),[9–12] 1 was a non-controlled clinical trial (CT),[13] 3 were retrospective studies (RSs),[14–16] 1 was a case report (CR),[17] 2 were technical notes (TNs),[18,19] 3 were cadaveric studies (Cad),[20–22] and 2 were systematic reviews.[23,24] The details of the included primary studies are presented in Table 1.

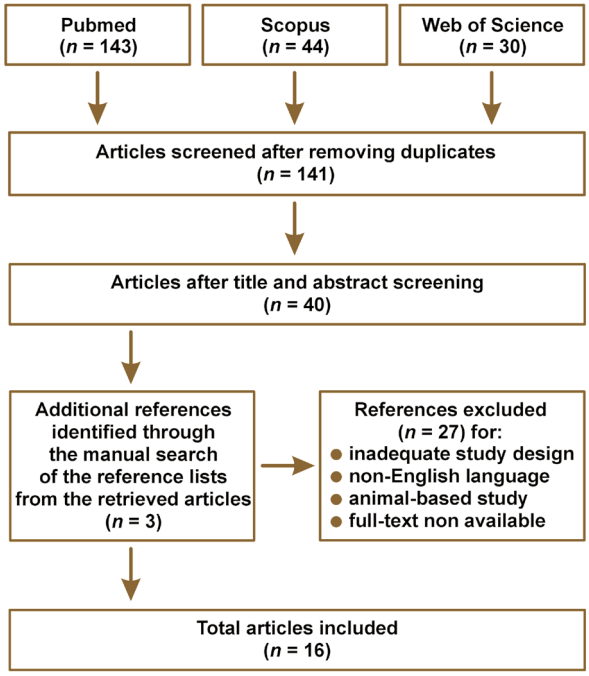

Fig. 1. Flowchart of the literature selection process

Minimally invasive procedures for TMJ pain

The literature describing TMJ pain management suggests that non-invasive strategies should precede invasive procedures[25]; this conservative approach proposes to perform all non-interventional procedures before executing minimally invasive procedures, such as IAI and arthrocentesis to restore jaw function and relieve pain.[2] The IAI of hyaluronic acid (HA) alleviates pain and the functional symptoms of TMD.[25–27] However, other drugs, such as corticosteroids (CSs) and non-steroidal anti-inflammatory drugs (NSAIDs), can be used with satisfactory results.[25] In a systematic review, Ferreira et al. reported that HA appeared to be more effective for pain resolution as compared to placebo or other therapies in arthrogenous TMD.[26]

Temporomandibular joint arthrocentesis (first described in 1991 by Nitzan et al.) is a simple, minimally invasive, inexpensive, and highly effective procedure that involves the irrigation of the upper joint space to remove the synovial fluid and inflammatory elements.[28] Its main purpose is to clean the joint space, remove inflammatory products, release disk adhesions, reduce pain, and mobilize the joint, for which several techniques have been described in the literature.[29] Şentürk and Cambazoğlu classified these techniques based on the number of punctures – either double-puncture arthrocentesis (DPA) or single-puncture arthrocentesis (SPA).[30] Single-puncture arthrocentesis is subclassified by the number of needles into 2 categories: type 1 (single-needle cannula method); and type 2 (double- or dual-needle cannula method).[29] Recent evidence suggests that SPA is as efficacious as DPA for pain reduction and mandibular range improvement; moreover, there is no superiority of SPA over DPA with regard to the secondary operator-related factors (e.g., the ease of operation, the operating time) and patient-related outcomes (e.g., the range of motion improvement, patient satisfaction).[31,32] In general, arthrocentesis can improve jaw function and reduce pain in patients with disk displacement without reduction and osteoarthritis. However, there are inconsistent findings about its possible superiority over other kinds of treatment for TMJ pain, with the exception of its superiority over splints.[33] Furthermore, a meta-analysis by Al-Moraissi et al. showed that non-invasive procedures had significantly lower therapeutic quality in terms of pain reduction and improvement of mouth opening, which supports a paradigm shift in the treatment of arthrogenous TMDs.[2] This recent evidence, although based on primary studies of very low to moderate quality, indicates that minimally invasive procedures (particularly in combination with the IAI of platelet-rich plasma (PRP), HA or CSs) are significantly more effective than the conservative treatment in reducing pain and improving mouth opening in the short and medium term in arthrogenous TMD cases. Therefore, minimally invasive procedures should be considered as first-line treatment.[2] Nonetheless, a systematic review by Li et al. suggests that when conservative treatment fails, early arthrocentesis may result in the greatest improvement in mouth opening and pain relief; however, when it is applied as initial treatment, without attempting the conservative treatment at first, the outcome may be less satisfactory.[34]

Temporomandibular joint arthrocentesis seems to be very safe given that a minimal number of major complications have been reported, and the ones reported are generally transitory, mostly due to the effect of anesthetic drugs or the extravasation of fluids to the surrounding soft tissues.[35] While the permanent complication rate is 0%, some short-term complications have been reported, such as facial nerve injury, preauricular hematoma, superficial temporal artery injury, the development of an arteriovenous fistula, joint bleeding, intracranial perforation, severe bradycardia, needle breakage inside the joint, failed needle insertion, the leakage of the washing liquid into the extra-articular

Table 1. Primary studies on the ultrasound(US)-guided temporomandibular joint (TMJ) interventional procedures

