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Comment

Decrypting the putative interrelation between sleep bruxism, masticatory muscle pain and sleep breathing disorders: Nosology and the role of hypoxia

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Keywords: sleep bruxism, masticatory muscle pain, sleep breathing disorders, hypoxia, nosology

This commentary on sleep medicine explores whether the potential relationship between sleep bruxism (SB), masticatory muscle pain (MMP) and sleep breathing disorders (SBDs) contributes to improving the management of co-occurring conditions.

The paper is divided into 2 sections: (1) reviewing the debate on SB nosology; and (2) based on the publications from the Martynowicz & Wieckiewicz research group, exploring the role of intermittent hypoxia as a putative mechanism endotype that may link such co-occurrence among individuals for whom characteristics are not yet clear.

Disentangling the nosology of sleep bruxism is essential before associating it with other conditions and investigating mechanisms

According to the consensus from a group of clinical scientists presented in a work-in-progress report, sleep bruxism (SB) is defined as "masticatory muscle activity during sleep that is characterized as rhythmic (phasic) or non-rhythmic (tonic), and is not a movement disorder or a sleep disorder in otherwise healthy individuals".[1] Sleep bruxism is currently considered an oro-motor behavior, with central interaction between the cerebral and cardiorespiratory autonomic systems. The specificity of the genetic contribution remains to be confirmed.[2]

Since it has become accepted that SB is not a parafunction or a disease, it remains a matter of debate whether it fits into the classical scheme of a disorder in otherwise healthy individuals.[1–3] Difficulty with clarifying whether SB is a behavior or a disorder is evident in a series of landmark commentaries; it is due to the gray area between a behavior without consequences and the point at which it becomes harmful.[4] Therefore, standardization is required so that firm, evidence-based conclusions could be generalized to clinical practice.[5] This is further corroborated by a recent theoretical analysis that does not support classifying SB as a disorder.[6,7] The American Academy of Sleep Medicine (AASM)

in the International Classification of Sleep Disorders – Third Edition, Text Revision (ICSD-3-TR) insists on using the word "related", since many sleep-related movement conditions do not entirely fit into the nosology of sleep disorders.[6] In a theoretical reappraisal of the ICSD-3 listing and definitions of disorders, it becomes even more clear that SB does not fit into the classical harmful dysfunction analysis (HAD) framework due to the lack of solid evidence.[7] Based on the above citations, it is evident that much more work is needed to identify rigid criteria and biomarkers for SB.

It remains perilous to directly and equally combine SB with MMP or SBDs. Although multiple associations have been found when analyzing population samples, not many are solid enough to guide our practice. For example, the phenotyping of obstructive sleep apnea (OSA) and the search for more definitive markers are ongoing. Therefore, the causal relationship between SB, MMP and SBDs should be considered on a personalized basis, as generalization is premature in the absence of unequivocal evidence.[8]

The resolution to this controversy may lie in pathophysiological, biochemical and molecular mechanisms, as well as genetic predispositions, leading to a cause-and-effect relationship or coexistence in some individuals.

Intermittent hypoxia as a common putative endotype of masticatory muscle pain in co-occurring sleep bruxism and sleep breathing disorders

Research by Wieckiewicz et al.[9] and Smardz et al.,[10] utilizing the video-polysomnographic evaluation of SB, did not demonstrate a direct relationship between temporomandibular disorders (TMDs) and TMD-related pain intensity in SB patients, with the distribution of TMDs among sleep bruxers and non-bruxers being similar. Therefore, it cannot be unambiguously assumed that a significant number of SB episodes alone is a risk factor for a higher prevalence of TMDs and TMD-related pain, including MMP. There are probably other factors related to sleep that could potentially affect this prevalence.

A recent study by Martynowicz et al. revealed a correlation between the asymmetry of temporal muscle pain and the presence of rhythmic masticatory muscle activity (RMMA) clusters in SB, with no such results being observed for masseter muscle pain.[11] An RMMA cluster was defined as a group of at least 3 RMMA events (the phasic or mixed form) with 3 or more burst increases lasting 0.5–2 s and an interval between the cluster events no longer than 50 s.[11] Furthermore, Seweryn et al. demonstrated a statistically significant association between a poor sleep quality and higher levels of temporal muscle pain.[12] This association was not observed for masseter muscle pain.[12] Therefore, it is not only the number of bruxism episodes, but also their duration, severity, structure, and other pathomechanisms that potentially influence MMP. Moreover, it can be assumed that temporal muscle pain is potentially more dependent on SB and sleep quality than masseter muscle pain. These hypotheses necessitate further reliable research on large groups, using video polysomnography (VPSG) and the objective assessment of MMP intensity.

In a study on a group of generally healthy individuals, Suzuki et al. found that oxygen saturation (SpO_2) was slightly but significantly lower than at baseline (maximum: –0.6%) at 4–6 s before the RMMA onset; in contrast, SpO_2 was markedly higher at 6–18 s after the RMMA onset (0.9%).[13] The end-tidal carbon dioxide ($ETCO_2$) value before the RMMA onset did not differ from that at baseline, and it decreased 8–10 s after the RMMA onset (–1.7 mmHg). However, no changes in SpO_2 or $ETCO_2$ in relation to the RMMA onset reached a critical clinical threshold. The authors concluded that mild and brief oxygen fluctuations before the RMMA onset may reflect a physiological response that appears to have little influence on SB genesis.[13]

The relationship between SB and SBDs is different in patients with OSA. Martynowicz et al. found that individuals with mild and moderate OSA (apnea–hypopnea index (AHI) <30) had a higher bruxism episode index (BEI) as compared to those with severe OSA (AHI ≥ 30).[14] A positive correlation between AHI and BEI was observed in the group with AHI < 30, highlighting the dependence of the relationship between OSA and SB on OSA severity. In patients with mild and moderate OSA, OSA was found to be correlated with SB. The study also demonstrated a positive linear correlation between phasic bruxism and the oxygen desaturation index (ODI), as well as between phasic bruxism and minimal SpO_2, in individuals with AHI < 30, confirming the association between hypoxia and SB.

Smardz et al. found a significant relationship between tonic electromyographic pathways in SB episodes and SBDs, with tonic muscle contractions identified as the potential cause and effect of respiratory events.[15] Qualitative analysis revealed a statistically significant correlation between increases both in AHI and ODI and an increase in tonic electromyographic pathways.[15]

Concluding remarks

Based on the results presented above, it can be concluded that repeated episodes of moderate or severe intermittent hypoxia may be the potential factor connecting SB, MMP and SBDs (Fig. 1). However, the authors emphasize that this is likely one of many factors, and a multifactorial etiology is more probable. Therefore, high-level evidence studies are needed to confirm or reject this hypothesis.

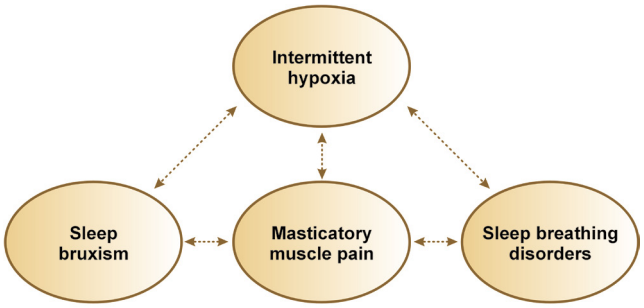

Fig. 1. Model depicting the possible relationship between sleep bruxism (SB), masticatory muscle pain (MMP), sleep breathing disorders (SBDs), and intermittent hypoxia

The model provides a potential avenue for exploring and further phenotyping the links between these conditions.

Clinicians should be aware that repeated episodes of moderate or severe intermittent hypoxia are harmful to the cardiovascular system,[16] causing sympathetic hyperexcitation and contributing to an increase in the generation of reactive oxygen species (ROS), systemic inflammation, metabolic dysregulation, and endothelial dysfunction,[17] and potentially leading to faster growth of cancerous tumors.[18–20] Further investigation is required to determine the possible link or causal role of these factors in the interaction of SB with MMP and SBDs with MMP, and to provide innovation in the management of such putatively deleterious co-occurring conditions.

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Perspective

Temporomandibular disorders and bruxism – up-to-date assessment and screening tools the general dentist should be aware of

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Keywords: assessment, bruxism, TMD, BruxScreen, bDC/TMD

The recently proposed shortened screening tools for temporomandibular disorders (TMD) and bruxism should enable a better assessment of these conditions by the general dentist.

Temporomandibular disorders (TMD) are a group of conditions that cause pain and dysfunction of the masticatory muscles, the temporomandibular joints (TMJs) and associated structures.[1] The prevalence of TMD ranges from 10% to 15%,[2] and therefore can present a significant public health burden. Bruxism is repetitive jaw muscle activity characterized by the clenching or grinding of the teeth and/or bracing or thrusting of the mandible.[3] It is widely accepted that bruxism is not a disorder, but rather a behavior that may be a risk factor for certain adverse clinical syndromes, such as excessive tooth wear, muscle pain, oral mucosa damage, and others.[3] According to their circadian appearance, 2 forms of bruxism are acknowledged, including bruxism during wakefulness (awake bruxism (AB)), with an estimated prevalence rate of 20–31%, and bruxism during sleep (sleep bruxism (SB)), with an estimated prevalence rate of 5.5–12.5%.[4] There is some controversy about the relationship between TMD and bruxism.[5,6] Nonetheless, it is generally accepted that extreme bruxing activity may lead to a breakdown in the stomatognathic system, orofacial pain and TMD.[7–9]

The relatively high TMD and bruxism prevalence, as well as their common risk factors and comorbidities, raise the need for reliable and validated screening tools, and structured clinical examinations. Several such tools have been developed and used in recent decades.

Temporomandibular disorders

The importance of incorporating the biopsychosocial model of chronic pain as an essential part of evaluating TMD patients was initially suggested in the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) published in 1992.[10] The tool was used mostly for research purposes. In 2014, the RDC/TMD Axis II protocols were modified to create the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) (http://rdc-tmdinternational.org).[11] The purpose of introducing DC/TMD was

to enable their use not only in research, but also in clinical settings. Axis II of DC/TMD includes a shorter and more feasible tool to assess subjects' levels of anxiety and depression (the Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire), which is a well-validated instrument.[11] Despite the vast knowledge collected through the use of DC/TMD, the tool is less feasible for the general dentist, and is mostly used in clinics specializing in TMD and by orofacial pain specialists.

A recent preprint publication by Durham et al. (published online in August 2023) suggests shortening DC/TMD to a more brief version (brief DC/TMD (bDC/TMD)) for use in non-specialist settings.[12] The bDC/TMD substantially reduce and simplify the examination items and decision trees. Axis I of bDC/TMD refers basically to 2 groups of diagnoses – painful TMD (including secondary headache) and joint-related TMD with functional implications, while the psychosocial assessment (Axis II) is based on 11 items only (Fig. 1). A recent publication regarding the long-term adverse implications of the coronavirus disease 2019 (COVID-19) pandemic in terms of TMD has already used the abovementioned binary Axis I classification (painful and non-painful TMD).[13]

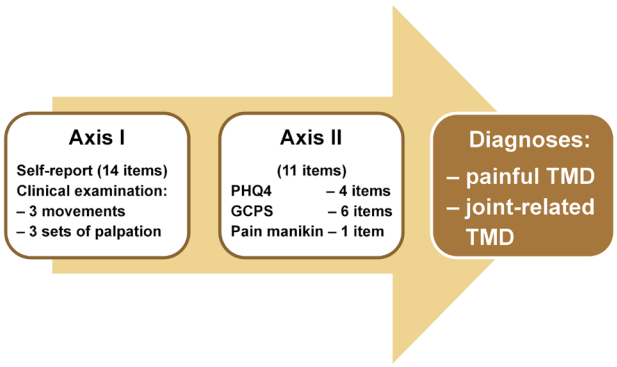

Fig. 1. Schematic representation of the brief Diagnostic Criteria for Temporomandibular Disorders (bDC/TMD) evaluation tool

PHQ4 – Patient Health Questionnaire-4; GCPS – Graded Chronic Pain Scale.

Bruxism

In 2018, an international consensus on the assessment of bruxism proposed 3 levels of bruxism evaluation: (i) "possible bruxism" – when the diagnosis is based merely on a subject's self-report; (ii) "probable bruxism" – when the clinical signs (such as masticatory muscle hypertrophy, linea alba and scalloped tongue) support the presence of bruxing behaviour; and (iii) "definite bruxism", which has to involve instrumental evaluation.[3]

The evaluation of definite SB must include a polysomnographic recording with electromyography (EMG) and a simultaneous audio-video recording.[3] Such a gold standard for a definite SB diagnosis is difficult to reach due to high expenses and complexity. Therefore, the most commonly used assessment grade in cross-sectional population studies is probable SB.[3,14]

Making a definite AB diagnosis is also complex due to the need to make continuous EMG recordings during daytime activities. Self-reporting and clinical assessment are insufficient in determining the intensity and duration of specific muscle activity, and its fluctuations over time.[15] Ecological momentary assessment (EMA) is one of the new semi-instrumental ways suggested for AB assessment, with the mode relying on a designated smartphone application that enables multiple-point, real-time, subjective reporting on masticatory muscle activity during wakefulness.[16] Combining self-reporting and EMA facilitates AB assessment,[17] and enhances the ability to define the psychosocial and behavioral phenotype of subjects with AB.[18]

Recently, the Standardised Tool for the Assessment of Bruxism (STAB) has been presented as a good strategy for defining the status, comorbidities, etiology, and consequences of bruxism.[19] The STAB is based on 2 axes; Axis A encompasses subject-based reporting (AB, SB and patient complaints), clinical reporting (the clinical findings regarding joints, muscles, intra- and extraoral tissues, the teeth, and restorations) and instrumental assessment (the information gathered using technological devices), while Axis B refers to psychosocial assessment, concurrent sleep-related and non-sleep-related conditions, the prescribed medications, substance use, and additional factors.[19]

While STAB aims to serve as a comprehensive tool for bruxism assessment, it is possibly too complex and time-consuming to be routinely used by the general dentist. An additional tool, the Bruxism Screener (BruxScreen), has been suggested for use in epidemiological research projects and general dental practices.[20] The BruxScreen includes a patient self-reporting questionnaire and clinical assessment by the dentist (Fig. 2). Hopefully, the BruxScreen will find its place as an efficient assessment tool for bruxism in clinical settings.

One of the main advantages of introducing TMD and bruxism assessment tools is global standardization,

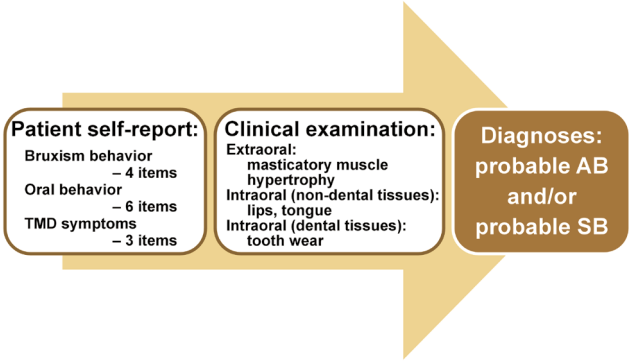

Fig. 2. Schematic representation of the Bruxism Screener (BruxScreen) tool

TMD – temporomandibular disorders; AB – awake bruxism; SB – sleep bruxism.

initially for research purposes. The relatively high TMD and bruxism prevalence among the general population raises the need for available standard screening and assessment tools for non-specialist settings. Such tools should be relatively short, rely on ordinary language and be easy to implement. Due to the multifactorial etiology of TMD and bruxism, two-axis evaluation is essential despite its possible complexity. Moreover, efforts to shorten and adapt the evaluation systems to make them more feasible for the general clinician are praiseworthy. Future research is needed to develop these tools further, and report their reliability and validity. At this time, it is crucial that every clinician becomes familiar with the recently proposed TMD and bruxism assessment tools, and incorporates them into their practice.

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Original paper

Charlson comorbidity index and the severity of community-acquired pneumonia caused by SARS-CoV-2: A retrospective analysis

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Abstract

Background. The Charlson comorbidity index (CCI) has been considered as a valid and reliable tool for predicting poor clinical outcomes and mortality in patients with coronavirus disease 2019 (COVID-19). However, its relationship with the severity of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has not been thoroughly explored.

Objectives. The aim of the present study was to identify the impact of the comorbidity burden, quantitatively assessed by applying CCI, on the severity of inpatient community-acquired pneumonia (CAP) caused by SARS-CoV-2.

Material and methods. The study was conducted using the medical records of 208 patients with CAP who had an epidemiological history of a plausible SARS-CoV-2 infection, with positive polymerase chain reaction (PCR) confirmation no later than 1 month before being admitted for inpatient treatment. The CCI was calculated using a custom computer program. The statistical analysis of data was carried out using Statistica, v. 7.0.

Results. Our study found a significant correlation between the comorbidity burden and the severity of CAP caused by SARS-CoV-2. Specifically, we observed a low CCI score in the majority of patients in the pneumonia risk class II and III groups, and a high CCI score ≥3 in the majority of patients in the pneumonia risk class IV group. Moreover, a direct correlation between CCI and age was established. The comorbidities most commonly associated with CAP caused by SARS-CoV-2 were congestive heart failure, moderate to severe liver diseases and diabetes mellitus (DM) with chronic complications.