Study	Study design	Condition to be treated	US-guided procedure				Drug injected	Control (blind technique) *n*	Route of scanning	Main results
			case subjects (TMJs) *n*	technique	joint space	US transducer				
Parra et al. 2010[14]	RS	JIA	83 (180)	IAI	U or L	15 MHz linear or 8 MHz curvilinear	CSs	–	CP	with US guidance, the needle tip was located intra-articularly in 91%
Habibi et al. 2012[15]	RS	JIA	34 (63)	IAI	NR	NR	CSs	–	NR	efficacy of 92.06%; in 100% – pain resolution, in 71.4% – chewing dysfunction diminished, in 92.8% – jaw deviation diminished with US guidance
Dayisoylu et al. 2013[18]	TN	NR	9 (NR)	DPA	U	7 MHz linear	HA	–	CP	technique description
Levorova et al. 2015[19]	TN	NR	NR (NR)	IAI	L	7.5–14 MHz linear	NR	–	CP	technique description
Sivri et al. 2016[9]	RCT	DD	10 (NR)	DPA	U	NR	HA	DPA	CP	US-guided arthrocentesis was not more successful than the conventional technique and it took more time
Chakraborty et al. 2016[17]	CR	structural abnormality	1 (1)	IAI	NR	high-frequency linear	CSs	–	CP	US guidance increased the efficacy of IAI, especially in the presence of TMJ structural abnormality
Ayoub Al-Delayme et al. 2017[13]	CT	DD	34 (NR)	IAI	U	NR	PRP	–	NR	US-guided IAI to the upper joint space brought the alleviation of signs and symptoms
Resnick et al. 2017[16]	RS	JIA	23 (35)	IAI	NR	high-frequency	CSs	type II SPA	NR	no statistical differences in short-term outcomes, but the procedure times were longer for the image-guided group
Antony et al. 2019[10]	RCT	DD	40 (NR)	DPA	U	NR	–	DPA	CP	the US-guided group showed a significant reduction of pain in the immediate postoperative period; however, it showed no significant alleviation of the overall symptoms as compared to the blind technique
Bhargava et al. 2019[11]	RCT	DD	10 (NR)	type II SPA	U	12 MHz linear	CSs	type II SPA	CP	no significant difference in pain between the groups, US-guided SPA minimized the number of attempts of needle manipulation
Şentürk et al. 2019[12]	RCT	DD	12 (12)	type II SPA	U	NR	–	type II SPA	CP	US guidance was effective in type II SPA in the long term; however, it did not improve the outcome results as compared to the blind technique
Cha et al. 2019[20]	Cad	NR	10 (10)	IAI	U and L	5–20 MHz linear	coloured agents	IAI	CP	the accuracy of US-guided IAI was significantly greater as compared to the blind technique (95% vs. 55%), the success rate for IAI into the upper joint space was similar for both techniques, US-guided IAI into the lower joint space had a much higher success rate than the blind technique (90% vs. 30%, $p = 0.020$)
Champs et al. 2019[21]	Cad	NR	13 (25)	IAI	U and L	NR	NR	–	CP	IAI was successful in all cases, the median time period between the skin puncture and IAI was 23 s
Torres-Gaya et al. 2021[22]	Cad	NR	NR (NR)	DPA	U	13–6 MHz linear	NR	–	OP	high-frequency US linear probe (7.5–20 MHz) and US preset in the MSK mode helped to reach the optimal image definition, the US probe placed oblique relative to the zygomatic arch facilitated orientation and puncture, introducing the needle parallel to the probe major axis allowed greater precision and safety

RS – retrospective study; TN – technical note; RCT – randomized clinical trial; CR – case report; CT – clinical trial; Cad – cadaveric study; JIA – juvenile idiopathic arthritis; DD – disk displacement; IAI – intra-articular injection; DPA – double-puncture arthrocentesis; SPA – single-puncture arthrocentesis; U – upper; L – lower; CS – corticosteroids; HA – hyaluronic acid; PRP – platelet-rich plasma; CP – coronal plane; OP – oblique plane; MSK – musculoskeletal; NR – not reported.

space, damage to the joint surface, and allergic reactions.[29] One promising strategy proposed to prevent some of these drawbacks is US guidance for needle insertion.

Ultrasound fundamentals

Ultrasound is a widely available, low-cost, non-invasive, and safe medical imaging method that enables real-time observation.[19,23] In this method, images are obtained based on the propagation and reflection of high-frequency sound waves in tissues. Ultrasounds are oscillating sounds with frequencies from 2 MHz to 20 MHz, which are beyond the upper limit that humans can hear.[36] These sound waves are emitted by a transducer placed on the patient's skin, combined with a water-soluble gel as a coupling agent.[37] The transducer acts as a transmitter and a receiver of acoustic energy, and then transforms it into images.[38] The emitted US waves are partly reflected when they pass through tissues, with a reflection coefficient that depends on the characteristics of different anatomical structures.

Ultrasound offers several advantages for dentomaxillofacial images, such as portability, the possibility of dynamic and repeated examinations, patient comfort, and availability.[39] Sonograms (US images) are sections of the region of interest, of a particular thickness, generated along the face of the transducer, which are composed of different shades of gray, where the brightness/darkness depends on the frequency of the reflected echoes, which in turn depends on the ability of a tissue/structure to reflect or absorb sounds; this concept is known as echogenicity. In sonograms, tissues are classified according to their echogenicity: hyperechoic or echogenic (very bright) – highly reflective tissues, such as bone or cartilage; moderately echogenic (bright), such as glands; hypoechoic (fairly dark), such as blood vessels and muscles; and anechoic (very dark), such as liquids and air.[36]

A US examination is a procedure that is highly dependent on the skill and experience of the operator. Differences of opinion between researchers/clinicians may be due to the lack of standardization in the performance of the examination,[40] probe selection and the configuration of equipment, all of which may generate differences in the interpretation of the results.[41] Nevertheless, researchers have proposed the use of US as a promising screening tool for the evaluation of maxillofacial structures, such as TMJs.[11,36,37,39,41]

Ultrasonographic features of TMJ

The TMJ area has some particularities, including a small examination area, limited access to deep structures and a high risk of sound reflecting from the bone tissue, which can make image interpretation very complex.[38] Soft tissue visualization is severely limited by bone, as sound energy is almost completely absorbed by soft-tissue interfaces and the bone tissue. Thus, the external placement of the transducer enables only the acquisition of the lateral third of the joint, and only in the axial and coronal planes.[37] Therefore, the main disadvantage of US in the TMJ area is the limited imaging of the upper and medial parts of the condyle and the disk; these structures are hidden by the acoustic shadowing caused by the rebounding and absorption of US waves by the zygomatic bone.[12,19,20,42] The TMJ images produced by US depend on the echogenicity of tissues as follows: the condylar head and the articular eminence are hypoechoic and appear black[39]; the bone margins are hyperechoic and appear white[39]; the connective and muscular tissues are isoechoic (an intermediate reflection of sound waves) and appear heterogeneously gray[23,39]; the joint capsule surface is highly reflective of sound waves, creating a hyperechoic line (white)[11,23,39,42]; the articular disk appears as a thin, hypo-to-isoechoic, homogeneous band[11,23,42]; articular fluid-filled spaces are hypoechoic and appear black,[11,23,42] although these are virtual cavities that are generally not detectable unless joint effusion is present[38]; bone marrow is usually hypoechoic and appears black.[38]

In most publications, TMJ US monitoring is based on the standardized protocol of Emshoff et al.[43] Most studies have adopted similar protocols, which include transversal and longitudinal scans to evaluate the joint compartments in the coronal, axial and oblique planes (Fig. 2).[41]

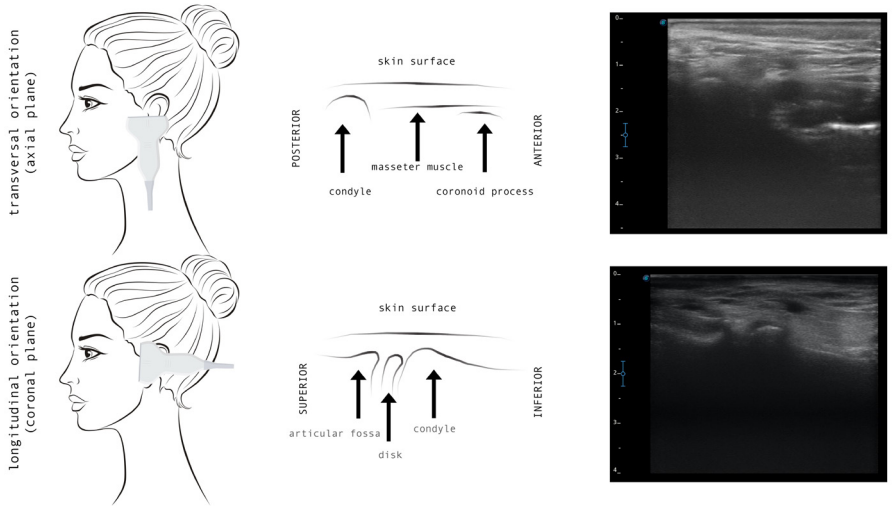

Fig. 2. Ultrasound (US) probe orientation for the observation of the temporomandibular joint (TMJ) in the axial and coronal planes

During the longitudinal scanning, the probe is placed over TMJ, perpendicular to the zygomatic arch and parallel to the mandibular ramus, and inclined until the best view is achieved; then static and dynamic evaluations are performed (Fig. 3).[38] The performance of the US diagnostics is outside the scope of the present review and has been extensively described for 3 main diagnostic domains: disk displacement; joint effusion; and cortical erosion.[38,40–42,44] It has been suggested that US can complement a clinical examination as an initial evaluation tool.[40]