Conclusions. The use of CCI to evaluate comorbid pathology in hospitalized patients with CAP caused by SARS-CoV-2 can assist the medical staff in developing timely preventive and therapeutic strategies, leading to improved patient prognosis.

Keywords: pneumonia, severity, Charlson comorbidity index, SARS-CoV-2

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Introduction

The emergence of a new zoonotic infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes – coronavirus disease 2019 (COVID-19) – posed an extraordinary challenge to the healthcare systems worldwide.[1] On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic due to its rapid spread, ways of transmission and health risk.[2] By April 11, 2023, WHO reported 685,044,510 cases of COVID-19, resulting in 6,838,093 deaths globally. By the same date, the number of confirmed cases of COVID-19 in Ukraine had reached 5,465,954, with 111,676 of these cases being lethal.[3]

Coronavirus disease 2019 is characterized by a range of heterogeneous clinical signs and symptoms, including nasal congestion, rhinorrhea, a sore throat, a cough, myalgia or fatigue, vomiting, fever, and headache, especially in patients with respiratory involvement.[4,5] While nearly 80% of patients are either asymptomatic or present with mild symptoms of acute respiratory infection (ARI),[6] some patients may rapidly develop pneumonia and severe dyspnea associated with the acute respiratory distress syndrome (ARDS).[7–9] Since the SARS-CoV-2 viral spike protein binds to the human angiotensin-converting enzyme 2 (ACE2) receptor, a high expression of this protein in the pulmonary tissue is one of the suggested mechanisms underlying severe lung damage.[10] For instance, alveolar epithelial type II (ATII) cells, being more susceptible to SARS-CoV-2, undergo apoptosis when infected.[11] These cells are involved in surfactant secretion. The destruction of pneumocytes leads to decreased surfactant levels in the alveoli, causing them to collapse, and resulting in pneumonia and ARDS.[12] One of the hallmarks of SARS-CoV-2 pneumonia evolving to ARDS, which further disrupts ACE signaling pathways, is a cytokine storm that leads to systemic inflammation, coagulation disorders, endothelial damage, and the dysregulation of the immune system.[13]

Old age and comorbidities are the main risk factors for the development of pneumonia and ARDS in COVID-19 patients.[14–17] Physiological changes and diseases affecting metabolism and/or immunity also may aggravate the course of SARS-CoV-2 infection.[18–20] When exposed to equivalent amounts of viral particles, patients with comorbidities develop an increased viral load as compared to those without comorbidities. Age is another factor that correlates with the severity of SARS-CoV-2-induced pneumonia.[19,21] This could be attributed to the age-related decline in the effectiveness of T cells and B cells, as well as the overproduction of type 2 cytokines, which may result in a reduced control of viral replication and a prolonged proinflammatory response, potentially leading to poor clinical outcomes in the elderly.[21,22]

The Charlson comorbidity index (CCI) was introduced in 1987 as a standardized score to estimate the likelihood of death in various medical situations, taking into account the impact of the coexisting medical conditions on the outcome.[19,23] Even though CCI has been shown to be a valid and reliable tool for predicting poor clinical outcomes and mortality in patients with COVID-19,[24] its association with the severity of pneumonia caused by SARS-CoV-2 has not been widely explored.

Therefore, the present study aimed to identify the impact of the comorbidity burden, quantitatively assessed by applying CCI, on the severity of inpatient community-acquired pneumonia (CAP) caused by SARS-CoV-2.

Material and methods

This non-interventional, single case–cohort study was conducted retrospectively using the medical records of 208 patients consecutively admitted for the treatment of CAP to the Department of Pulmonology of Ternopil Regional Clinical Hospital, Ukraine, from mid-January to the end of April 2021. At the time of admission, all patients tested negative for SARS-CoV-2 (the swab test).

The most common scoring systems used to predict severity and mortality in the case of CAP are CURB-65 (confusion, urea, respiratory rate, blood pressure (BP), age ≥65 years), SMART-COP (systolic blood pressure, multilobar infiltrates, albumin, respiratory rate, tachycardia, confusion, oxygen, and pH) and the pneumonia severity index (PSI), with the latter being originally developed within the Pneumonia Patient Outcomes Research Team (PORT) project. The PORT score determines PSI, predicts the risk of death and provides recommendations for efficient treatment. According to the total scoring of the disease signs (prognostic criteria), 5 classes of an increased risk of mortality are distinguished: class I: age <50 years, no comorbidity, no abnormal vital signs, <50 points; class II: 51–70 points; class III: 71–90 points; class IV: 91–130 points; and class V: >130 points.[25]

The diagnoses of CAP and the distribution of patients into risk classes according to the PORT scores were confirmed using the 2019 Ukrainian evidence-based clinical guidelines entitled "Nosocomial pneumonia in adults: Etiology, pathogenesis, classification, diagnostics, antimicrobial therapy, and prevention",[26] adapted from the National Institute for Health and Care Excellence (NICE) Clinical Guideline CG191 – Pneumonia in adults: Diagnosis and management.[27]

Based on the medical records, the patients were categorized into 3 groups according to their PORT scores: group II – patients with pneumonia of risk class II (n = 124); group III – patients with pneumonia of risk class III (n = 68); and group IV – patients with pneumonia of risk class IV (n = 16).

The study inclusion criteria were as follows: a positive swab test for SARS-CoV-2 no later than 1 month before being admitted for inpatient treatment; the presence of ARI symptoms; and the evidence of CAP on a high-resolution

computed tomography (CT) scan. Patients under the age of 18, and pregnant or lactating women were excluded from the study.

A comparison group (CG, group I; n = 27) comprised patients admitted to the Department of Pulmonology of Ternopil Regional Clinical Hospital during the same period, who had a positive swab test for SARS-CoV-2 no later than 1 month before the admission for inpatient treatment, the symptoms of ARI and no evidence of pneumonia on a high-resolution CT scan.

The CCI was calculated using a custom computer program and the following input data: the age-based score starting at ≥50 years, with an increase of 1 point for every 10 years; a history of definitive or probable myocardial infarction (+1 point); congestive heart failure (+1 point); peripheral vascular disease (+1 point); cerebrovascular disease (+1 point); dementia (+1 point); chronic obstructive pulmonary disease (COPD) (+1 point); connective tissue disease (+1 point); peptic ulcer disease (+1 point); a liver disease (mild: +1 point; moderate to severe: +3 points); diabetes mellitus (DM) (+1 point; with chronic complications: +2 points); hemiplegia (+2 points); moderate to severe chronic kidney disease (CKD) (+2 points); a solid tumor (localized: +2 points; with metastases: +6 points); leukemia (+2 points); malignant lymphoma (+2 points); and the acquired immunodeficiency syndrome (AIDS) (+6 points). A CCI score ≥3 was considered diagnostically significant.[28,29]

The data was collected by one researcher, and then verified by a second researcher.

Statistical analysis

Statistical analysis was performed using Statistica, v. 7.0 (StatSoft Inc., Tulsa, USA). The normality of quantitative variables was assessed using the Kolmogorov–Smirnov test. The variables were described as mean and standard deviation (M ±SD) or as number and percentage (n (%)). The comparative analysis of absolute values was conducted using the parametric analysis of variance (ANOVA) test. Pearson's test was used for the comparison of relative values, which were presented as a percentage ratio. The χ^2 test and Fisher's exact test were used to compare the variables between the groups. Correlations were calculated using the Pearson correlation coefficient (r). Differences were considered statistically significant at a p-value <0.05.

Results

The mean patient age did not significantly differ between the study groups and CG (Table 1). At the same time, the median age of patients with CAP caused by SARS-CoV-2 was 59 years. Approximately 42% of the study population were 65 years of age or older.

Table 1. Age of patients with varying severity of community-acquired pneumonia (CAP) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and of controls

Groups	Number of patients	Age [years] M ±SD	p-value
CG (I)	27	53.52 ±16.68	$p_{I–II}$ = 0.130 $p_{I–III}$ = 0.386 $p_{I–IV}$ = 0.558 $p_{II–III}$ = 0.908 $p_{II–IV}$ = 0.998 $p_{III–IV}$ = 0.998
Group II	124	59.73 ±16.68	
Group III	68	58.37 ±12.88	
Group IV	16	59.06 ±12.32	

Groups: CG (I)– control group; group II – patients with pneumonia of risk class II; group III – patients with pneumonia of risk class III; group IV – patients with pneumonia of risk class IV.
M – mean; SD – standard deviation.

The retrospective analysis of the data showed no significant differences in the severity of CAP caused by SARS-CoV-2 between male and female patients (Table 2).

Table 2. Gender of patients with varying severity of community-acquired pneumonia (CAP) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and of controls

Groups	M	F	χ^2	p-value
CG (I)	16 (59.26)	11 (40.74)	1.26	0.739
Group II	64 (51.61)	60 (48.39)		
Group III	33 (48.53)	35 (51.47)		
Group IV	7 (43.75)	9 (56.25)		

Data presented as number (percentage) (n (%)).
M – male; F – female.

The CCI revealed significant differences among the inpatient groups with CAP caused by SARS-CoV-2 in terms of risk classes, indicating a higher comorbidity burden in subjects with a higher risk class. The comparison of CCI between inpatients with CAP caused by SARS-CoV-2 and CG showed significantly higher scores in subjects with pneumonia risk class III (by 57.89%) and risk class IV (by 167.67%) (Table 3).

Table 3. Charlson comorbidity index (CCI) scores of patients with varying severity of community-acquired pneumonia (CAP) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and of controls

Groups	CCI score (points)	p-value
CG (I)	1.33 ±1.21	$p_{I–II}$ = 0.978 $p_{I–III}$ = 0.049* $p_{I–IV}$ < 0.001* $p_{II–III}$ = 0.004* $p_{II–IV}$ < 0.001* $p_{III–IV}$ = 0.003*
Group II	1.32 ±1.67	
Group III	2.10 ±2.09	
Group IV	3.56 ±1.75	

Data presented as mean ± standard deviation (M ±SD).
* statistically significant.

A weak direct correlation was found between the patients' CCI score and age (Fig. 1).

The severity of comorbid diseases was recorded and scored using the CCI formula. A cut-off value of 3 points was a substantial independent risk factor in predicting mortality and an indicator of a high comorbidity burden, while a CCI score of 0–2 points indicated a low comorbidity burden. The study established a significant correlation between the comorbidity burden and the severity of pneumonia. In particular, patients in the pneumonia risk class II and III groups had a low CCI score, while those in group IV had a high CCI score. It is worth noting that among patients with a low CCI score, there were 31.99% more individuals in the pneumonia risk class III group than in the pneumonia risk class IV group (Table 4).

The analysis of the frequency of concomitant pathology, taking into account the severity of CAP caused by SARS-CoV-2, revealed significant relationships between the diagnosed cases of congestive heart failure, moderate to severe liver diseases and DM with chronic complications and the pneumonia risk class. In group IV, the frequency of diagnosed congestive heart failure, moderate to severe liver diseases and DM with chronic complications was significantly higher as compared to patients from group III (by 29.04%, 15.07% and 19.49%, respectively) and group II (by 37.30%, 27.22% and 24.80%, respectively) (Table 5).

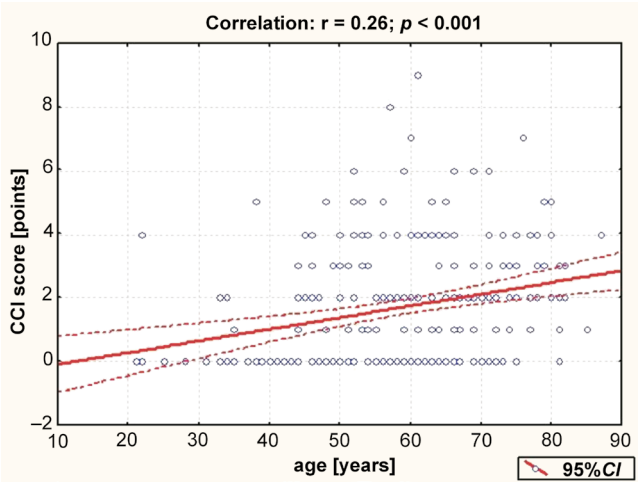

Fig. 1. Relationship between the Charlson comorbidity index (CCI) and age in patients with community-acquired pneumonia (CAP) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

r – Pearson correlation coefficient; *CI* – confidence interval.

Table 4. Charlson comorbidity index (CCI) low and high scores of patients with varying severity of community-acquired pneumonia (CAP) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and of controls

Groups	CCI score (points)		χ^2	*p*-value
	0–2	≥3		
CG (I)	24 (88.89)	3 (11.11)	21.93	<0.001*
Group II	97 (78.23)	27 (21.77)		
Group III	43 (63.24)	25 (36.76)		
Group IV	5 (31.25)	11 (68.75)		

Data presented as *n* (%).
* statistically significant.

Table 5. Comorbidities in patients with varying severity of community-acquired pneumonia (CAP) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in controls

Comorbidity	Groups				χ^2	*p*-value
	CG (I)	group II	group III	group IV		
Myocardial infarction	1 (3.70)	4 (3.23)	2 (2.94)	1 (6.25)	0.46	0.928
Congestive heart failure	11 (40.74)	39 (31.45)	27 (39.71)	11 (68.75)	8.87	0.031*
Peripheral vascular disease	10 (37.04)	34 (27.42)	16 (23.53)	4 (25.00)	1.82	0.610
Cerebrovascular disease	1 (3.70)	3 (2.42)	1 (1.47)	2 (12.50)	5.74	0.125
Dementia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	–	–
COPD	2 (7.41)	5 (4.03)	6 (8.82)	3 (18.75)	5.55	0.136
Connective tissue disease	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	–	–
Peptic ulcer disease	0 (0.00)	3 (2.42)	2 (2.94)	0 (0.00)	1.20	0.753
Mild liver disease	2 (7.41)	6 (4.84)	10 (14.71)	2 (12.50)	5.87	0.118
Moderate to severe liver disease	0 (0.00)	5 (4.03)	11 (16.18)	5 (31.25)	20.48	<0.001*
DM	1 (3.70)	3 (2.42)	2 (2.94)	1 (6.25)	0.78	0.855
DM with chronic complications	1 (3.70)	8 (6.45)	8 (11.76)	5 (31.25)	11.75	0.008*
Hemiplegia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	–	–
Moderate to severe CKD	1 (3.70)	11 (8.87)	6 (8.82)	2 (12.50)	1.16	0.763
Solid tumor	2 (7.41)	6 (4.84)	6 (8.82)	2 (12.50)	2.03	0.567
Leukemia	0 (0.00)	0 (0.00)	1 (1.47)	0 (0.00)	2.47	0.481
Malignant lymphoma	0 (0.00)	1 (0.81)	0 (0.00)	0 (0.00)	0.90	0.827
AIDS	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	–	–

Data presented as *n* (%).
COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; CKD – chronic kidney disease; AIDS – acquired immunodeficiency syndrome;
* statistically significant.

Discussion

COVID-19 patients with multiple comorbidities are at a higher risk of poorer outcomes and mortality due to the increased severity of lung injury. Guan et al. evaluated the risk of serious adverse outcomes in COVID-19 patients by stratifying their comorbidity status, and showed that subjects with underlying diseases had poorer clinical outcomes than those without.[30] Huang et al. demonstrated that 32% of hospitalized patients with pneumonia caused by SARS-CoV-2 had underlying diseases, including DM (20%), hypertension (HTN) (15%) and cardiovascular disease (CVD) (15%).[31] Chen et al. reported that 51% of inpatients with pneumonia caused by SARS-CoV-2 had comorbidities, with the most prevalent being cardiovascular and cerebrovascular diseases (40%) and DM (13%).[32] A prospective observational cohort study using the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) found that chronic cardiac disease (30.9%), DM without complications (20.7%), COPD excluding asthma (17.7%), CKD (16.2%), and asthma (14.5%) were the most common major comorbidities among 20,133 hospital inpatients with COVID-19, while 22.5% of patients had no documented major underlying disease.[33] In a retrospective study of 1,590 COVID-19 patients who were admitted to hospital and had a laboratory-confirmed diagnosis, 25.1% reported having at least one underlying health condition.[30] Among these comorbidities, the most prevalent one was HTN (16.9%), followed by DM (8.2%) and other CVD (3.7%). Furthermore, individuals with severe COVID-19 were more likely to have multiple comorbidities as compared to non-severe cases (40.0% vs. 29.4%). Patients with multiple comorbidities were older (mean age: 66.2 years vs. 58.2 years) and were more likely to experience shortness of breath (55.4% vs. 34.1%).[30] Wu et al. conducted a retrospective cohort study involving 201 patients with COVID-19 pneumonia, of which 84 (41.8%) developed ARDS.[34] The study found that older age, neutrophilia, organ dysfunction, and elevated D-dimer levels were associated with an increased risk of ARDS or death. Moreover, among patients who developed ARDS, comorbidities such as HTN (23 out of 84 (27.4%)) and DM (16 out of 84 (19.0%)) were more common as compared to individuals who did not develop ARDS (16 out of 117 (13.7%) and 6 out of 117 (5.1%) patients, respectively).[34] In their multicenter retrospective cohort study involving 191 patients with COVID-19 pneumonia, Zhou et al. found that older age, higher Sequential Organ Failure Assessment (SOFA) scores and D-dimer levels greater than 1 μg/mL upon admission were associated with an increased risk of death during hospitalization.[22]

Our results indicate that patients with comorbidities experienced more severe pneumonia as compared to those without comorbidities. Patients in the risk class IV group had a high CCI score (≥3), while the majority of patients in the risk class II and III groups had a low CCI score (0–2). The comorbidities most commonly associated with CAP caused by SARS-CoV-2 were congestive heart failure, moderate to severe liver diseases and diabetes with chronic complications. In group IV, the frequency of congestive heart failure, moderate to severe liver diseases and DM with chronic complications was significantly higher as compared to patients from group III (by 29.04%, 15.07% and 19.49%, respectively) and group II (by 37.30%, 27.22% and 24.80%, respectively).