Ultrasound-guided minimally invasive procedures for TMJ pain

In addition to its diagnostic use, US has been proposed as a useful tool in interventional procedures, such as US-guided peripheral venous access, central venous access, abscess drainage, the aspiration of hip and shoulder joints, pleural effusions, paracentesis, and TMJ arthrocentesis.[11] It has been suggested that US may allow more precise execution with real-time observation.[45] The lysis and lavage of the upper joint space is an effective method for controlling TMJ pain, so identifying this space is important for a satisfactory procedure.[11] However, the traditional blind technique (based on anatomical landmarks) requires experience to reach the upper joint space and carries a potential risk of damage to the collateral disk ligaments and the adjacent soft tissue, especially if multiple attempts are made.[18,20] Furthermore, the confirmation of the correct needle placement can sometimes be ambiguous in clinical practice.[20] Given the complex TMJ anatomy, clinicians have used image-guided techniques to aid the verification of the needle position, and reduce potential damage to joint tissues and neurovascular structures, or needle penetration in the middle cranial fossa during minimally invasive procedures.[12,21,23] Some image-guided techniques using magnetic resonance imaging (MRI) or cone-beam computed tomography (CBCT) have shown promising results; however, their routine use is not feasible in The MJ procedures due to cost and the need for a hospital environment.[23] On the other hand, it has been postulated that US-guidance minimizes trauma to the joint, and improves the accuracy and efficiency of the procedure. Furthermore, real-time images, the lack of ionizing radiation and easy access make US a promising aid for minimally invasive TMJ procedures, such as arthrocentesis and IAI.[23] While US is widely used for large joints to visualize internal structures and guide IAI, this technique has only recently gained popularity for the TMJ procedures. Hence, the literature on this topic is scarce. The articles regarding US-guided TMJ arthrocentesis or IAI available in PubMed, Scopus and Web of Science, published since 2010 are listed in Table 1 (the main characteristics are provided to facilitate the comparison of the studies). The uncontrolled RT by Parra et al. from 2010 was the first to report the accuracy of US-guided TMJ IAI; they observed that the needle was located intra-articularly in 91% of cases.[14] Dayisoylu et al. (2013) were the first to describe a reliable technique for US-guided TMJ arthrocentesis, which was suggested to be "better than arthroscopy" with regard to cost-benefits.[18]

Ultrasound-guided punctures may approach the target (joints, vessels or nerves) from a position perpendicular or parallel to the US beam, referred to as 'out-of-plane' and 'in-plane', respectively (Fig. 4). The in-plane approach enables the operator to visualize the needle shaft and tip, as it is directed toward the target, but it requires skill and may result in a false sense of security, despite having been demonstrated to result in faster and more accurate performance. On the other hand, the out-of-plane technique is more difficult and relies on tissue movement or fluid localization rather than strict needle visibility to confirm its position.[46] In the TMJ US-guided injections using the out-of-plane approach, the correct position of the needle is achieved by extending and narrowing the joint space by the infiltration and aspiration of fluid, respectively.[19]

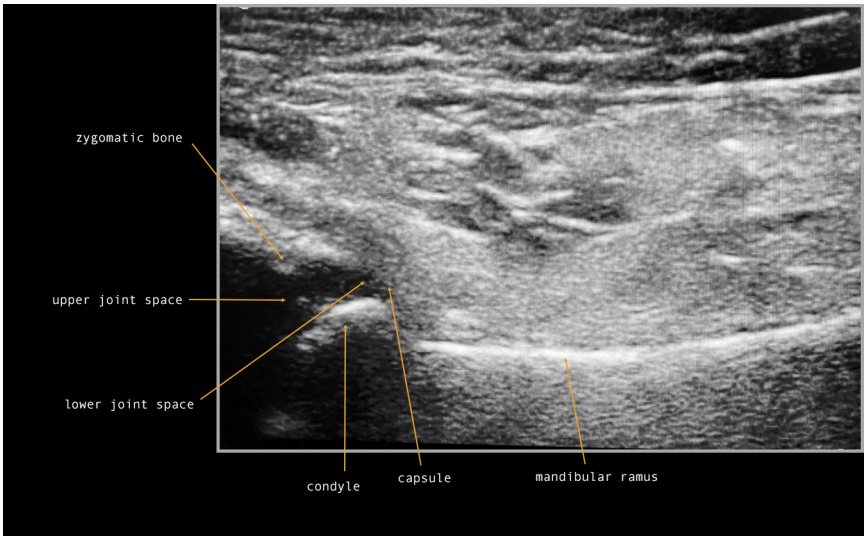

Fig. 3. Ultrasound (US) anatomy of the temporomandibular joint (TMJ) in the coronal plane

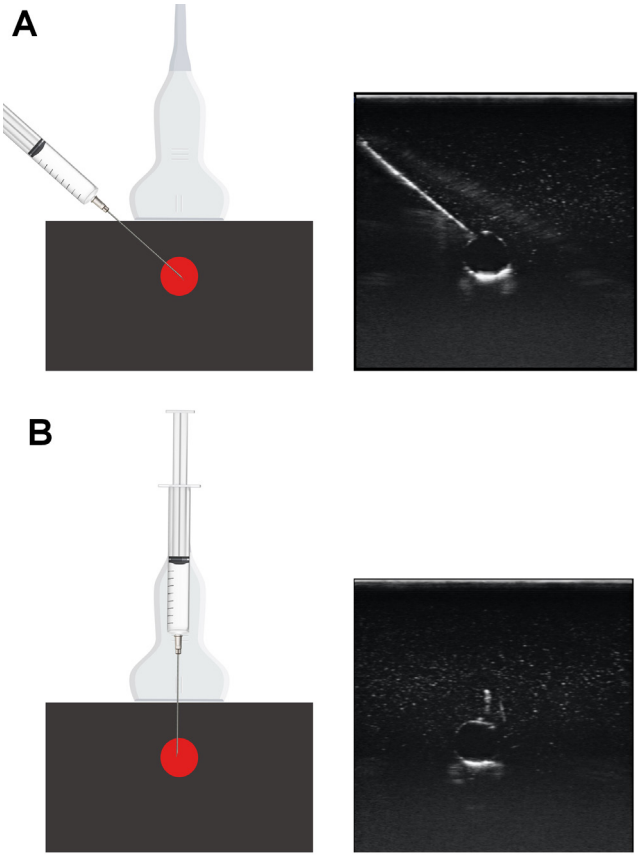

Fig. 4. Needle and probe orientation in ultrasound (US)-guided procedures
A – in-plane (long axis) approach; B – out-of-plane (short axis) approach.

Champs et al. validated a longitudinal US-guided in-plane approach for TMJ IAI, in which the needle is inserted at an angle of 30°, with the US probe in the preauricular region, approx. 1 cm in front of the tragus, parallel to the mandibular ramus and perpendicular to the zygomatic arch.[21] This technique proposes a direct visualization of the needle all the way to the joint with great precision and provides noticeably higher accuracy during puncture.[21] Most clinical and cadaveric studies use the coronal route of scanning and in-plane needle insertion (Fig. 5),[9–12,14,17–21] whereas other reports did not report these technical details.[13,15,16]

Most articles describing TMJ minimally invasive procedures (and daily clinical practice) are based on washing-out the upper joint space in both the US-guided and blind techniques. Nevertheless, some evidence has demonstrated that IAI directed to the lower or both TMJ spaces has a better effect than IAI into the upper space alone.[47] Lower joint space injection is believed to be a difficult procedure because of a narrow space, a small volume and the 'hidden' location. The blind technique for lower joint space injection was described by Li et al.[47] Clinical information on US-guided IAI into the lower joint space appears to be very limited.[20] Levorova et al. reported a technique for US-guided TMJ intra-articular infiltration directed toward the lower joint space (Fig. 6).[19] Cha et al., in a cadaver-based study, observed that upper joint space injection showed

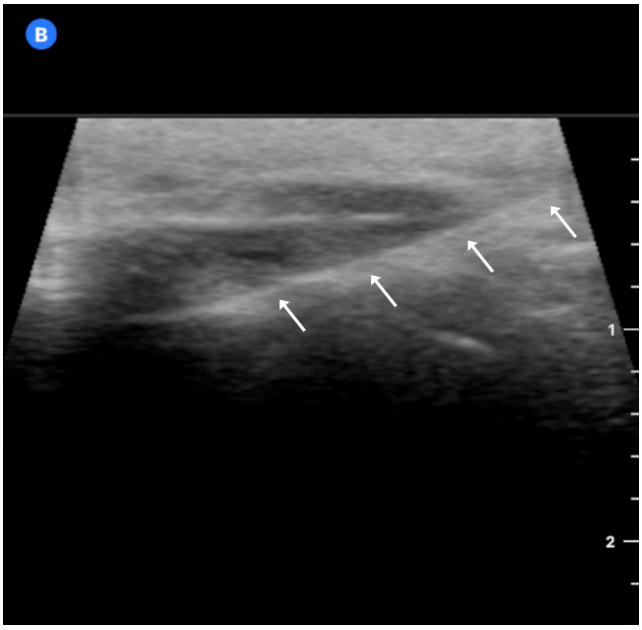

Fig. 5. In-plane needle insertion for upper joint space injection under ultrasound (US) guidance (the needle is marked with white arrows for academic reasons)

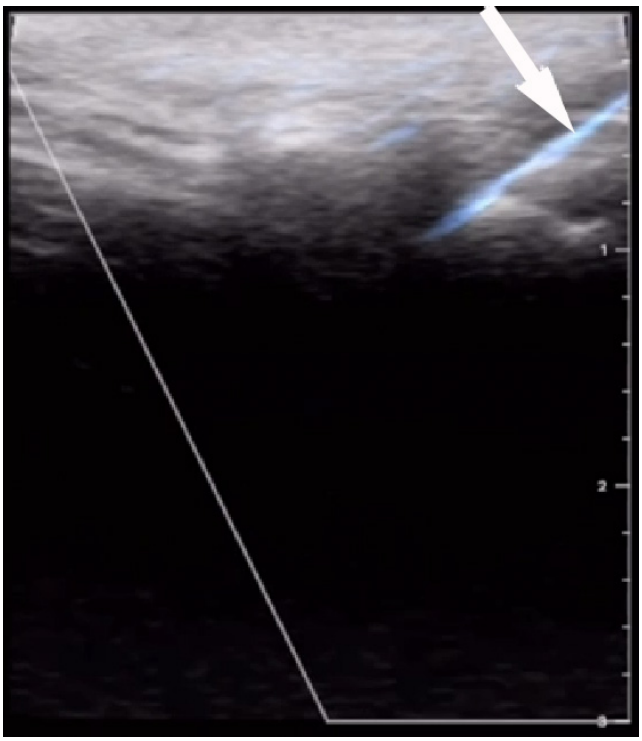

Fig. 6. In-plane needle insertion for lower joint space injection under ultrasound (US) guidance (the needle can be seen in light blue and is marked with a white arrow for academic reasons)

a similar level of success for the blind and US-guided techniques.[20] However, for the lower joint space, the US-guided technique had a significantly higher success rate (90% vs. 30%) and the blind technique was associated with a considerable proportion of unsuccessful/inappropriate injections to the lower joint space.[20] To date, only 4 controlled CTs that compare the blind and US-guided techniques for TMJ arthrocentesis have been published.[9–12] Two of them used