Diabetes mellitus is a major risk factor for the development of severe pneumonia caused by viral infections.[35] A single-center prospective cohort study found a strong association between DM and the diagnosis of pneumonia in patients with SARS-CoV-2 infection.[36] The study observed that individuals with DM had a 3.5-fold higher prevalence of pneumonia as compared to those without the condition.[36] According to Bornstein et al., patients with DM have up to a 50% higher risk of a fatal outcome from COVID-19 than those without DM.[37] In a study by Zhu et al., patients with type 2 DM were more likely to experience a severe course of COVID-19, and those with poorer blood glucose control had a higher mortality rate than those with better blood glucose management.[38]

Among other comorbidities, congestive heart failure has also been associated with poor pneumonia outcomes due to alveolar flooding and reduced microbial clearance.[39] A prospective study conducted by Petrilli et al. showed that chronic heart failure was associated with a 4.4-fold higher risk of hospitalization and a 1.9-fold higher risk of critical illness in COVID-19 patients.[40] However, a study conducted by Bruno et al. examined the impact of the pre-existing chronic heart failure on the clinical outcomes of critically ill elderly patients (≥70 years) receiving intensive care for COVID-19, and concluded that the pre-existing condition did not influence 30-day mortality.[41]

Due to immune dysregulation, chronic liver diseases are believed to put affected individuals at risk of adverse outcomes following infection with SARS-CoV-2. Recent reports have indicated that patients with the pre-existing chronic liver diseases have a high mortality rate for COVID-19, with an associated mortality rate of 39.8%.[42] According to a study by Marjot et al., the stage of liver disease is strongly correlated with COVID-19 mortality.[43]

We found a CCI score ≥3 in the majority of patients in the risk class IV group. It should be noted that a CCI score >3 (*OR* (odds ratio): 2.71; 95% *CI* (confidence interval): 1.85–3.97) was found to be independently associated with mortality in COVID-19 inpatients.[44] Gregoriano et al. reported a significant burden of comorbidities among adult COVID-19 patients hospitalized in Aarau Cantonal Hospital, Switzerland, between February 26, 2020, and April 30, 2020.[45] The patients had a median CCI of 3 points, and there was a high prevalence of HTN, CKD and obesity.[45] In a systematic review and meta-analysis conducted by Tuty Kuswardhani et al., it was found that a CCI score

of 1–2 or ≥3 was prognostically associated with higher mortality and poor outcomes in patients with COVID-19 as compared to a CCI score of 0.[25] Each incremental point in the CCI score raised the mortality risk by 16%. Thus, a higher mean CCI score was significantly associated with both mortality and disease severity.[25] These and similar findings were used by Nuevo-Ortega et al., who proposed a method for predicting the prognosis of patients with COVID-19 pneumonia.[46] The method combines age-adjusted CCI and the pneumonia severity scale (CURB-65), with the addition of the measurement of arterial saturation with pulse oximetry as the only supplementary diagnostic tool.[46]

This study is the first research in Ukraine to evaluate the impact of the comorbidity burden, quantitatively assessed by applying CCI, on the severity of CAP caused by SARS-CoV-2. Our results demonstrated that patients with higher CCI scores had more severe CAP. This finding suggests that the CCI score can be used as an alternative to pneumonia-specific severity scores, not only to predict the risk of death. Moreover, our research can be useful for identifying patients who are at high risk of poor outcomes and may guide clinical decision-making.

Limitations

The present study has several limitations. First, its retrospective character makes it susceptible to knowledge bias. Second, some previous medical history was not classified according to the International Classification of Diseases 10th Revision (ICD-10) diagnosis codes, and some information about comorbidities might be missing. Third, the duration of COVID-19 illness prior to hospitalization was not considered in this study. Fourth, the sample size of the risk class IV group was limited. Additionally, we cannot rule out the hypothesis that the patients included in the study do not represent the entire cohort of patients with CAP caused by SARS-CoV-2 in Ukraine. However, our results reflect a heterogeneous real-world population representative of clinical practice.

Conclusions

The present study suggests that the comorbidity burden has a significant impact on the severity of CAP caused by SARS-CoV-2. The majority of patients in the pneumonia risk class II and risk class III groups had a low CCI score of 0–2, while the majority of patients in the risk class IV group had a high CCI score (≥3). Moreover, a direct correlation was established between the CCI score and the age of inpatients with CAP caused by SARS-CoV-2. The use of CCI to evaluate comorbid pathology in hospitalized patients with CAP caused by SARS-CoV-2 can assist the medical staff in developing timely preventive and therapeutic strategies, leading to improved patient prognosis.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee at I. Horbachevsky Ternopil National Medical University, Ukraine (No. 73, 03.04.2023).

Data availability

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

Consent for publication

Not applicable.

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Original paper

Comparative evaluation of the efficacy of probiotic, *Aloe vera*, povidine-iodine, and chlorhexidine mouthwashes in the treatment of gingival inflammation: A randomized controlled trial

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

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Abstract

Background. Chemical plaque control with mouthwashes as an adjunct to mechanical plaque control with a toothbrush and dental floss has been considered an effective method for controlling gingivitis. The anti-inflammatory effects of chemical plaque control benefit the oral tissues by reducing inflammation and bleeding.

Objectives. The aim of the present study was to evaluate and compare the clinical efficacy of probiotic, *Aloe vera*, povidine-iodine, and chlorhexidine (CHX) mouthwashes in treating gingivitis patients by assessing changes in their clinical parameters.

Material and methods. This prospective study was conducted on 40 patients from our outpatient department, divided into 4 groups of 10 patients each: probiotic mouthwash group (group 1); herbal (*Aloe vera*) mouthwash group (group 2); povidone-iodine mouthwash group (group 3); and CHX mouthwash group (group 4). All participants were provided with the same type of manual toothbrush, the Pepsodent® toothpaste and a respective mouthwash for twice-daily use until the end of a 28-day observation period. Clinical parameters, such as the marginal plaque index (MPI) and bleeding on interdental brushing (BOIB), were recorded at baseline, and on the 14th and 28th day of the study period.

Results. All groups showed a significant decrease in the MPI and BOIB scores. The results were similar in patients who used a probiotic mouthwash and those who used a CHX mouthwash. A comparable change in the mean scores was observed among the herbal and povidone-iodine groups from baseline to day 28.

Conclusions. In the treatment of chronic gingivitis patients, a probiotic mouthwash was nearly as effective as CHX in reducing the plaque and bleeding scores. It showed better results in all clinical parameters than herbal and povidone-iodine mouthwashes. Using a mouthwash along with routine tooth brushing can help in treating gingivitis and slow the progression of the periodontal disease.

Keywords: chlorhexidine, gingival inflammation, probiotic mouthwash, *Aloe vera* mouthwash

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Introduction

Dental caries and periodontal diseases are the most prevalent oral diseases worldwide. Periodontal diseases are inflammatory in nature and exist in 2 forms – reversible gingivitis and irreversible periodontitis. Dental plaque with various microorganisms makes up the prime factor in the initiation and progression of periodontal diseases, leading to severe destruction of the tooth-supporting structures.[1] Hence, maintaining plaque control is an essential part of routine oral hygiene, as dental diseases in their initial phase are primarily halted through regular and precise plaque removal.[2]

Various plaque control measures are applied in routine oral hygiene. Mechanical plaque control is considered the first line of periodontal therapy, accompanied by oral hygiene instruction.[3] The mechanical removal of plaque with a toothbrush and dental floss has been considered an effective method for controlling gingivitis. Nevertheless, achieving adequate brushing time, efficient cleaning of all tooth surfaces and regular oral hygiene can be challenging due to variations in oral health practices among individuals. This accounts for the high prevalence of gingivitis. Therefore, adjunctive chemical plaque control methods, such as using mouthwashes and probiotics, have been suggested as additional therapeutic strategies.[2]

Choosing the best mouthwash is often difficult for both patients and practitioners, given the availability of several products with various active ingredients. Chlorhexidine (CHX) is the most potent anti-plaque agent, but it has several downsides.[4] The need for a safe and effective alternative to a CHX mouthwash has led to the development of a number of oral care products that are low-cost, readily available and free from significant adverse effects. When used in mouthwashes, natural herbs, povidone-iodine and probiotics have demonstrated significant benefits, similar to CHX.[5]

The use of herbs for dental care is prevalent in indigenous systems of medicine. Herbs such as *Terminalia chebula*, *Aloe vera*, *Azadirachta indica*, *Piper betle*, and *Ocimum sanctum* have antibacterial, ulcer-healing, anti-plaque, and anti-halitosis properties. The *Aloe vera* extract helps reduce plaque formation owing to its anti-inflammatory, antioxidant, antibacterial, antiviral, and antifungal properties, and thus can be regarded as oral hygiene aid in managing periodontal diseases.[6]

Povidone-iodine is an iodophor that has a broad-spectrum antimicrobial effect on bacteria, viruses, fungi, and protozoa. It delivers free iodine to the bacterial cell membrane, which reduces plaque formation, and eventually the severity of gingivitis and radiation-induced oral mucositis.[7]

Probiotics have been identified as a potential area of research in periodontal care. Various studies have demonstrated that probiotics can shift the balance of the oral microbiota toward beneficial species, thereby reducing gingivitis.[4] The World Health Organization (WHO) defines probiotics as "live microorganisms which, when administered in adequate amounts in food or as dietary supplements, confer a health benefit on the host."[4] Probiotics repopulate healthy bacteria, which can help destroy pathogenic organisms and prevent the disease. Replacing pathogenic bacteria with beneficial ones has gained acceptance in recent years due to the growing global problem of antibiotic resistance. Oral probiotics have caused a paradigm shift in the field of periodontal healthcare, offering an alternative approach to reducing the prevalence of oral microbiome-mediated diseases like gingivitis.

The purpose of this randomized controlled clinical study was to evaluate the effects of probiotic, herbal (*Aloe vera*) and povidone-iodine mouthwashes in the treatment of chronic periodontitis (CP) patients, in comparison with the gold standard, a CHX mouthwash.

Material and methods

Trial design

This study was designed as a four-pronged randomized controlled trial (RCT) with a 1:1:1:1 allocation ratio. It was conducted at the Department of Periodontology, Sibar Institute of Dental Sciences, Takkellapadu, India, between February 2021 and April 2021. The study was approved by the institutional research ethics committee (ethical clearance No. Pr.2115/IEC/SIBAR(UG)2021), and was conducted in compliance with the ethical standards established by the World Medical Association (WMA) in the Declaration of Helsinki. Each patient was given a detailed verbal and written description of the study, and provided signed consent to participate in it.

Sample size calculation

The sample size was calculated using the following formula (Equation 1):

$$N = \left[\frac{Z_1 - \alpha/2 + Z_1 - \beta}{\mu_A - \mu_B} \right]^2 \quad (1)$$

where:
N – sample size;
Z_1 – Z-value;
α – level of significance;
β – level of power; and
$\mu_A - \mu_B$ – mean difference between the samples.

As per the calculation, a minimum of 10 participants was required to achieve a power of 80% and detect differences in the mean plaque and bleeding scores between the 4 study groups by the end of a 28-day period. Therefore, the study recruited a total of 60 patients to account for potential dropouts. The study followed the Consolidated Standards of Reporting Trials (CONSORT) statement (Fig. 1).

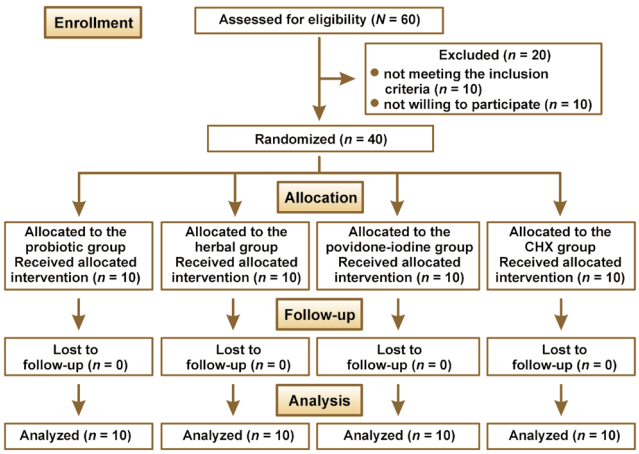

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram
CXH – chlorhexidine.

Eligibility criteria

The trial participants were selected randomly from among individuals who reported for consultation at the Department of Periodontology, Sibar Institute of Dental Sciences, Takkellapadu, India, according to the following eligibility criteria: patients within the age range of 18–45 years; of both genders; with no history of allergies to the components used in the study; and who were systemically healthy. The study excluded patients who had habits such as smoking, tobacco chewing or alcohol consumption, as well as those who used drugs in any form, were systemically compromised, were pregnant or lactating, or were unable to attend follow-up visits.

Randomization and blinding

The selected 40 subjects were randomly assigned to groups, using the Research Randomizer software, v. 2.0 (https://www.randomizer.org).

Blinding of the patients to the intervention was maintained throughout the trial.

Interventions

Forty patients, aged 18–45 years, were randomly divided into 4 groups of 10 patients each: probiotic (Darolac® sachets; Aristo Pharmaceuticals, Vijayawada, India) mouthwash group (group 1); herbal (*Aloe vera*) mouthwash group (group 2); povidone-iodine mouthwash group (group 3); and CHX mouthwash group (group 4). All participants were instructed to brush their teeth twice daily with the same type of manual toothbrush for effective plaque removal. They were provided with the Pepsodent® toothpaste and a respective mouthwash for twice-daily use until the end of the observation period.[8]

Estimation of clinical parameters

Following the initial screening and oral prophylaxis, clinical parameters, such as the new marginal plaque index (MPI) and bleeding on interdental brushing (BOIB), were recorded at baseline, and on the 14th and 28th day of the study period.

New marginal plaque index

Plaque was assessed at the proximal and cervical sections of the gingival margin. Plaque deposits were identified using a disclosure solution that stains old plaque deposits blue and fresh deposits pink.

The new MPI, proposed by Deinzer et al. in 2014,[9] assesses the presence (score 1) or absence (score 0) of plaque within 8 equal areas of a tooth (4 at the vestibular and 4 at the oral gingival margin). The gingival margin of each site (vestibular and oral) is divided into 4 equal areas: 1) distal; 2) cervico-distal; 3) cervico-mesial; and 4) mesial. Eight measures were recorded per tooth: 1) vestibular distal; 2) vestibular cervico-distal; 3) vestibular cervico-mesial; 4) vestibular mesial; 5) oral distal; 6) oral cervico-distal; 7) oral cervico-mesial; and 8) oral mesial. These measures can be combined to obtain all MPI values as the overall mean of all sections scoring 1, the MPI proximal values (i.e., the percentage of distal plus mesial sections scoring 1) and the MPI cervical values (i.e., the percentage of cervico-distal plus cervico-mesial sections scoring 1). The index also enables separate aggregation of recordings at the vestibular and oral sites (Fig. 2).

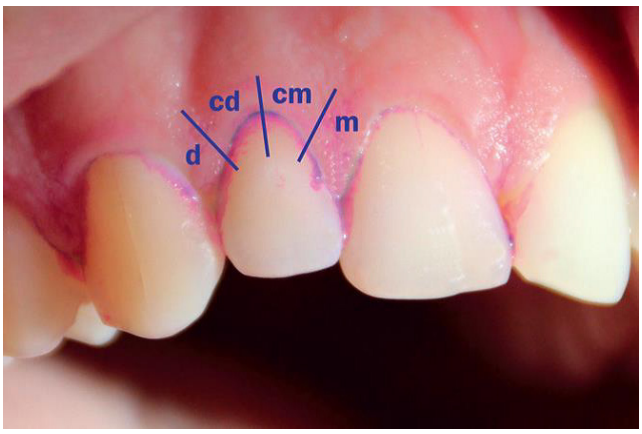

Fig. 2. New marginal plaque index (MPI) (Deinzer et al., 2014[9])
d – distal; cd – cervico-distal; cm – cervico-mesial; m – mesial.

Bleeding on interdental brushing

In 2010, Hofer et al. developed the BOIB index.[10] The measurement involves inserting a light interdental brush buccally, just below the contact point, and gliding between the teeth in a jiggling motion without force. Bleeding is scored as either present or absent for each interdental site after 30 s. The number of sites with bleeding on probing is noted.

Outcomes

The mean changes in the plaque and bleeding scores were evaluated among the 4 groups before and after the intervention, from baseline to day 28.

Statistical analysis

Statistical analysis employed IBM SPSS Statistics for Windows, v. 23.0 (IBM Corp., Armonk, USA). The data obtained from the clinical evaluation is presented as mean and standard deviation (*M* ±*SD*). The MPI and BOIB parameters were analyzed using the one-way analysis of variance (ANOVA) and the post hoc test for pairwise comparisons (Tukey's honestly significant difference (HSD) test). For all tests, a p-value <0.05 was considered statistically significant.