DPA[9,10] and the others used type II SPA[11,12] (the comparison of these studies is presented in Table 1). Şentürk et al., in a CT, reported the longest follow-up (1 year) in a comparison between the blind and US-guided techniques for TMJ arthrocentesis.[12] The results show that US guidance is effective in type 2 SPA, as it aids the visualization of the needle during puncture; however, it did not resolve pain or improve the range of motion as compared to the blind technique.[12] The clinical effectiveness of US guidance for TMJ arthrocentesis and IAI is mostly analyzed based on 4 aspects: pain reduction; the range of movement; needle positioning (or repositioning) attempts; and the total procedure time. The literature comparing US-guided arthrocentesis vs. the blind technique is scarce. Two systematic reviews have been published recently,[23,24] in which very similar conclusions were reached, since they both selected the same articles for the final analysis.[9–12] Both reviews found no significant differences in pain reduction and the maximum mouth opening, no conclusive results were observed in reducing needle repositioning, and also data on the potential to reduce the procedure time was inconclusive.[23,24] Although achieving access to the joint space occupies most of the surgical time, studies show that the total time is longer in the US-guided procedures, since a US examination itself requires additional time.[9] These conclusions are shared by all studies, as some publications suggest that US guidance would improve the precision of needle placement, especially when the lavage of the lower joint space is performed.[20] Cadaver-based studies observed that US-guided IAI and arthrocentesis techniques had a higher accuracy when the needle was located inside the joint spaces,[20,21] as they provide the image verification of having punctured the joint space and the real-time screen visualization of the distension of the space after infiltrating fluid.[22] Antony et al. observed that the US-guided technique resulted in a significantly greater pain reduction in the immediate postoperative period.[10] Bhargava et al. found that in type 2 SPA, US guidance minimized the number of attempts of needle manipulation as well as possible complications, and provided easier access to the upper joint space.[11] Additionally, Anthony et al. suggested that in patients with obesity, US-guided arthrocentesis could be more precise in locating the joint spaces, whereas the blind technique arthrocentesis required multiple punctures to achieve successful lavage.[10]

Finally, from a clinical point of view, some technical suggestions can be made for the execution of US-guided TMJ intra-articular procedures[12,18,19,48]: 1) always perform an initial US TMJ evaluation to observe anatomy in the coronal and axial views; 2) use high-resolution (over 12 MHz) linear probes[22,38]; 3) administer a local anesthetic solution (lidocaine or mepivacaine, without a vasoconstrictor) with a 27-gauge needle into the TMJ capsule,[48] otherwise, the auriculotemporal nerve blockage may be needed; 4) it is not necessary to use anatomical reference landmarks when puncture is guided by US imaging[22]; 5) after reaching the upper or lower joint spaces, HA, CSs or platelet concentrates should be injected slowly; 6) washing the articular space with saline or Ringer's lactate solution if arthrocentesis is intended; 7) close the injection area using a sticking plaster with light pressure to avoid the formation of hematoma; and 8) use ice or cold-pack applications and NSAIDs after the procedure.[48]

Conclusions

This review summarizes the recent evidence regarding the use of US as an auxiliary tool in minimally invasive procedures for arthrogenic TMD. Ultrasound guidance has shown promising advantages; it reduces the number of needle placement attempts, minimizes trauma to TMJ, improves the accuracy and efficiency of joint injections, results in a significantly greater pain reduction in the immediate postoperative period, provides easier access to both joint spaces, and has a significantly higher success rate when lower joint space injection is attempted. Future research is required to confirm the impact US may have on the clinician's performance, and the consequent benefit to the patient.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Review

Influence of dentofacial characteristics on the appearance of self-reported bullying: A review

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2022;59(4):657–661

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on March 3, 2021
Reviewed on June 7, 2021
Accepted on June 8, 2021

Published online on November 24, 2022

Abstract

Bullying is a social problem that affects children and adolescents in particular. It deteriorates the self-esteem of its victims, decreases their quality of life and generates future psychological problems. The aim of this review was to determine the influence of dentofacial characteristics on the appearance of self-reported bullying through a literature review.

A systematic search was carried out in the databases of international scientific literature on health sciences, including MEDLINE via PubMed, Scopus, LILACS, and SciELO. Up to October 10, 2020, a total of 348 articles were identified, but only 36 were ultimately selected for the review. Specific keywords in English were used in the search: "dentofacial features"; "soft tissue"; and "malocclusion". It was found that the appearance of bullying was associated with altered facial profiles, namely the presence of different classes of malocclusion, with class II or class III malocclusion being the most impactful.

Altered dentofacial characteristics can make an individual the target of harassment, leading to low quality of life, emotional instability, low self-esteem, and the lack of confidence with regard to dentofacial appearance as well as poor long-term social and academic performance. There is a need to develop preventive measures that would be applied by both parents and authorities, with disseminating information on bullying in schools as well as on adequate oral hygiene and the importance of going to the dentist. Traditional and cybernetic bullying share similarities. While working out strategies against bullying, it is essential to raise awareness among victims and bullies, families, and society, and to determine how bullying is perceived by children and teenagers.

Keywords: bullying, malocclusion, dentofacial alteration, labial incompetence, self-reported bullying

Cite as
Morales-Salazar SA, Monteagudo-Sangama JM, Arriola-Guillén LE. Influence of dentofacial characteristics on the appearance of self-reported bullying: A review. *Dent Med Probl.* 2022;59(4):657–661. doi:10.17219/dmp/138636

DOI
10.17219/dmp/138636

Introduction

Bullying is a global social problem. It involves repetitive and intentional aggression with power imbalance between bullies and victims[1] that generates mental and physical weakness.[2] Harassment can be face-to-face or cybernetic, with 'cyberbullying' having similar characteristics to those of traditional bullying, including intimidation, verbal abuse and teasing. Cyberbullying is defined by the United Nations International Children's Emergency Fund (UNICEF) as bullying with the use of digital technologies,[3] producing mental and physical deterioration, panic, hopelessness, and distress.[4–6]

Some studies have associated facial appearance with bullying,[7] demonstrating that distinctive facial features generate emotional impact in girls and boys, and especially among teenagers. It has been reported that 20–40% of adolescents are affected, with the phenomenon being more prevalent in females.[8–11] Bullying has been associated with malocclusion, mainly when both the mandible and the maxilla are affected.[12] Children with class III malocclusion are more likely to experience bullying as compared to those with mild or absent malocclusion.[13] Consequently, dentofacial appearance influences the self-esteem of children and teenagers, which in turn significantly impacts the educational performance and quality of life of the victims of bullying.[14–18]

A recent systematic review evaluating the relationship between bullying and malocclusion determined that dentofacial appearance influenced children's social attractiveness,[18] which is one of the most characteristic consequences of bullying.[17–19] However, in the evaluation of the 'bullying' variable, the review did not take into account soft tissues, but rather focused only on the class of malocclusion. Until now, to the best of our knowledge, no systematic or literature review has comprehensively evaluated the association between bullying and malocclusion, and how facial appearance (soft tissues, the facial profile, and the shape and position of the lips) can provoke bullying.

Methodology

Protocol and registration

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. The study protocol was approved by the Ethics Committee for Systematic Reviews at the Scientific University of the South (Universidad Científica del Sur), Lima, Peru (No. 640-2020-PREB8).

Information sources and search strategy

This review based its bibliographic search on the principal sources of information, using MEDLINE via PubMed, Scopus, LILACS, and SciELO as databases. Scientific search keywords connected with Boolean operators "AND" and "OR" were employed: ("dentofacial characteristics" OR "malocclusion" OR "dentofacial alteration" OR "crossbite" OR "class II malocclusion" OR "open bite" OR "deep bite" OR "class III malocclusion" OR "biprotrusion" OR "lip incompetence" OR "lip protrusion" OR "lip shape") AND ("self-reported bullying" OR "bullying" OR "teasing").

The strategies used in the search for scientific articles in particular databases are shown in Table 1.

Eligibility criteria

Observational, analytical and descriptive studies, literature review articles, and systematic reviews were included, whereas case reports, editorials, opinion articles, and theses were excluded. Thus, 348 articles were retrieved, but only 36 fulfilled the selection criteria. These studies were evaluated for later analysis in the development of theoretical topics. No language restrictions were applied. Articles were obtained until October 10, 2020.

Study selection

In the data collection process, 2 trained observers (SAMS and JMMS) independently generated the search strategy for retrieving articles. In the analysis of the information,

Table 1. Strategies used in the search for scientific articles in particular databases

Database	Search terms
PubMed	((((((((((((dentofacial characteristics) OR (malocclusion*)) OR (dentofacial alteration*)) OR (crossbite)) OR (class II malocclusion)) OR (open bite)) OR (deep bite)) OR (class III malocclusion)) OR (biprotrusion)) OR (lip incompetence)) OR (lip protrusion)) OR (lip shape)) AND (((self-reported bullying) OR (bullying)) OR (teasing))
Scopus	TITLE-ABS-KEY (dentofacial characteristics) OR (malocclusion*) OR (dentofacial alteration*) OR (crossbite) OR (class II malocclusion) OR (open bite) OR (deep bite) OR (class III malocclusion) OR (biprotrusion) OR (lip incompetence) OR (lip protrusion) OR (lip shape) AND TITLE-ABS-KEY (self-reported bullying) OR (bullying) OR (teasing)
LILACS/sciELO	dentofacial characteristics OR malocclusion OR dentofacial alteration OR crossbite OR class II malocclusion OR open bite OR deep bite OR class III malocclusion OR biprotrusion OR lip incompetence OR lip protrusion OR lip shape AND self-reported bullying OR bullying OR teasing

publications related to the topic "influence of dentofacial characteristics on the appearance of self-reported bullying" were incorporated, and the authors individually assessed the documentation obtained from different databases.