Formulation of hypotheses

The null hypothesis (H0) states that there is no difference in clinical parameters with regard to various treatment modalities. The alternate hypothesis (Ha) suggests that there is a difference in clinical parameters with regard to various treatment modalities.

A p-value <0.05 was considered statistically significant. If the obtained p-value is <0.05, the null hypothesis can be rejected and the alternate hypothesis considered.

Results

Pre-treatment equivalence

Forty patients were randomly assigned to one of the 4 groups (n = 10 patients per group), using a 1:1:1:1 allocation ratio, between February 2021 and April 2021. All patients were included in the statistical analysis, and no patients were lost during follow-up (Fig. 1). The mean age of the patients in the probiotic, herbal, povidone-iodine, and CHX groups was 28.5 ±7.0, 30.8 ±6.7, 25.7 ±8.1, and 27.4 ±4.2 years, respectively (Table 1).

Clinical parameters were recorded at baseline, and on the 14th and 28th day for all patients. The baseline clinical parameters were not significantly different between the groups, indicating that all groups were evenly matched at the beginning of the study (Table 1). The final differences were not influenced by the initial defect characteristics, allowing the post-treatment results to be compared.

None of the patients in any of the groups exhibited any adverse effects from the agents used.

Clinical parameters

Clinical parameters –MPI and BOIB – were recorded at baseline, on the 14th day and on the 28th day. Any differences in the mean scores of the indices were recorded at baseline and on the 28th day for all groups.

Table 1. Demographic data and the values of clinical indices for the probiotic, herbal, povidone-iodine, and chlorhexidine (CHX) groups at baseline

Baseline parameters	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)	Group 4 (n = 10)	p-value
Age [years] *M* ±*SD*	28.5 ±7.0	30.8 ±6.7	25.7 ±8.1	27.4 ±4.2	0.710
Gender (M/F) *n*	4/6	5/5	5/5	4/6	–
MPI *M* ±*SD*	0.70 ±0.06	0.70 ±0.06	0.69 ±0.06	0.68 ±0.03	0.860
BOIB *M* ±*SD*	76.6 ±11.1	72.9 ±14.1	74.6 ±11.1	76.6 ±14.1	0.820

Groups: group 1 – probiotic mouthwash group; group 2 – herbal (*Aloe vera*) mouthwash group; group 3 – povidone-iodine mouthwash group; group 4 – CHX mouthwash group.
M – mean; *SD* – standard deviation; M – male; F – female; MPI – marginal plaque index; BOIB – bleeding on interdental brushing.

Table 2. Mean values of clinical indices for the probiotic, herbal, povidone-iodine, and chlorhexidine (CHX) groups on the 14th day and on the 28th day

Time point	Parameter	Group 1	Group 2	Group 3	Group 4
14th day	MPI	0.22 ±0.01	0.48 ±0.07	0.31 ±0.07	0.48 ±0.06
	BOIB	31.9 ±0.9	51.6 ±2.3	49.6 ±0.0	60.3±2.4
28th day	MPI	0.30 ±0.01	0.56 ±0.08	0.38 ±0.06	0.55 ±0.05
	BOIB	47.3 ±4.7	59.6 ±4.7	56.9 ±4.7	66.3 ±2.4

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

At baseline, the mean MPI score for groups 1, 2, 3, and 4 was 0.70 ±0.06, 0.70 ±0.06, 0.69 ±0.06, and 0.68 ±0.03 (Table 1, Fig. 3). On day 14 after intervention, it was 0.22 ±0.01, 0.48 ±0.07, 0.31 ±0.07, and 0.48 ±0.06, and on day 28, it was 0.30 ±0.01, 0.56 ±0.08, 0.38 ±0.06, and 0.55 ±0.05, respectively (Table 2, Fig. 3). The mean BOIB score at baseline was 76.6 ±11.1, 72.9 ±14.1, 74.6 ±11.1, and 76.6 ±14.1, respectively (Table 1, Fig. 4); on day 14 after intervention, it was 31.9 ±0.9, 51.6 ±2.3, 49.6 ±0.0, and 60.3 ±2.4, and on day 28, it was 47.3 ±4.7, 59.6 ±4.7, 56.9 ±4.7, and 66.3 ±2.4, respectively (Table 2, Fig. 4).

The ANOVA revealed significant differences in MPI and BOIB between the groups and within the groups at different time points. Specifically, there were no significant differences in MPI at baseline (p = 0.863), but significant differences were observed on days 14 and 28 (p = 0.000) (Table 3). Similarly, there were no significant differences in BOIB at baseline (p = 0.822), but significant differences were observed on days 14 and 28 (p = 0.000) (Table 4).

The comparative analysis of MPI with the use of the post hoc test was conducted at different time points.

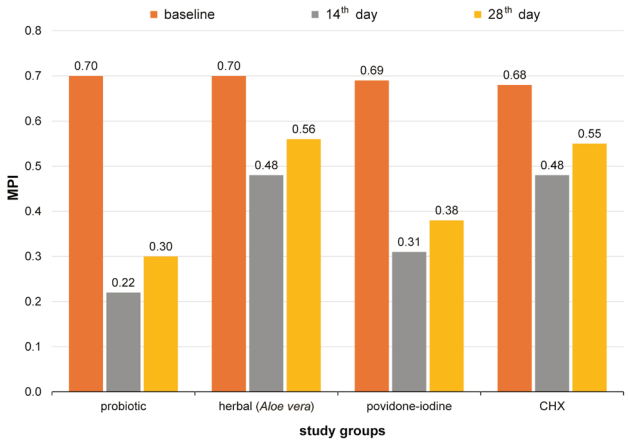

Fig. 3. Intergroup comparison of the mean marginal plaque index (MPI) scores at baseline, on the 14th day and on the 28th day

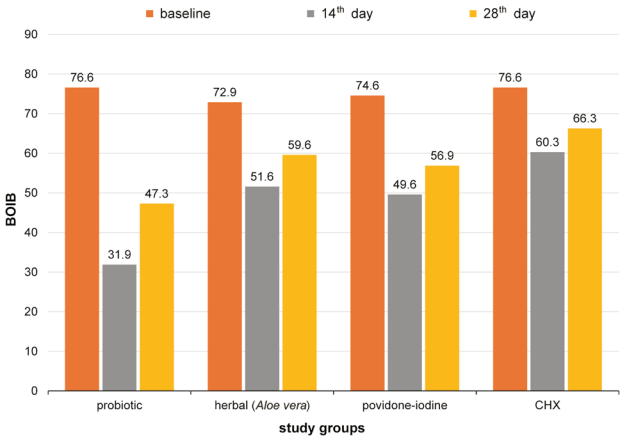

Fig. 4. Intergroup comparison of the mean bleeding on interdental brushing (BOIB) scores at baseline, on the 14th day and on the 28th day

Table 3. Comparison of the mean differences in the marginal plaque index (MPI) scores between and within the study groups (ANOVA)

Time point	Comparison	Sum of squares	df	Mean square	F	*p*-value
Baseline	between the groups	0.003	3	0.001	0.247	0.863
	within the groups	0.130	36	0.004	–	–
	total	0.132	39	–	–	–
14th day	between the groups	0.480	3	0.160	38.258	0.000*
	within the groups	0.150	36	0.004	–	–
	total	0.630	39	–	–	–
28th day	between the groups	0.490	3	0.163	38.363	0.000*
	within the groups	0.153	36	0.004	–	–
	total	0.643	39	–	–	–

df – degrees of freedom; * statistically significant.

Table 4. Comparison of the mean differences in the bleeding on interdental brushing (BOIB) scores between and within the study groups (ANOVA)

Time point	Comparison	Sum of squares	df	Mean square	F	*p*-value
Baseline	between the groups	94.160	3	31.387	0.305	0.822
	within the groups	3,703.534	36	102.876	–	–
	total	3,797.694	39	–	–	–
14th day	between the groups	4,236.628	3	1,412.209	31.193	0.000*
	within the groups	1,629.827	36	45.273	–	–
	total	5,866.455	39	–	–	–
28th day	between the groups	1,862.904	3	620.968	12.873	0.000*
	within the groups	1,736.507	36	48.236	–	–
	total	3,599.411	39	–	–	–

* statistically significant.

At baseline, there were no significant differences between the groups (p = 0.990). On the 14th day, groups 1 and 3 did not demonstrate significant differences as compared to each other, with a p-value of 0.020, while groups 2 and 4 showed no significant changes when compared to each other (p = 1.000). On the 28th day, groups 1 and 3 did not demonstrate significant differences as compared to each other (p = 0.057), and groups 2 and 4 also did not show significant changes when compared to each other (p = 0.997) (Table 5). Therefore, it can be inferred that all groups exhibited a similar reduction in the plaque scores from baseline to the 28th day, and probiotics were found to be more effective and comparable to CHX.

The comparative analysis of BOIB with the use of the post hoc test was conducted at different time points. At baseline, there were no significant differences between the groups (p = 1.000). On the 14th day, group 1 demonstrat-

Table 5. Comparison of the mean marginal plaque index (MPI) scores between groups at baseline, on the 14th day and on the 28th day, using post hoc analysis (Tukey's HSD test)

Time point	Groups		Mean difference	*SE*	*p*-value	95% *CI*	
						lower bound	upper bound
Baseline	1	2	0.0077	0.02684	0.992	–0.0646	0.0800
		3	0.0190	0.02684	0.893	–0.0533	0.0913
		4	0.0195	0.02684	0.886	–0.0528	0.0918
	2	1	–0.0077	0.02684	0.992	–0.0800	0.0646
		3	0.0113	0.02684	0.975	–0.0610	0.0836
		4	0.0118	0.02684	0.971	–0.0605	0.0841
	3	1	–0.0190	0.02684	0.893	–0.0913	0.0532
		2	–0.0113	0.02684	0.975	–0.0836	0.0610
		4	0.0005	0.02684	1.000	–0.0718	0.0728
	4	1	–0.0195	0.02684	0.886	–0.0918	0.0528
		2	–0.0118	0.02684	0.971	–0.0841	0.0605
		3	–0.0005	0.02684	1.000	–0.0728	0.0718
14th day	1	2	–0.2532	0.02891	0.000*	–0.3311	–0.1753
		3	–0.0888	0.02891	0.020*	–0.1667	–0.0109
		4	–0.2552	0.02891	0.000*	–0.3331	–0.1773
	2	1	0.2532	0.02891	0.000*	0.1753	0.3311
		3	0.1644	0.02891	0.000*	0.0865	0.2423
		4	–0.0020	0.02891	1.000	–0.0799	0.0759
	3	1	0.0888	0.02891	0.020*	0.0109	0.1667
		2	–0.1644	0.02891	0.000*	–0.2423	–0.0865
		4	–0.1664	0.02891	0.000*	–0.2443	–0.0885
	4	1	0.2552	0.02891	0.000*	0.1773	0.3331
		2	0.0020	0.02891	1.000	–0.0759	0.0799
		3	0.1664	0.02891	0.000*	0.0885	0.2443
28th day	1	2	–0.2560	0.02918	0.000*	–0.3346	–0.1774
		3	–0.0770	0.02918	0.057	–0.1556	0.0016
		4	–0.2500	0.02918	0.000*	–0.3286	–0.1714
	2	1	0.2560	0.02918	0.000*	0.1774	0.3346
		3	0.1790	0.02918	0.000*	0.1004	0.2576
		4	0.0060	0.02918	0.997	–0.0726	0.0846
	3	1	0.0770	0.02918	0.057	–0.0016	0.1556
		2	–0.1790	0.02918	0.000*	–0.2576	–0.1004
		4	–0.1730	0.02918	0.000*	–0.2516	–0.0944
	4	1	0.2500	0.02918	0.000*	0.1714	0.3286
		2	–0.0060	0.02918	0.997	–0.0846	0.0726
		3	0.1730	0.02918	0.000*	0.0944	0.2516

SE – standard error; *CI* – confidence interval; * statistically significant.

ed significant changes when compared to other groups, with a *p*-value of 0.000. Similarly, group 4 also demonstrated statistically significant changes when compared to the other 3 groups ($p = 0.000$, $p = 0.032$ and $p = 0.006$, respectively). When groups 2 and 3 were compared to each other, the results were not significant ($p = 0.910$), but with regard to groups 1 and 4, the differences were significant. On the 28th day, group 1 showed statistically significant differences when compared to other groups, with $p < 0.05$. In contrast, the comparison of groups 2 and 3 showed non-significant differences ($p = 0.826$), as well as the comparison of groups 2 and 4 ($p = 0.158$) (Table 6). It can be inferred that all groups showed a similar reduction in the bleeding scores from baseline to the 28th day, and probiotics were found to be more effective and comparable to CHX.

No adverse effects or harmful events were observed in any of the groups.

Table 6. Comparison of the mean bleeding on interdental brushing (BOIB) scores between groups at baseline, on the 14th day and on the 28th day, using post hoc analysis (Tukey's HSD test)

Time point	Groups		Mean difference	*SE*	*p*-value	95% *CI*	
						lower bound	upper bound
Baseline	1	2	3.6670	4.5360	0.850	−8.5494	15.8834
		3	2.0030	4.5360	0.971	−10.2134	14.2194
		4	0.0020	4.5360	1.000	−12.2144	12.2184
	2	1	−3.6670	4.5360	0.850	−15.8834	8.5494
		3	−1.6640	4.5360	0.983	−13.8804	10.5524
		4	−3.6650	4.5360	0.850	−15.8814	8.5514
	3	1	−2.0030	4.5360	0.971	−14.2194	10.2134
		2	1.6640	4.5360	0.983	−10.5524	13.8804
		4	−2.0010	4.5360	0.971	−14.2174	10.2154
	4	1	−0.0020	4.5360	1.000	−12.2184	12.2144
		2	3.6650	4.5360	0.850	−8.5514	15.8814
		3	2.0010	4.5360	0.971	−10.2154	14.2174
14th day	1	2	−19.6670	3.0091	0.000*	−27.7712	−11.5628
		3	−17.6690	3.0091	0.000*	−25.7732	−9.5648
		4	−28.3340	3.0091	0.000*	−36.4382	−20.2298
	2	1	19.6670	3.0091	0.000*	11.5628	27.7712
		3	1.9980	3.0091	0.910	−6.1062	10.1022
		4	−8.6670	3.0091	0.032*	−16.7712	−0.5628
	3	1	17.6690	3.0091	0.000*	9.5648	25.7732
		2	−1.9980	3.0091	0.910	−10.1022	6.1062
		4	−10.6650	3.0091	0.006*	−18.7692	−2.5608
	4	1	28.3340	3.0091	0.000*	20.2300	36.4382
		2	8.6670	3.0091	0.032*	0.5628	16.7712
		3	10.6650	3.0091	0.006*	2.5608	18.7692
28th day	1	2	−12.3340	3.1060	0.002*	−20.6992	−3.9688
		3	−9.6670	3.1060	0.018*	−18.0322	−1.3018
		4	−18.9990	3.1060	0.000*	−27.3642	−10.6338
	2	1	12.3340	3.1060	0.002*	3.9688	20.6992
		3	2.6670	3.1060	0.826	−5.6982	11.0322
		4	−6.6650	3.1060	0.158	−15.0302	1.7002
	3	1	9.6670	3.1060	0.018*	1.3018	18.0322
		2	−2.6670	3.1060	0.826	−11.0322	5.6982
		4	−9.3320	3.1060	0.024*	−17.6972	−0.9668
	4	1	18.9990	3.1060	0.000*	10.6338	27.3642
		2	6.6650	3.1060	0.158	−1.7002	15.0302
		3	9.3320	3.1060	0.024*	0.9668	17.6972

* statistically significant.

Discussion

Maintaining adequate oral hygiene is crucial in preventing dental diseases. Several researchers have proposed using chemical plaque control measures as an adjunct to mechanical plaque control at home. In vitro microbiological research studies have shown that antimicrobial agents can penetrate the bacterial biofilm and exert their bactericidal properties.[11,12] Furthermore, chemical agents can reach interproximal areas that are difficult to clean, and inhibit bacterial growth and the subsequent biofilm formation on soft tissues. The use of these agents is safe and does not appear to increase the resistance of bacterial species.[13]

Various types of mouthwashes are available on the market and they are commonly used for routine oral hygiene. However, to the best of our knowledge, few studies evaluated the clinical efficacy of different mouthwashes and compared them with CHX. Hence, the present study was conducted to evaluate the clinical efficacy of probiotic, herbal (*Aloe vera*) and povidone-iodine mouthwashes in the treatment of CP patients in comparison with a positive control using a CHX mouthwash.

In the present study, group 1 participants were advised to use a probiotic mouthwash. On day 28, a significant mean change was demonstrated with regard to MPI and BOIB, with a *p*-value of 0.000. The present study employed Darolac sachets dissolved in water, using the swish-and-swallow technique, in accordance with a study conducted by Jindal et al.[14] Our study showed a statistically significant reduction in bleeding on probing, which is consistent with the findings of studies conducted by Vivekananda et al.,[15] Penala et al.,[16] İnce et al.,[17] Vicario et al.,[18] and Della Riccia et al.[19] The decrease in the plaque index observed in our study was congruent with the results of studies conducted by Penala et al.,[16] İnce et al.,[17] Vicario et al.,[18] Riccia et al.,[19] Krasse et al.,[20] and Nadkerny et al.[21]

The role of probiotics is based on the premise that they produce antibacterial compounds, enhance the epithelial barrier and sequester essential nutrients from pathogens, which prevents their adhesion and growth. Probiotics can adhere to surfaces and balance the replacement of pathogenic microorganisms with non-pathogenic strains.