Results and discussion

Malocclusion and bullying

The growth of soft tissues, muscles, bones, and teeth is associated with the development of their functions. While the proper development of the masticatory process as well as proper dentofacial appearance are important,[20] they cannot always be achieved, as the growth of the tissues is sometimes non-harmonious. Esthetic facial appearance involves proportionate lips, nose and chin.[21] Different classes of malocclusion refer to the alterations in facial bones and the facial profile, resulting from the overdevelopment or discontinuous development of the tissues. The reports on the Sudanese and Turkish populations have shown that soft tissues develop differently in these populations, not only in relation to gender, but also the race of each individual, including biological aspects according to phenotype.[22,23]

Malocclusion influences the harmony of the facial profile, affecting not only esthetics, but also the mastication and speech functions, being correlated with the mandibular size and the position of the chin as well as alterations in the development of the teeth and disproportion in the bony tissue of the oral area. These alterations modify the facial angle and the position of the lips, among others.[24]

Altered dentofacial characteristics often cause bullying, which is manifested as verbal aggression with offensive comments toward the victim. It includes teasing about the color, shape and position of the teeth, bone structures and other facial features, such as the texture, size and shape of the lips, nose and chin, found in people with different classes of malocclusion. In patients with malocclusion, verbal abuse decreases their self-esteem, and thereby reduces their quality of life in the social and emotional environment, producing short- and long-term psychological problems that limit personal and social development.[25] Support groups should be created to stop bullying in order to avoid psychological damage to both victims and bullies.

Effect of bullying on the quality of life

As mentioned previously, bullying significantly affects the short- and long-term physical and emotional quality of life. In a study including 336 adolescents aged 10–14 years, it was stated that 12.8% suffered from bullying due to functional limitations, physical incompetence and physical appearance; this abuse had a negative impact on their self-esteem.[26] After orthodontic treatment, schoolchildren showed a slight increase in self-esteem as compared to adults, a remarkable point to be taken into consideration for the benefit of patients.[27]

Tooth decay may also cause bullying, being significant among adolescents, and leading to poor academic and social performance.[28] Anxiety is a consequence of rejection[29] by groups of students treating others in an unpleasant way and making jokes about their appearance; it leads to low scores in health-related quality of life, reduced self-esteem and poor mental health.[30] Bullying must be managed and controlled by authorities and parents.

Strategies to control bullying

The consequences of traditional face-to-face bullying are similar to those of cyberbullying, with both being considerable public health problems that result in psychological conflict. Therefore, to reduce the prevalence of bullying among children and teenagers, strategies for the prevention and control of this phenomenon must be applied.[31] Young children confront bullying by informing their parents after fighting with the aggressor or having tried to ask a friend for help, or surrendering to their bully. Thus, according to the affective relationships present at home, adults play an important role in stopping or preventing bullying. It has been shown that a child raised in a warm home with positive affective relationships and support among household members is protected against harassment by a perpetrator. A study by Lee and Ju evaluated the prevention of bullying with the application of the program developed by F.D. Alsaker, known as the Bernese Program against Victimization in Kindergarten and Elementary School, which focuses on educating teachers about handling bullying among young children.[32]

Strategies such as role playing, victims facing bullying and group support for teenagers as well as the information provided to guide parents can promote prevention and awareness about the adverse effects of being a victim of bullying. These strategies provide victims with skills to defend themselves, which results in a reduction of up to 67% in victimization and 50% in the number of aggressors.[33] Nonetheless, despite the use of these strategies, it has been observed that some teenagers continue to be victims of bullying over time, remaining vulnerable throughout their lives.[33,34]

Despite similarities between traditional and cybernetic bullying, specific strategies are needed for each class of bullying. The Media Heroes (Medienhelden) program, which was initially developed to control traditional bullying, has shown encouraging results for treating cyberbullying as well.[35] The program was found to significantly reduce traditional bullying by promoting understanding, the recognition of risk and consequences, and by providing techniques that allow individuals to defend themselves against perpetrators.[35]

Programs aimed at combating bullying among children and teenagers should be elaborated from the questions directed at students about how they perceive bullying in order to develop adequate programs to learn how to control emotions, promote empathy among peers, and design school policies against traditional and cybernetic bullying.[36,37]

Finally, it is important to point out that the cross-cultural aspects concerning appearance can trigger bullying in relation to maxillary alterations, such as severe malocclusion. Society must be made aware of this problem and respect behaviors toward others should be promoted. Furthermore, medical practitioners, including psychiatrists and dentists, can play an important role in fighting bullying. Dentists can help with improving esthetics by treating maxillary alterations, and can also refer patients to other health professionals when necessary. The scientific literature has described the influence of some socio-demographic variables on bullying and how they can increase the risk of such behavior, especially among gender identity minorities and certain racial groups, and in particular age periods, such as adolescence.[38–51] All the above issues must be considered by society and more strategies are needed to improve the quality of life for all, as stated in a bulletin from the World Health Organization (WHO), which points out that bullying prevention strategies can help governments ensure safe and healthy learning and working conditions while reducing expenditures on bullying-related injuries and ill health.[52]

Conclusions

This systematic review demonstrates how dentofacial characteristics and facial profiles can lead to different forms of self-reported bullying. It describes the alterations present in patients with different classes of malocclusion and those observed in the soft tissues of the face, lips, lip contour, chin, and nose, producing functional deterioration.

Facial profiles are very important at different levels of personal development, raising self-concept and self-confidence, and the ability to adequately interact in personal and social areas. All the people involved in bullying (both the attackers and their victims) suffer the consequences of traditional and cybernetic bullying. Therefore, bullying among either adults or children must be prevented and stopped by the development of systems, applications, talks, videos, and images to raise awareness and involve society, families, victims, bullies, and medical professionals. Among the latter, dentists play an important role in the analysis of alterations in the oral cavity, providing orthodontic treatment and referring to other medical specialties when necessary.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee for Systematic Reviews at the Scientific University of the South (Universidad Científica del Sur), Lima, Peru (No. 640-2020-PREB8).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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