The results of group 2, in which the participants were instructed to use a herbal mouthwash, demonstrated a significant reduction in the plaque and bleeding scores, as in the probiotic group. Yet, even though a herbal (*Aloe vera*) mouthwash showed significant results, it was not as effective as probiotic and CHX mouthwashes. The decrease in the plaque and bleeding indices was similar to that observed in studies conducted by Lee et al.,[22] Chandrahas et al.[23] and Moghaddam et al.[24]

Aloe vera has various beneficial properties, such as anti-inflammatory (due to the presence of sterols and anthrax quinones) and anti-septic (due to the presence of lupeol, salicylic acid, phenols, and sulfur) activity, and has the capability to enhance wound healing.[25] These characteristics make it a good agent for preventing gingivitis. In our study, the clinical efficacy of the *Aloe vera* mouthwash was found to be good, although not as good as in the case of CHX and probiotic mouthwashes. The clinical improvement attributed to *Aloe vera* may have been due to its antibacterial, anti-plaque and healing properties.

The results of group 3, in which the participants were instructed to use a povidone-iodine mouthwash, demonstrated a significant decrease from baseline to day 28 in the plaque and bleeding scores. This may be attributed to the antimicrobial activity of povidone-iodine. Yet, the improvement was not comparable to that in the probiotic group.

In a study conducted by Yoneyama et al., using povidone-iodine gargle and mouthwash (benzethonium chloride (BEC) and chlorhexidine gluconate (CHG)) samples from healthy volunteers, povidone-iodine was found to show stronger bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* than BEC and CHG.[26]

Limitations

The study did not include a negative control group or a no-treatment group. Future studies presenting microbiological comparisons between groups may provide a better insight while evaluating different mouthwashes in terms of gingival inflammation reduction.

Conclusions

The results of the present study indicate that the use of a mouthwash leads to a significant reduction in the plaque and bleeding indices. Within the study limitations and based on the obtained results, it can be inferred that although CHX is considered the gold standard, a probiotic mouthwash demonstrates comparable results to CHX, and is equally effective in reducing the plaque and bleeding scores. Therefore, conducting additional studies that would employ microbiological analysis, with a negative control, may provide a better insight into the treatment of gingival inflammation and confirm the improved outcomes.

Ethics approval and consent to participate

The study was approved by the institutional research ethics committee (ethical clearance No. Pr.2115/IEC/SIBAR(UG)2021), and was conducted in compliance with the ethical standards established by the World Medical Association (WMA) in the Declaration of Helsinki. Each patient was given a detailed verbal and written description of the study, and provided signed consent to participate in it.

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

Post-endodontic pain in curved canals prepared with different rotary instrumentation techniques: A randomized controlled trial

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Abstract

Background. Curved root canals are associated with the highest number of procedural errors during endodontic instrumentation. Recently, numerous rotary instruments have been developed, with both manual and automated mechanisms, to facilitate endodontic treatment and manage the complications related to it.

Objectives. The aim of the study was to assess post-endodontic pain after using the HyFlex® EDM OneFile (HEDM), WaveOne® Gold (WOG) and XP-endo® Shaper (XPS) systems in the preparation of curved canals in patients with asymptomatic irreversible pulpitis.

Material and methods. A total of 45 molars with curved canals and asymptomatic irreversible pulpitis were randomly divided into 3 equal groups based on the instrumentation used: HEDM (group A); WOG (group B); and XPS (group C). All teeth were prepared according to the manufacturers' instructions. Post-endodontic pain was assessed using the visual analog scale (VAS) at 6, 12, 18, 24, 48, and 72 h after root canal instrumentation. The data was analyzed using the one-way analysis of variance (ANOVA) and the paired-samples *t* test with the Bonferroni correction, with a *p*-value of 0.05 set for statistical significance.

Results. The highest levels of post-endodontic pain were recorded at 6 h after treatment. Then, the values gradually decreased until the pain nearly vanished after 72 h. No statistically significant differences were observed in the VAS scores between groups A and B. At the same time, group C showed the lowest VAS scores at all follow-up time points.

Conclusions. The use of the XPS system resulted in the lowest pain scores at all follow-ups. The HEDM and WOG groups showed no differences in the pain scores throughout the whole follow-up period.

Keywords: visual analog scale, curved canals, post-endodontic pain, automated preparation

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Introduction

Post-endodontic pain is an unpleasant outcome for both patients and clinicians. The degree of post-endodontic pain ranges from 25% to 40% worldwide. The incidence and intensity of post-endodontic pain are related to microbial factors, iatrogenic factors, like chemical and mechanical injuries to the periapical tissues during instrumentation, and patient-related factors, such as age, gender, pulp vitality, and the pathologies affecting the periapical tissues.[1,2]

The goal of patient management is to relieve pain, maintain function and preserve esthetics. However, orofacial pain may occur during any step of treatment. The pain induced by interventions can interfere with orofacial pain, which is multifactorial and characterized by a wide spectrum of signs and symptoms.[2]

It is uncommon to find a tooth with both a straight root and a straight root canal, as most teeth exhibit some degree of canal curvature, even if the root is straight.[3] Curved root canals are associated with the highest number of procedural errors during endodontic instrumentation, including perforations, blocked canals, ledges, and apical transportation. Treating a tooth with a curved canal remains a challenge, and requires suitable instruments and techniques.[4] Apical debris extrusion is believed to induce acute inflammatory reactions and is considered a direct cause of post-endodontic pain.[5,6]

Nowadays, numerous rotary instruments have been developed with advanced metallurgy and mechanisms to facilitate endodontic treatment. Nonetheless, all preparation instruments and techniques are still associated with some degree of debris extrusion, which may cause post-endodontic pain.[7]

Most nickel–titanium (NiTi) rotary and reciprocating instrument systems extrude less debris than stainless steel hand K-files, potentially reducing the risk of post-endodontic pain.[8]

The new HyFlex® EDM OneFile (HEDM) instrument (Coltène/Whaledent AG, Altstätten, Switzerland) is manufactured with the use of electrical discharge techniques. As a result, the file has a uniquely hardened surface, which is extremely flexible and highly resistant to fracture.[9,10]

On the other hand, the WaveOne® Gold (WOG) system, launched in 2015 by Dentsply Sirona (Ballaigues, Switzerland), is manufactured using a new gold heat treatment. The file is made of a traditional NiTi alloy that first undergoes the grinding process and is then heat-treated to obtain a gold color. The heating process, combined with the latest reciprocating technology, enhances the flexibility of the file and its resistance to cyclic fatigue.[11,12] Also, WOG has a unique design that improves efficiency and fracture resistance. Due to its triangular, convex cross-section and 2 cutting edges, there are only 1 or 2 contact points between the cutting edges and the canal wall.[13]

A study performed by Alnassar et al. concluded that the manual instrumentation of root canals in primary molars might cause more pain as compared to automated preparation systems.[14] In other words, the use of automated preparation systems in the root canal treatment of primary molars could reduce post-endodontic pain.[14]

The XP-endo® Shaper (XPS) (FKG Dentaire, La Chaux-de-Fonds, Switzerland) is manufactured using a NiTi MaxWire alloy. It has size 30 and a 0.01 taper. The XPS reaches the martensitic phase at 20°C and transforms to the austenitic phase at 37°C when placed in the canal. The file tip (Booster Tip) has 6 cutting edges, which enables the gradual shaping of the canal from size 15 to size 30 while keeping the instrument centered to prevent the straightening of the root canal. Due to its design, XPS shows good efficiency and fracture resistance.[15,16]

Numerous studies have compared the effects of different reciprocating and rotary systems on post-endodontic pain, yielding varying results. Therefore, more research is necessary to determine the impact of different endodontic instruments on post-endodontic pain. The aim of the present study was to assess post-endodontic pain after using the HEDM, WOG and XPS systems in the preparation of curved canals in patients with asymptomatic irreversible pulpitis.

Material and methods

This randomized clinical study was conducted over a period of 2 years (2019–2020) at the Department of Endodontics, Faculty of Dentistry, Damascus University, Syria. The authors followed a pre-set protocol for the HEDM, WOG and XPS instrument systems. The study received ethical approval from the scientific committee at the Faculty of Dentistry of Damascus University (FMD\rct-758).

Sample selection

The study sample consisted of 45 molars with curved canals (20–45°), according to Schneider,[17] and asymptomatic irreversible pulpitis.

Inclusion criteria

A clinical examination was performed to ensure the presence of acute, pulsating and continuous pain. Molars with acute pulpitis identified during previous examinations and curved canals (20–45°) were included.

Exclusion criteria

The exclusion criteria were molars with symptomatic/necrotic pulp, apical periodontitis, root resorption, and open apices, as well as patients with signs of systemic infection or uncontrolled systemic disease, and those using analgesics or non-steroidal or steroidal anti-inflammatory drugs.

Randomization

The study followed the Consolidated Standards of Reporting Trials (CONSORT) statement (Fig. 1).[18] Prior to treatment, the patient selected a card from a dark box containing 45 cards (15 red cards for HEDM, 15 yellow cards for WOG and 15 blue cards for XPS).

Then, the 45 molars were divided into 3 equal groups based on the instrumentation used: HEDM (group A); WOG (group B); and XPS (group C).

Treatment procedure

First, local anesthesia was performed using lidocaine 2% with epinephrine (1:100,000). Then, the access cavity was prepared using a round bur with a high-speed handpiece. A glide path was established with an ISO K-file up to size 15 after the working length was determined to be 1 mm from the apical foramen. All teeth were prepared according to the manufacturers' instructions.

Group A: HEDM OneFile (25/~; Coltène/Whaledent AG) was used in a rotary motion (500 rpm, 2.5 N·cm). It was introduced into the canal with 3 in-and-out movements with a stroke amplitude of 3 mm until the full working length was reached.

Group B: WOG Primary File (25/.07; Dentsply Sirona) was used in the reciprocating mode after adjusting the working length. The file was introduced into the canal with an in-and-out picking motion (3 pecks with a stroke amplitude of 3 mm) while applying slight apical pressure until the full working length was obtained.

Group C: XPS single file (30/.01–.04; FKG Dentaire) was used in a continuous rotary movement at a speed of 1,000 rpm and a torque of N·cm. The file was inserted into the canal with an in-and-out motion, applying 5 strokes until the file reached its full working length.

Post-endodontic pain was assessed using the visual analog scale (VAS) at 6, 12, 18, 24, 48, and 72 h after root canal instrumentation. For pain evaluation, the patients were asked to rate their pain level on VAS as follows: 0–24 – no pain; 25–49 – slight pain; 50–74 – moderate pain; and 75–100 – severe pain (Fig. 2).[19] They were reminded to register the pain values at different time points. If the pain was unbearable, the patients were allowed to take anti-inflammatory drugs after registering their pain level.

After 72 h, canal obturation was performed and the teeth were restored with composite.

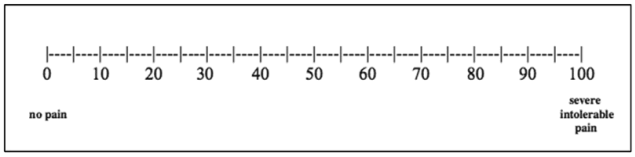

Fig. 2. Visual analog scale (VAS)

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows software, v. 22.0 (IBM Corp., Armonk, USA).

The data was analyzed using the one-way analysis of variance (ANOVA) and the paired-samples *t* test with the Bonferroni correction, with a *p*-value of 0.05 set for statistical significance.

Results

The study sample consisted of 45 molars in patients aged 19–55 years, divided into 3 equal groups. The descriptive analysis of all groups in terms of VAS pain scores is shown in Table 1.

The results of the study indicate that the highest VAS pain values were observed at 6 h after canal instrumentation. Then, the values gradually decreased until the pain nearly vanished after 72 h.

The mean pain values after 6 h for HEDM, WOG and XPS were 37.00, 42.33 and 22.00, respectively. Then, the values gradually decreased over the specified periods until they reached 0 in the XPS group after 72 h (Fig. 3).

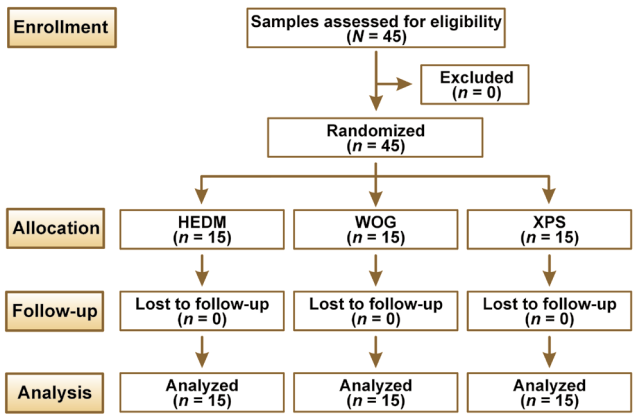

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram

HEDM – HyFlex EDM OneFile (group A); WOG – WaveOne Gold (group B); XPS – XP-endo Shaper (group C).

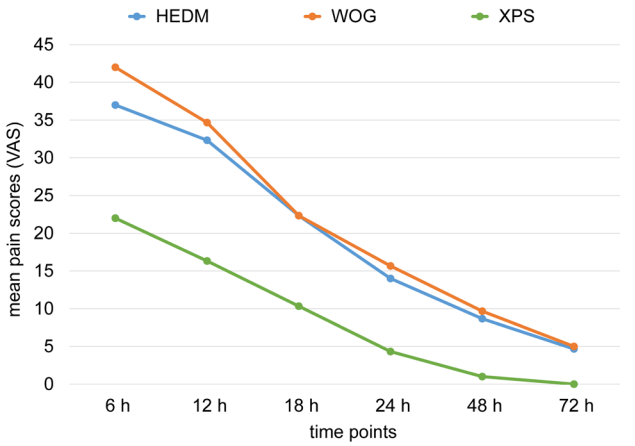

Fig. 3. Mean pain scores (visual analog scale – VAS) at different time points in all study groups

The XPS group exhibited the lowest mean VAS scores at all follow-up time points.

The one-way ANOVA was applied to detect intergroup differences in the VAS pain scores. At 6, 12, 18, 24, 48, and 72 h after root canal instrumentation, the *p*-values were lower than 0.05, indicating significant differences between the groups (Table 2).

The Bonferroni test was used to determine pairwise differences between the study groups. There were significant differences between group C (XPS) and groups A and B at all studied time points ($p < 0.05$). However, at a 95% confidence level, there were no significant differences in the VAS pain scores between groups A and B at any of the studied time points ($p > 0.05$) (Table 3).

Discussion

Post-endodontic pain is a serious complication following root canal treatment.[20] The prevalence of post-endodontic pain ranges from 1.5% to 50%.[21,22]

Only asymptomatic teeth were included in this study to minimize bias and isolate pre-endodontic pain as a variable factor that might affect post-endodontic pain, as previously reported.[23]

Besides, our study only included molars with curved canals (20–45°) due to a wide range of challenging cases; the preparation and shaping of curved canals may result in many post-treatment complications, such as pain and perforation.[24,25]

Table 1. Pain scores (visual analog scale – VAS) at different time points for all study groups

Follow-up time points	System studied (groups)	*M* ±*SD*	*SE*	min	max
6 h	HEDM	37.00 ±5.61	1.45	30.00	45.00
	WOG	42.33 ±8.21	2.12	30.00	55.00
	XPS	22.00 ±5.61	1.45	15.00	30.00
12 h	HEDM	32.33 ±4.17	1.08	30.00	40.00
	WOG	34.67 ±6.67	1.72	30.00	50.00
	XPS	16.33 ±7.19	1.86	10.00	25.00
18 h	HEDM	22.33 ±5.30	1.37	10.00	30.00
	WOG	22.33 ±8.21	2.12	10.00	30.00
	XPS	10.33 ±9.72	2.51	0.00	20.00
24 h	HEDM	14.00 ±8.06	2.08	0.00	25.00
	WOG	15.67 ±11.78	3.04	0.00	30.00
	XPS	4.33 ±5.63	1.45	0.00	15.00
48 h	HEDM	8.67 ±6.40	1.65	0.00	20.00
	WOG	9.67 ±7.67	1.08	0.00	20.00
	XPS	1.00 ±2.07	0.53	0.00	5.00
72 h	HEDM	4.67 ±3.99	1.03	0.00	10.00
	WOG	5.00 ±4.63	1.20	0.00	10.00
	XPS	0.00 ±0.00	0.00	0.00	0.00

M – mean; *SD* – standard deviation; *SE* – standard error; min – minimum; max – maximum.

Table 2. Intergroup differences in the pain scores (VAS) at different time points (ANOVA)

Follow-up time points	Comparison	df	Mean square	F	*p*-value
6 h	between the groups	2	1,667.222	38.404	0.000*
12 h	between the groups	2	1,493.889	39.461	0.000*
18 h	between the groups	2	720.000	11.368	0.000*
24 h	between the groups	2	561.667	7.156	0.000*
48 h	between the groups	2	337.222	9.723	0.000*
72 h	between the groups	2	117.222	9.408	0.000*

df – degrees of freedom; * statistically significant.

Table 3. Pairwise differences between the study groups in the pain scores (visual analog scale – VAS) at different time points (Bonferroni test)

Dependent variable			Mean difference	*SE*	*p*-value
6 h	HEDM	WOG	–5.33	2.406	0.096
		XPS	15.00	2.406	0.000*
	XPS	WOG	–20.33	2.406	0.000*
12 h	HEDM	WOG	–2.34	2.247	0.915
		XPS	16.00	2.247	0.000*
	XPS	WOG	–18.34	2.247	0.000*
18 h	HEDM	WOG	0.00	2.906	1.000
		XPS	12.00	2.906	0.001*
	XPS	WOG	–12.00	2.906	0.001*
24 h	HEDM	WOG	–1.67	3.235	1.000
		XPS	9.67	3.235	0.014*
	XPS	WOG	–11.34	3.235	0.003*
48 h	HEDM	WOG	–1.00	2.150	1.000
		XPS	7.67	2.150	0.003*
	XPS	WOG	–8.67	2.150	0.001*
72 h	HEDM	WOG	–0.33	1.289	1.000
		XPS	4.67	1.289	0.002*
	XPS	WOG	–5.00	1.289	0.001*

* statistically significant.

Following pain assessment, all teeth were instrumented, and then obturated to control for the potential effect of obturation materials.[26]

Pain is difficult to assess and the evaluation of pain is considered subjective. Therefore, it is necessary to ensure that patients have a clear and full understanding of the questionnaires. In this study, VAS was chosen due to its ease of use, reliability and widespread application in previous pain assessment studies.[27,28]

The results of our study show that the mean pain values were the highest at 6 h after endodontic treatment and gradually decreased over 72 h. This may be due to the irritation of the periapical area caused by the extrusion of instrumentation debris, leading to local inflammatory reactions and subsequent pain. The pain typically subsides after the healing of the periapical area at 72 h.[5]

This study found statistically significant differences in post-endodontic pain between the tested instrumentation techniques at 6, 12, 18, 24, 48, and 72 h. The XPS group had the lowest VAS pain values and the lowest amount of extruded debris, with the result being similar to that reported by Uslu et al.[29]

There were no statistically significant differences between the HEDM and WOG techniques. Similarly, Fontana et al.[6] and Yeter et al.[30] found that HEDM and WOG were comparable in terms of the amount of extruded debris.

These results are contrary to a study by Xavier et al., where the incidence of postoperative pain was higher in the XPS group than in the WOG group.[28] It could be due to their study sample, which included premolars and molars, regardless of whether the canal was curved or straight.[28]

Contrary to the present study, Kherlakian et al. found no difference between the rotary and reciprocal systems.[19] The researchers used different systems with varying tapers and sizes, and performed endodontic treatment during just one visit.[19]

Limitations

This study used the VAS score, which is a subjective method. In further research, we advise to extend the educational phase with regard to the patients included in the study. The other limitation is the type of rotary file used and the amount of excruded debris; slight differences might affect the results.

Conclusions

All systems used in the study caused pain, with the highest levels observed at 6 h after treatment. The pain gradually decreased until it almost disappeared at 72 h in all studied groups. The XPS group had the lowest pain values, whereas the HEDM and WOG groups showed no differences in pain values at all follow-up time points. In the XPS group, the pain reached its peak (22.00) at 6 h and gradually decreased to 0 after 72 h.

Trial registration

Trial registration number: 1119/2019.

Ethics approval and consent to participate

The study received ethical approval from the scientific committee at the Faculty of Dentistry of Damascus University, Syria (FMD\rct-758).

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

Changes in the periodontium against the background of systemic vascular reactions in young individuals with obesity

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Abstract

Background. Overweight and obesity are defined as abnormal or excessive fat accumulation that impairs health. The global prevalence of obesity has been increasing significantly among all age groups. Furthermore, obesity is a comorbid factor for numerous diseases, including cardiovascular and periodontal pathologies.

Objectives. The present study aimed to investigate the influence of overweight and obesity on the periodontium of young adults in relation to the functional state of the cardiovascular system.

Material and methods. The oral health status of 132 males and females aged 18–22 years was examined. They were divided into 4 groups according to their body mass index (BMI): normal weight; overweight; class I obesity; and class II obesity. A periodontal chart, the records on oral hygiene and caries, and periodontal indices were provided for each participant. The main functional parameters of the cardiovascular system were measured before and after the dental examination.

Results. Overweight or obesity did not affect the intensity of caries in young adults. The prevalence and severity of gingivitis were significantly higher in obese individuals. A moderate correlation was found between gingivitis and BMI in patients with class I and II obesity. Disturbances in the cardiovascular system function and in the autonomic nervous system tone were also diagnosed in obese patients. An impaired vascular response and significant functional changes in the cardiovascular system developed against the background of obesity. These changes show the development of subcompensation in young adults with obesity.

Conclusions. In obese individuals, significantly worse oral hygiene was observed as compared to normal-BMI patients. Moreover, the clinical manifestation and intensity of gingivitis in obese individuals were high even in those with satisfactory oral hygiene. In young obese individuals, the periodontal disease manifested as gingivitis is due to significant adaptive and compensatory mechanisms.

Keywords: periodontitis, gingivitis, oral manifestations, preventive dentistry, obesity

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Introduction

Overweight and obesity are characterized by the accumulation of abnormal or excessive amounts of fat that leads to health impairment. According to the widely accepted classification designed by the National Institutes of Health, the body mass index (BMI) is used to calculate the degree of excess/lack of weight.[1] Using this index, a patient can be defined as underweight, normal-weight, overweight, or obese.[1] Based on the latest World Health Organization (WHO) update (2022), approx. 60% of the European population is overweight or obese. Overweight and obesity are preconditions for a more severe course of infectious and non-infectious diseases, and they increase the mortality rate. The prevalence of obesity is dependent on region and country, and in 2019, the highest prevalence rates were registered in the USA (23.2%), Mexico (18.4%) and Turkey (17.5%).[2] Furthermore, in India, the prevalence of overweight and obesity among middle-school students aged 12–16 years was reported to be 20.3%.[3] Such a high prevalence of obesity can be explained by numerous factors, including changes in the modern diet, a decrease in physical activity, negative environmental factors, chronic stress, and the burden of inheritance.[4] Overweight and obesity significantly exacerbate the course of numerous somatic and infectious diseases. They are also significant risk factors for the development of cardiovascular diseases, such as atherosclerosis and heart failure. Indeed, the risk of death increases as BMI becomes more elevated. Consequently, obesity is a burden on the global healthcare system, as the treatment of obese patients requires a significantly higher usage of healthcare resources as compared to individuals with a normal BMI.[5]

The cardiovascular system of obese individuals undergoes several changes. Rheological changes to the blood are observed, as well as new small-caliber vessels and capillaries, which are created to provide blood supply to the newly formed excess of the adipose tissue. The processes of compensation occur to satisfy the growing need for extra blood supply to the larger tissue volume. Functional changes also occur, including increased heart rate (HR) and cardiac output (CO), along with structural changes, such as the hypertrophy of the left ventricular myocardium, the enlargement of the left atrium and the development of sinus node weakness syndrome.[6] Furthermore, obesity leads to the development of metabolic abnormalities, like dyslipidemia or insulin resistance, and chronic mild systemic inflammation.[5,7] Obesity is also a predisposing factor for several metabolic, musculoskeletal, digestive system, and liver diseases, and it induces alterations to the hard tissues of the teeth and the periodontium.[8–10]

The periodontium is a highly vascularized and innervated structure that is extremely sensitive to the influence of pathogenic factors. Even minor systemic changes in hemodynamics are reflected as disturbances in periodontal microcirculation.[11] Indeed, a capillaroscopic examination revealed morphological alterations in the periodontal microcirculation of patients with hypercholesterolemia.[11] These include changes in the total diameter of the afferent and efferent loops, and in the periodontal tissue density.[12] Other clinical manifestations include the formation of recessions, and dystrophic and resorptive processes in the jaw bones. Although many studies have indicated the existence of a connection between obesity and periodontal diseases, the available literature on the relationship between obesity/overweight and dental or periodontal health is generally ambiguous and controversial. Indeed, previous studies were mostly based on the epidemiological surveys of children or adult populations within a wide age range (8–14 and 18–55 years).[9,13–17]

The current research is part of a larger scientific effort dedicated to the study of the etiology, pathogenesis and treatment of periodontal diseases among young individuals with obesity. Young patients were chosen in order to explore the mechanisms responsible for the onset of periodontal diseases, and to identify the manifestation of the early stages of periodontal diseases and systemic vascular reactions typical for this age group.

The study aimed to investigate the influence of overweight and obesity in young people with diverse BMI on the oral health status in relation to the functional state of the cardiovascular system. This was achieved by exploring the prevalence and structure of periodontal diseases in individuals aged 18–22 years.

Material and methods

Study design and sampling

The study is part of a larger research topic: "Pathogenetic approach in the treatment of inflammatory periodontal diseases in young individuals with obesity", realized in the Department of Therapeutic Dentistry of Poltava State Medical University, Ukraine, and it was meant to discover the mechanisms of the onset and development of oral cavity diseases in patients with obesity.

The research involved 132 male and female students of Poltava State Medical University aged 18–22 years. The inclusion criteria were: age of 18–22 years; diverse BMI; Ukrainian nationality; and informed signed consent to participate in the research. The exclusion criteria were as follows: pregnancy; breastfeeding; drug use; alcoholism; mental illness; participation in another study at least 2 months before inclusion in the present one; active tuberculosis; viral hepatitis; and the presence of non-removable orthodontic appliances in the oral cavity. The oral cavity examination was performed at the Clinical Facility of the Department of Therapeutic Dentistry of Poltava State

Medical University. The patients were split into 4 groups according to their BMI: group I (n = 33) – normal BMI (18.5–24.9 kg/m^2); group II (n = 36) – overweight (BMI of 25–29.9 kg/m^2); group III (n = 31) – class I obesity (BMI of 30–34.9 kg/m^2); and group IV (n = 32) – class II obesity (BMI of 35–39.9 kg/m^2).

To meet the research objectives, and according to the sample size calculation (with 95% confidence intervals (*CI*s)), the sample comprised a group of 132 individuals representing both genders. The sample size calculation was performed according to the recommendations for cross-sectional studies, using the "Sample Size Calculator" program (https://www.gigacalculator.com/calculators/power-sample-size-calculator.php). The minimum size of each group was calculated to be 29, with a type I error rate α = 5% (the estimated prevalence of 26.9%; 95% *CI*: 22.4–27.3) and a margin of error of 85%.

Determination of the oral health status

The periodontal chart for each patient was registered with the automated computer detecting system pa-on Parometer® (orangedental, Biberach, Germany). This probe allows the objective assessment of periodontal health, the follow-up of the dynamics of the periodontal status indicators and the prediction of the development of pathological changes in the periodontium by considering local and individual common risk factors for the onset of periodontal diseases (Fig. 1). During the measuring process, the same unified load of 20 g is applied and the measurements are taken with a disposable tip. The device enables the assessment of the functional state of the periodontium by determining the periodontal pocket depth (PPD), clinical attachment loss (CAL), gingival recession, and the degree of tooth mobility.

The initial periodontal status was evaluated using the decayed, missing, and filled teeth (DMFT) index, the Green–Vermillion oral hygiene index (OHI), the approximal plaque index (API), the papillary-marginal-alveolar index (PMA), the Community Periodontal Index (CPI), the papillary bleeding index (PBI), Schiller's iodine test, and the white tongue coating (WTC) index.

Periodontal charts were completed for all patients. The periodontal diagnosis was determined using the Classification of Periodontal and Peri-Implant Diseases and Conditions.[18]

Determination of the cardiovascular system function and the autonomic nervous system tone

The initial state of the central nervous system and any functional disturbances were determined by means of Wayne's questionnaire.[19–22] The questionnaire refers to 9 parameters, which are evaluated by a doctor during an objective functional examination of the patient. Each parameter is evaluated on a scale of 3–8 points. The result is calculated as a total sum of the points scored. In healthy individuals, the score for all parameters should not exceed 15 points. If a score of 15 points is exceeded, then autonomic dysfunction syndrome is diagnosed.

Evaluation of the functional hemodynamic state

The functional state of the patient's hemodynamics was determined before and after the dental examination. The dental examination lasted for 30 ±3 min. To characterize the autonomic nervous system tone, HR, systolic blood pressure (SBP) and arterial diastolic pressure (ADP) were

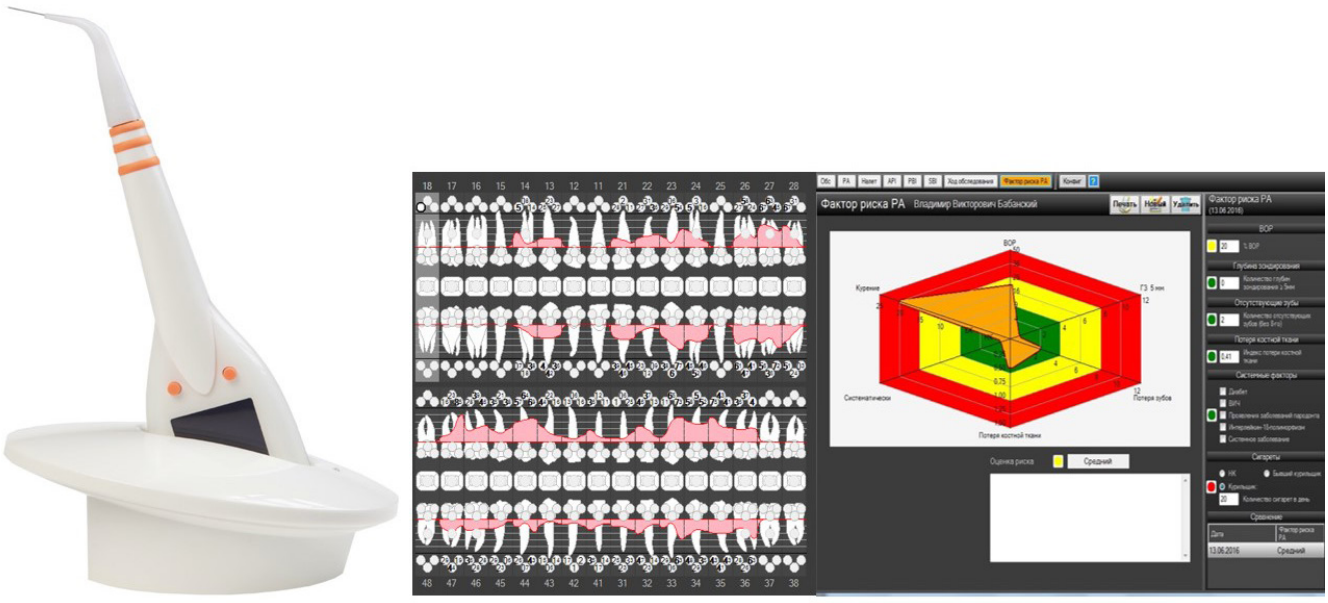

Fig. 1. pa-on Parometer® and an example of a periodontal chart

determined. The HR was determined using the fingertip pulse oximeter OX-832 (Dongguan Crayfish Electronic Technology, Dongguan, China), while SBP and ADP were measured using the A&D UA-200 manual tonometer (A&D Company, Tokyo, Japan). Common, widely accepted and simple medical indices, which are employed by general physicians during routine check-ups, were used for the determination of the hemodynamic parameters.

Kerdo's vegetative index (VI) was calculated as follows (Equation 1):

$$VI = (1 - ADP / HR) \times 100 \text{ [a.u.]} \quad (1)$$

where:
VI – Kerdo's vegetative index;
ADP – arterial diastolic pressure; and
HR – heart rate.

A value of VI = 0 indicates a complete vegetative balance of the cardiovascular system (eutonia); if VI < 0, then the parasympathetic tone prevails (parasympathetico-tonia), whilst VI > 0 signifies the predominance of the sympathetic nervous system (sympatheticotonia).[23–25]

Blood circulation, which determines the adaptation strategy, was assessed with Robinson's index (RI), which is called the 'double product' (Equation 2)[26,27]:

$$RI = SBP \times HR / 100 \text{ [a.u.]} \quad (2)$$

where:
RI – Robinson's index;
SBP – systolic blood pressure; and
HR – heart rate.

An increase in RI indicates an increase in the intensity of the heart's work. A decrease in RI at rest indicates an increase in the aerobic capacity of the body; hence, the adaptive capacity of the cardiovascular system increases during this period.[28]

Based on the anthropometric data and the vegetative tone data, the adaptive potential (AP) in terms of hemodynamics, which evaluates the level of adaptation in points, was determined (Equation 3)[29–31]:

$$AP = 0.011 \times HR + 0.014 \times SBP + 0.008 \times ADP + 0.014 \times age + 0.009 \times \text{body weight} - 0.009 \times \text{height} - 0.27 \quad (3)$$

where:
AP – adaptive potential;
HR – heart rate;
SBP – systolic blood pressure; and
ADP – arterial diastolic pressure.

The interaction between the contractility of the myocardium and the vascular capacitive-conductive function, as well as the productivity of the sinus node, the activity of which is affected by the central and adrenergic nervous system, were determined with the myocardial index (MI) (Equation 4)[19,32]:

$$MI = (SBP / ADP - 1) \times HR / (1 - ADP / SBP) \text{ [a.u.]} \quad (4)$$

where:
MI – myocardial index;
SBP – systolic blood pressure;
ADP – arterial diastolic pressure; and
HR – heart rate.

Heart stroke volume (HSV) was calculated using the following formula (Equation 5)[19,32]:

$$HSV = (SBP - ADP) \times 200 / (SBP + ADP) \text{ [L]} \quad (5)$$

where:
HSV – heart stroke volume;
SBP – systolic blood pressure; and
ADP – arterial diastolic pressure.

Cardiac output (CO) was calculated as follows (Equation 6)[32,33]:

$$CO = HSV \times HR \text{ [L/min]} \quad (6)$$

where:
CO – cardiac output;
HSV – heart stroke volume; and
HR – heart rate.

Total peripheral vascular resistance (TPVR) was calculated with the formula (Equation 7)[33,34]:

$$TPVR = 1{,}333 \times 60 \times (SBP + ADP) / (CO \times 2) \text{ [dyn·s/cm}^5\text{]} \quad (7)$$

where:
TPVR – total peripheral vascular resistance;
SBP – systolic blood pressure; and
ADP – arterial diastolic pressure; and
CO – cardiac output.

Bias

The possible sources of bias include the fact that the retrospective analysis concerned patients who were treated by 3 of the authors (MS, TP and IS). Additionally, the other 2 authors (KN and VP) extracted data from the selected clinical records. However, an independent biostatistician conducted the statistical analysis.

Statistical analysis

The OriginPro program, v. 8.5.1.315 (OriginLab Corporation, Northampton, USA), was used for statistical

processing. The data was expressed as mean ± standard deviation (*M* ±*SD*). The one-factor analysis of variance (one-way ANOVA) was used for processing the unrelated samples, and Bonferroni's correction was used for multiple comparisons. Student's *t* test was used for paired samples. The difference between the groups was considered statistically significant at $p < 0.05$. Correlation relationships were determined using Spearman's rank correlation test. The statistical analysis of the percentage data was conducted using the variation statistic method by Øyvind.

Results

The BMI in group I was 22.69 ±0.29 kg/m^2, in group II, it was 27.84 ±0.21 kg/m^2, in group III, it was 32.00 ±0.28 kg/m^2, and in group IV, it was 38.18 ±0.68 kg/m^2.

Periodontal health of the examined individuals

A relationship between BMI and the prevalence of inflammatory changes in the gums was revealed, and generalized catarrhal gingivitis was diagnosed. The percentage of individuals with intact periodontium was significantly higher in the group with a normal BMI. Intact periodontium was diagnosed in 45.5% of individuals in group I, 25.0% in group II, 19.4% in group III, and 9.4% in group IV. Gingivitis associated with biofilm alone was diagnosed in 54.5% of individuals in group I, 75.0% in group II, 13.0% in group III, and 9.4% in group IV. Dental plaque-induced gingivitis, mediated by systemic risk factors (obesity), was diagnosed in 67.6% of individuals in group III and 81.2% of persons in group IV.

A moderate correlation was detected between gingivitis and BMI in groups III and IV ($r = 0.57$ and $r = 0.64$, respectively). The analysis of local disease-causing factors in relation to pathological changes in the gums was carried out in all patients as well. The assessment of the oral health status in terms of various indices is presented in Table 1.

In all groups, a high level of correlation ($r = 0.6–0.9$) was found between all oral hygiene indices, which is natural. Oral hygiene was significantly worse in obese patients as compared to the normal-BMI group. The indices determining the prevalence and severity of gingivitis were also significantly higher in obese individuals as compared to patients with a normal BMI, as was the WTC index. In group I, a positive correlation was found between DMFT and the WTC index ($r = 0.51$). In groups I and II, a strong ($r > 0.75$) and moderate ($r = 0.64$) correlation was observed between the presence of gingivitis and OHI and API, respectively, while the correlations were weak in groups III and IV. Clinical attachment loss was not diagnosed in any of the groups.

Table 1. Assessment of the participants' oral health status with the oral cavity indices

Oral cavity index	Group I	Group II	Group III	Group IV	*p*-value
DMFT	2.66 ±0.37	3.35 ±0.40	2.71 ±0.59	4.25 ±0.85	$p_{I–II} > 0.05$ $p_{I–III} > 0.05$ $p_{I–IV} > 0.05$ $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
OHI	1.17 ±0.07	0.95 ±0.07	1.42 ±0.10	1.40 ±0.07	$p_{I–II} > 0.05$ $p_{I–III} > 0.05$ $p_{I–IV} > 0.05$ $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
API [%]	18.2 ±3.3	9.1 ±2.8	8.9 ±1.9	7.1 ±2.1	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$
PMA [%]	11.40 ±1.36	10.63 ±1.80	15.40 ±1.17	15.64 ±0.80	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
CPI	1.57 ±0.09	1.69 ±0.10	1.85 ±0.09	2.02 ±0.09	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
PBI	6.4 ±0.9	13.6 ±2.4	19.7 ±2.3	22.9 ±2.6	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
Schiller's test	1.41 ±0.05	1.43 ±0.05	1.67 ±0.05	1.71 ±0.05	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
WTC index	1.56 ±0.20	1.35 ±0.17	2.09 ±0.13	2.56 ±0.20	$p_{I–II} > 0.05$ $p_{I–III} > 0.05$ $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$

DMFT – number of decayed, missing, and filled teeth; OHI – Green–Vermillion oral hygiene index; API – approximal plaque index; PMA – papillary-marginal-alveolar index; CPI – Community Periodontal Index; PBI – papillary bleeding index; WTC – white tongue coating index; * statistically significant.

Determination of the cardiovascular system function and the autonomic nervous system tone

The functional state of the cardiovascular system and the tone of the autonomic nervous system were significantly different in obese and normal-BMI individuals.

In some obese individuals, the deterioration of the functional state of the cardiovascular system and of the tone of the autonomic nervous system were diagnosed. There were correlations between Wayne's score and the WTC index in group III (r = 0.52) and group IV (r = 0.53) (Table 2).

Table 2. Functional state of the cardiovascular system and the tone of the autonomic nervous system assessed by means of Wayne's scale

Assessment	Group I	Group II	Group III	Group IV	*p*-value
Wayne's score	5.68 ±0.70	5.70 ±1.13	13.38 ±1.90	13.72 ±1.20	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
Normal [%]	100	100	93.5	96.9	–
Disturbance [%]	–	–	6.5	3.1	–

* statistically significant.

Functional changes in the cardiovascular system before and after the dental examination

Patients with BMI > 25 kg/m^2 had a significantly higher HR before and after the oral cavity examination (which is a stress factor) as compared to the individuals with a normal BMI. According to the VI measurements, sympatheticotonia (the activation of the sympathetic nervous system) was prevalent in all groups before the examination (the 1st stage of stress – alarm reaction stage). After the examination, a transition from sympatheticotonia to parasympatheticotonia was observed in 80% of group I, while the level of sympatheticotonia was still high in obese individuals after the check-up. The RI score before and after the examination was significantly higher in obese individuals as compared to normal-BMI and overweight individuals.

Before the check-up, AP was tensive (>2.1) in all groups, and it returned to the regular state only in patients with a normal BMI after the examination. The AP decreased in the other groups after the examination, but it was still high. The MI was significantly higher before the dental examination in patients with BMI > 30 kg/m^2. A positive correlation was observed between HSV and BMI, and these indicators were directly proportional to each other. The CO significantly decreased in each group after the dental examination, and it was directly proportional to BMI in all groups. The TPVR was slightly higher in the group with a normal BMI before the examination than it was in overweight and obese individuals. After the examination, TPVR was likely to decrease in patients with a normal BMI, while changes in overweight and obese patients were not significant. The data is presented in Table 3.

In group I, moderate correlations were found between CPI and HSV (r = 0.51), and between CPI and TPVR (r = –0.52). In group III, moderate correlations were found between PBI and RI (r = –0.50), and between PBI and AP (r = –0.53). Similar results were found for group IV, which showed moderate correlations between PBI and RI (r = –0.56), and between PBI and AP (r = –0.54). In group III, a moderate correlation was found between WTC and RI (r = 0.51), AP (r = 0.55) and Wayne's score (r = 0.52). In group IV, correlations were found between OHI and RI (r = –0.54), and between OHI and AP (r = –0.51).

Discussion

In the current study, no relationship was found between the intensity of dental caries and BMI in young adults. The development of caries was likely caused by the overconsumption of carbohydrates, a weak buffer capacity of saliva, inadequate salivation, and the neglect of oral hygiene, but not the presence or absence of obesity. Such results can also be explained by the relatively young age of the patients, i.e., 18–22 years. A significant correlation was found between obesity and BMI and the presence of gingivitis in young adults. The prevalence and severity of gingivitis in young subjects with class I and class II obesity were significantly higher than in the other groups. Dental plaque-induced gingivitis, mediated by the systemic risk factor obesity, was predominant in obese individuals. A study on obese females aged 18–35 years showed a significantly higher prevalence of caries and periodontal diseases in obese individuals, and the level of oral hygiene was 2.5 times worse than the national level.[17] According to the results of bacteriological studies, lower quantities of *Streptococcus mutans* were found in obese individuals as compared to individuals with a normal BMI, which is surprising.[17] In a study on 19–55-year-old overweight and obese adults, it was found that obese individuals showed significant differences in eating behavior, which included the overconsumption of sweets.[14] Obese individuals also had poorer oral hygiene and, as a result, a higher prevalence of periodontal disease, which correlated with BMI.[14] Young obese adults were mostly diagnosed with the disturbances regarding the cognitive restraint and emotional eating components of eating behavior.[4] In the clinical observations of 7–15-year-old obese children, a higher intensity of primary and permanent teeth caries was detected.[16] In addition, a higher prevalence of gingivitis, a poorer level of oral hygiene, a decrease in salivation, and a decrease in the buffer capacity of saliva were found, in comparison with normal-BMI children.[16] In a study on 8–11-year-old children, a significant relationship was found between overweight, obesity and the prevalence of caries.[13] A higher prevalence of caries, gingivitis and

Table 3. Functional changes of the cardiovascular system in response to a stress factor (dental examination) in young people with a diverse body mass index (BMI)

Hemodynamic parameter		Group I	Group II	Group III	Group IV	*p*-value
HR (1) [beats/min]		72.72 ±1.34	79.80 ±2.10	83.32 ±2.10	80.03 ±1.61	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$
HR (2) [beats/min]		69.50 ±0.88	74.80 ±1.90	78.03 ±2.87	76.34 ±2.07	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
VI (1) [a.u.]	general	3.98 ±1.82	5.03 ±3.53	8.45 ±3.78	5.70 ±3.10	–
	<0 (parasymphatheticotonia)	33.4%	27.8%	22.6%	28.1%	–
	around 0 (eutonia)	–	2.8%	3.2%	12.5%	–
	>0 (symphatheticotonia)	66.6%	69.4%	74.2%	59.4%	–
VI (2) [a.u.]	general	–9.59 ±2.40	7.17 ±3.10	0.52 ±3.30	–4.90 ±3.60	–
	<0 (parasymphatheticotonia)	78.8%	30.5%	45.2%	53.1%	–
	around 0 (eutonia)	–	8.4%	13.0%	6.25%	–
	>0 (symphatheticotonia)	21.2%	61.1%	41.8%	40.65%	–
RI (1) [a.u.]		85.20 ±2.30	95.31 ±3.40	107.62 ±3.37	106.14 ±3.30	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
RI (2) [a.u.]		82.30 ±1.09	98.51 ±3.43	98.53 ±4.51	98.32 ±3.40	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$
AP (1)		2.34 ±0.03	2.35 ±0.05	2.63 ±0.05	2.78 ±0.05	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
AP (2)		2.10 ±0.02	2.39 ±0.05	2.55 ±0.06	2.74 ±0.05	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} < 0.05$* $p_{III–IV} < 0.05$*
MI (1) [a.u.]		121.36 ±3.03	134.82 ±4.39	150.21 ±4.11	149.91 ±5.65	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
MI (2) [a.u.]		109.75 ±2.40	128.63 ±4.59	129.14 ±4.63	130.34 ±4.87	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$
HSV (1) [L]		46.04 ±1.60	46.85 ±1.74	53.77 ±3.47	55.87 ±2.48	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} < 0.05$* $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$

Hemodynamic parameter	Group I	Group II	Group III	Group IV	*p*-value
HSV (2) [L]	44.31 ±1.58	46.12 ±1.88	49.18 ±2.02	53.61 ±2.24	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} < 0.05$* $p_{III–IV} > 0.05$
CO (1) [L/min]	3,761.23 ±140.40	3,977.60 ±178.20	4,474.86 ±257.00	4,504.60 ±242.63	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} < 0.05$* $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$
CO (2) [L/min]	3,082.90 ±117.60	3,447.80 ±188.70	3,785.50 ±170.15	3,989.77 ±204.00	$p_{I–II} > 0.05$ $p_{I–III} < 0.05$* $p_{I–IV} > 0.05$ $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$
TPVR (1) [dyn·s/cm^5]	2,649.20 ±111.83	2,118.90 ±114.80	2,261.70 ±101.84	2,284.63 ±135.40	$p_{I–II} < 0.05$* $p_{I–III} < 0.05$* $p_{I–IV} > 0.05$ $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$
TPVR (2) [dyn·s/cm^5]	2,242.72 ±78.00	2,252.60 ±138.90	2,052.05 ±129.53	2,011.66 ±119.60	$p_{I–II} > 0.05$ $p_{I–III} > 0.05$ $p_{I–IV} > 0.05$ $p_{II–III} > 0.05$ $p_{II–IV} > 0.05$ $p_{III–IV} > 0.05$

Note: (1) – before the dental examination; (2) – after the dental examination. HR – heart rate; VI – Kerdo's vegetative index; RI – Robinson's index; AP – adaptive potential; MI – myocardial index; HSV – heart stroke volume; CO – cardiac output; TPVR – total peripheral vascular resistance; * statistically significant.

dental plaque was observed in 11–18-year-old obese individuals as compared to individuals with a normal BMI.[15] Meanwhile, other studies indicated no relationship between obesity and oral diseases in adults.[35]

Oral hygiene was found to be unsatisfactory in all individuals examined, although the worst levels were found in individuals with class I and class II obesity. However, periodontal disease and obesity were mutually dependent factors in young people. A significantly higher prevalence of gingivitis was found in 87% of obese adults. Mostly, gingivitis was associated with dental plaque, but was mediated by the systemic risk factor obesity. In obese individuals, the severity of the disease, reflected by PMA, CPI, PBI, and Schillers's test, was not correlated with their oral hygiene status. Indeed, the severity of the disease was not only caused by dental plaque, but also by a modified reaction to dental plaque. This reaction was due to inflammation and hypoxia in the periodontal tissues, which were caused by an impaired blood supply.

In overweight and normal-BMI patients, the severity of gingivitis was correlated with the amount of dental plaque. In obese individuals, an impaired colonization resistance of the oral cavity was also observed. This indicates that the modification of the local, non-specific protective responses of the oral cavity, as well as greater susceptibility to pathogenic and opportunistic oral cavity microorganisms, caused the development of the disease.[36] Against the background of obesity, the activation of free-radical oxidation, the development of alterations in the nitrosative stress response and an increase in the concentration of connective tissue monomers were observed in the periodontium. This indicates the development of destructive processes in the periodontium in response to the systemic inflammatory processes caused by the secretion of numerous pro-inflammatory adipocytokines by the adipose tissue.[37,38] Obese individuals have more tongue plaque deposits as compared to individuals with a normal BMI, which may indicate gastrointestinal diseases and metabolic disorders.[39]

Significantly higher values of the indices of the cardiovascular system functional state were observed in obese adults. They were over 2 times higher than those found in individuals with a normal BMI. Autonomic dysfunction syndrome was detected only in a few individuals; it was manifested as the dysfunction of the autonomic nervous system, and functional (inorganic) disorders in all systems and organs of the body. Autonomic dysfunction appears as the suppression of one part of the nervous system through the hyperactivation of another. However, under physiological conditions, an increased function of one part of the autonomic nervous system results in compensatory tension in the regulatory mechanisms of another. The system shifts to the new level of functioning and homeostatic parameters are restored. Suprasegmental formations and segmental autonomic reflexes play a crucial role in these processes. When in a tense state, or a state

of adaptation failure, the regulatory function is disrupted and the activity of one part of the nervous system increases, resulting in changes in other parts of the system.[40]

The small number of patients with disturbances in the functional state of the cardiovascular system and the autonomic nervous system tone can be explained by their young age and a significant adaptive potential.

A high proportion of obese individuals (78%) complained of constant fatigue, and the correlation between a poor level of oral hygiene and complaints of constant fatigue was also high (r = 0.85). This suggests that obese patients do not take oral hygiene measures, and skip tooth brushing and flossing due to constant fatigue. The assessment of the cardiovascular system function was conducted before and after the oral cavity examination to monitor the patient's response to the stress factor, which was the dental examination. Any dental intervention, even a routine dental examination, evokes an acute stress reaction in all patients. This is primarily caused by a feeling of fear while waiting for dental manipulations, the anxiety of experiencing pain, previous negative experiences, and childhood fears, among other reasons.[41–43] Indeed, the concentration of cortisol in saliva was reported to be 2 times higher in adults before dental treatment than after treatment.[43] By definition, stress is a non-specific neurohumoral response of the body to an exogenous or endogenous (pain) trigger.

Each individual has a different response to stress, which is reflected in the physiological reactions of systems and organs, and behavioral and neurohumoral changes in the body. This complex of reactions is specific for each individual and is called stress resistance. The specific changes are dependent on the functional state of the cardiovascular system and symphathetic innervation. A higher resting HR was recorded in obese subjects as compared to patients with a normal BMI. Nonetheless, HR decreased slightly in all subjects after the dental examination. Sympatheticotonia (the activation of the sympathetic nervous system) prevailed in patients before the examination, which is typical for the 1st stage of stress (the alarm reaction stage) and is accompanied by the activation of the sympathoadrenal system.[44]

After the dental examination, parasympatheticotonia (parasympathetic innervation) was prevalent in 80% of individuals with a normal BMI, which is typical for the resting state.[23,24] In obese patients, even after the examination, sympathetic innervation dominated. Such a phenomenon, in our opinion, may indicate the rigidity of blood vessels, as they cannot quickly adapt to changes. The RI was significantly higher in obese individuals before the examination, which indicates an increase in the body's oxygen needs and tension in the work of the heart. However, there was a significant decrease in RI after the examination. The RI was almost the same before and after the examination in subjects with BMI < 30. A directly proportional correlation was observed between RI and BMI. High AP was also observed in all groups before the examination, which indicates tension in the adaptive and compensatory capacity. After the examination, AP returned to normal only in individuals with a normal BMI. Significantly higher AP was recorded in individuals with high BMI.

Before the dental examination, MI, HSV and CO were high in all groups, which indicates the activation of the sympathoadrenal system as a response to stress. However, MI, HSV and CO were yet significantly higher in obese individuals. Increases in MI, HSV and CO, even after the examination, indicate the development of compensatory processes in obese individuals, which are aimed at supplying more tissues with blood. This is made possible through increasing the intensity of the work of the heart, which leads to "wear and tear"; consequently, compensatory mechanisms are no longer able to provide sufficient blood supply to tissues and organs. This is why damage occurs to target organs that are most sensitive to hypoxia, including the periodontium.[45]

Several studies have demonstrated the exacerbation of periodontal diseases in patients with chronic or severe systemic diseases; similar mechanisms of developing chronic and acute vascular reactions in the periodontal tissues have been observed in patients with some non-infectious and infectious diseases.[46–48] Indeed, in patients with coronavirus disease 2019 (COVID-19), a cytokine storm and thromboembolic complications were observed.[46] Such complications cause alterations in the oral cavity immune response and result in a severe course of periodontitis; a similar immune response is observed in obese individuals. However, in COVID-19 patients, systemic inflammation develops acutely, while in obesity, it is a chronic process.[46] Chronic cardiovascular diseases, such as atherosclerosis, lead to dyslipidemia and chronic inflammation, which contribute to severe periodontal tissue alterations.[47] Furthermore, a pathological link between periodontal diseases and prostatitis was found, and patients with moderate and severe prostatitis had a significantly worse periodontal status.[48] Currently, it is thought that an inflammatory systemic factor that modifies the host immune response to periodontal pathogens plays an important role in the development of periodontal diseases.

There is relative oxygen starvation of the brain in obese individuals, since the volume of blood supplied to the brain remains relatively unchanged, which is clinically manifested as drowsiness and constant fatigue. At the beginning of the dental examination, an increase in TPVR was observed only in individuals with a normal BMI, which indicates an adequate reaction in response to the stress factor. There was also a decrease in TPVR immediately after the stressful examination. The TPVR did not change significantly after the examination in obese individuals. In our opinion, this indicates the development of the dysfunction of the cardiovascular system in obese individuals. We are strongly convinced that obesity has a direct effect on the development and course of periodontal disease in young individuals by triggering a systemic inflammatory

process, and acts indirectly by modifying the circulatory system. The pathogenesis of periodontal disease in obese individuals is presented in Fig. 2.

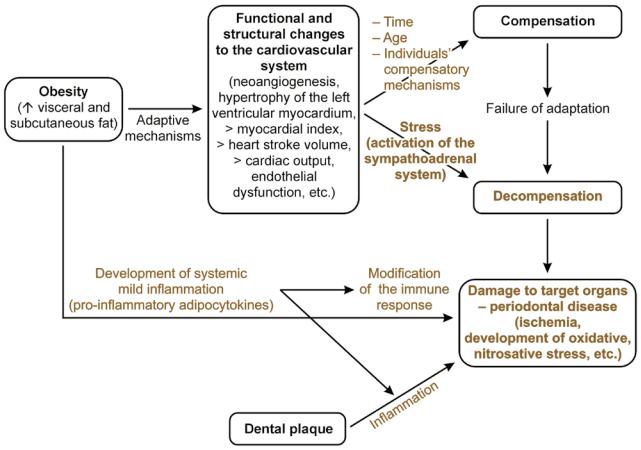

Fig. 2. Scheme of the pathogenesis of periodontal disease and obesity development in young people

Limitations

The study was limited by its small sample size. If the sample size had been larger, then some results might have been statistically significant. Another limitation of the study is that it did not measure the dynamics of observations, so it was not possible to detect how the oral health status changed over time.

Conclusions

Obesity and overweight did not influence the intensity of caries in young individuals. However, oral hygiene was worse in obese individuals than in normal-BMI individuals. Furthermore, the prevalence and severity of gingivitis were significantly higher in obese individuals, and the course of the disease was also modified. In young adults with obesity, significant functional changes developed in the cardiovascular system and an impaired vascular response to acute stress was observed. The reaction of obese patients to stress was more intense, which was manifested by significant changes in the already compromised cardiovascular system. Therefore, it is necessary to consider these specific factors during an oral examination. In our opinion, the age of 18–22 years is critical for gingivitis treatment in all patients, especially those suffering from obesity. Most often, irreversible damage to the periodontium (CAL) has not yet happened.

Ethics approval and consent to participate

This cross-sectional, observational study was approved by the Committee on Ethical Issues and Biomedical Ethics of Poltava State Medical University, Ukraine (No. 197).

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 between passive smoking and dental caries status in children: A cross-sectional analytical study

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Abstract

Background. Several risk factors contribute to the development of dental caries in children, including sociodemographic, dietary, oral hygiene-related and other miscellaneous factors. Maternal smoking was highly associated with dental caries when compared to smoking by fathers or other household members.

Objectives. The aim of the study was to determine the prevalence of dental caries and their association with exposure to environmental tobacco smoke (ETS) among 5- to 10-year-old students attending private and government schools.

Material and methods. A cross-sectional analytical study was conducted among schoolchildren. Data was collected from the primary caregivers using a pre-tested form to assess the ETS exposure under 5 domains based on history: antenatal exposure; exposure during the index period; exposure in the school neighborhood; exposure in restaurants/roadside stalls; and exposure in bus stops/railway stations. Dental caries was assessed based on the World Health Organization (WHO) guidelines from 1997. The association was reported using prevalence ratios (*PR*s) (95% confidence interval (*CI*)).

Results. Data was obtained from 211 schoolchildren attending government (39.8%) and private schools (60.2%). The overall prevalence (95% *CI*) of dental caries was 49.3% (42.5–56.1%). Among all the risk factors evaluated in the study, exposure to ETS was associated with a significantly increased risk of dental caries. The adjusted prevalence ratio (*APR*) of ETS exposure varied with the mother's educational status and high sugar exposure, although this was statistically insignificant.

Conclusions. The prevalence of dental caries among schoolchildren aged 5 to 10 years in the city was moderate and similar to the national average. Among the risk factors assessed in the study, antenatal exposure to ETS was found to significantly increase the prevalence of dental caries by 41% after adjusting for other factors. Therefore, it is important to educate parents on the causal role of ETS exposure in dental caries.

Keywords: prevalence, risk factors, dental caries, environmental tobacco smoke (ETS) exposure

Introduction

Dental caries is a microbial disease defined as "a biofilm-mediated, diet modulated, multifactorial, non-communicable, dynamic disease resulting in net mineral loss of dental hard tissues."[1] The prevalence of dental caries has increased globally among the age group of 5 to 10 years over the past few decades.[2] Dietary habits and other exposures outside the home are often initiated during this time, as schooling typically begins at this age. From 2000 to 2015, the global median prevalence (range) of dental caries among lower-middle-income countries in 5- to 6-year-old children was 83.4% (64.0–88.6%).[3] In India, the pooled prevalence of dental caries in children aged 5 to 10 years was 49%.[4]

The development of dental caries can be attributed to various risk factors, including sociodemographic, dietary, oral hygiene-related and other miscellaneous factors.[5] Among dietary factors, sugar exposure has been consistently associated with dental caries.[6] Although extensively studied, ambiguity remains regarding some hypothesized risk factors, such as exposure to environmental tobacco smoke (ETS). The ETS, or secondhand smoke, is defined as the smoke exhaled by a tobacco smoker and the smoke released from the lighted end of a cigarette. There is evidence supporting the causal relationship between smoking and dental caries in adults. Additionally, ETS exposure is linked to a reduction in vitamin C levels. It was demonstrated that low vitamin C levels could increase the proliferation of *Streptococcus mutants*.[7] An in vitro study was conducted to observe the growth of *S. mutants* and *Streptococcus sanguinis* in 3 different media atmospheres, namely air, carbon dioxide and cigarette smoke.[8] Research has shown that nicotine can facilitate the proliferation of these cariogenic bacteria.[9] In addition, exposure to ETS has been shown to impair immunity through various mechanisms, including the reduction of serum immunoglobulins (IgG), suppression of T-helper cells and limitation of phagocytosis.[10,11]

Children are more susceptible to the adverse effects of ETS exposure due to their rapid breathing rate and high surface-to-volume ratio. They tend to inhale more toxic chemicals per unit of time than adults. A systematic review of studies on permanent dentition reported that 10 out of 11 studies showed a significant association of ETS exposure with dental caries.[12] The impact of smoking on dental caries was often overshadowed by the effect of sugar intake in children.

Systematic reviews on the effect of ETS on dental caries in children have demonstrated the causative role of antenatal exposure; however, postnatal exposure is still debated.[13,14] A recent systematic review and meta-analysis reported a positive association between postnatal exposure to smoking and dental caries.[15] Maternal smoking was associated with a higher prevalence of dental caries in children compared to paternal or other household members' smoking.[15] Most studies on the effect of passive smoking and dental caries in children have been conducted in upper-middle and high-income countries where smoking among women is prevalent. In India, however, the prevalence of smoking among women is low. As per the Global Adult Tobacco Survey-2 (GATS-2), the estimated prevalence of tobacco smoking is 2%.[16] Since exposure to ETS in India is low, its effect could remain hidden. Evidence suggests an association between passive smoking and dental caries in Indian children. Hence, the present study was designed to assess the prevalence of dental caries and their association with ETS exposure.

Material and methods

This cross-sectional analytical study was conducted from July 2019 to January 2021 in children aged 5 to 10 years who were enrolled in selected government and private schools. Most schools conduct regular health check-ups, including oral health screening, for their students. Children with any systemic illness or psychiatric disorders were excluded from the study. The estimated sample size was 207. The sample size was calculated using OpenEpi v. 3.1 (https://www.openepi.com/Menu/OE_Menu.htm) with a type I error of 5%, assuming a caries prevalence of 65% and a relative precision of 10%. Stratified cluster sampling was conducted to select schools for the study. Each school was considered a cluster of the survey. We divided primary schools in the city into government and private schools, and the sample size was proportionally distributed between them. Schools were selected from each stratum to ensure the representation of different municipal wards in the district. The primary investigator obtained permission from each school principal to recruit children for the study. Parents were informed about the study by teachers via the school diary. Four government schools and 4 private schools agreed to participate in the study. All eligible children from the selected schools were enrolled in the study after obtaining informed consent from the mother or primary caregiver. A total of 211 children were included in the study, 127 from private schools and 84 from government schools. The age of the children was 7.8 ±1.8 years.

A pre-tested semi-structured form was used to collect information from the mothers or primary caregivers of the children. The study form included data on possible risk factors such as sociodemographic factors, diet-related risks, oral hygiene, and ETS exposure. The form was piloted with the mothers of children visiting the outpatient department and was modified based on their feedback for final use. The education level of the parents was determined using the International Standard Classification of Education (ISCED),[17] their occupation was recorded using the International Standard Classification of Occupations (ISCO-08),[18] and their composite socioeconomic status was classified using a modified Kuppuswamy socioeconomic status scale 2019.[19]

The child's oral hygiene was assessed based on the following parameters: the mode of teeth cleaning; the frequency of teeth cleaning; brushing by parents or under parental supervision; brushing before bedtime; and the type of toothpaste used

or its alternatives. In addition, the information on the brand of toothpaste was noted to confirm the use of fluoride-based toothpaste. The duration of breastfeeding, breastfeeding during sleep time and bottle feeding (duration, age and frequency) were also recorded. The child's current sugar intake was obtained from the mother using a 24-hr dietary recall method. Information was collected on the type and amount of meals consumed. Sugar exposure was scored based on the consistency, style and frequency.[20] The primary caregiver was interviewed to obtain information on ETS exposure. The child's exposure to ETS was assessed in 3 domains: exposure during the antenatal period, i.e., 1 year from the date of interview, and exposure outside the household. Exposure to ETS was considered present if any household member had a smoking history during the antenatal or index period. The index period for this study was 1 year, based on expert consultation. The study assessed exposure to ETS outside the household at 3 key locations: the school neighborhood; restaurants/roadside stalls; and bus stops/railway stations. Exposure to ETS was considered present if the primary caregiver observed smoking at any of these premises.

Clinical examination followed the World Health Organization (WHO) type III diagnostic criteria for oral health surveys.[21] During the data collection period, none of the children reported symptoms suggestive of coronavirus disease 2019 (COVID-19) due to strict isolation measures implemented by the school authorities. The children were examined in daylight and their dental caries status was determined using the Decayed, Missing and Filled Teeth (DMFT) index. The DMFT index was used to document the dental caries status in permanent dentition, while the decayed, extracted, filled teeth (deft) index was used in mixed dentition. To avoid inter-examiner variability, a single calibrated investigator conducted all examinations, and an assistant recorded the values. Based on the diagnosis, appropriate treatment was provided, or a referral was made based on the condition.

Statistical analysis

The study reported the prevalence of dental caries with a 95% confidence interval (*CI*). The association between ETS exposure, other risk factors and dental caries was examined using the χ^2 test. The effect estimate was summarized as the prevalence ratio (*PR*) (95% *CI*). Prevalence ratios were assessed using the binomial regression function in Stata 14 (StatCorp LLC, College Station, USA). The mean/median difference in the DMFT index and deft score between the exposed and unexposed was assessed using the Mann–Whitney *U* test. Multivariate analysis was conducted using log-binomial regression to determine the adjusted prevalence ratio (95% *CI*). In the univariate analysis, all variables with a *p*-value <0.5 were included in the multivariate analysis, and variables showing multicollinearity were excluded. The analysis was conducted using IBM SPSS Statistics for Windows software, v. 20.0 (IBM Corp., Armonk, USA).

Results

Data was collected from 211 children. Of these, 60.2% (n = 127) attended private schools, and the majority were boys (56.9%; n = 120). The mean age (± standard deviation (*SD*)) of children in government schools was 7.7 (±1.7), which was comparable to that of private schools (7.9 (±1.8)). The sociodemographic distribution of the study sample is presented in Table 1. At least one-third of the mothers (33.6%) and two-fifths of the fathers (42.2%) of the children completed graduation, i.e., reached

Table 1. Sociodemographic distribution of the study sample

Sociodemographic characteristics		*n* (%)
School type	government	84 (39.8)
	private	127 (60.2)
Gender	female	91 (43.1)
	male	120 (56.9)
Birth order	1	99 (46.9)
	2	90 (42.7)
	3 or more	22 (10.4)
Mother's education (ISCED level[17])	0	39 (18.5)
	1	45 (21.3)
	2	36 (17.1)
	3	20 (9.5)
	6	47 (22.3)
	7	24 (11.3)
Father's education (ISCED level[17])	0	30 (14.2)
	1	46 (21.8)
	2	30 (14.2)
	3	16 (7.6)
	6	54 (25.6)
	7	35 (16.6)
Occupation of the head of the family (ISCO-08[18])	elementary	53 (25.1)
	plant & machine operators and assemblers	1 (0.5)
	craft & related trade workers	10 (4.7)
	skilled workers, shop & market sales workers	44 (20.9)
	clerks	2 (0.9)
	technicians and associate professionals	50 (23.7)
	professionals	15 (7.1)
	legislators, senior officials and managers	36 (17.1)
Socioeconomic status (modified Kuppuswamy SES 2019[19])	upper lower	65 (30.8)
	lower middle	51 (24.2)
	upper middle	71 (33.6)
	upper	24 (11.4)

ISCED – International Standard Classification of Education; ISCED level 1 – completed primary education; ISCED level 2 – completed middle school; ISCED level 3 – completed high school; ISCED level 6 – completed graduation; ISCED level 7 – completed post-graduation; ISCO-08 – International Standard Classification of Occupations; SES – socioeconomic status scale.

ISCED levels 6 and 7. One-fourth of the households were engaged in elementary occupations, such as daily-wage work, while 30% were involved in higher-level occupations, including technicians, associate professionals and professionals. A similar distribution was observed in the socioeconomic class, with a slight majority (54.6%) belonging to the lower strata, i.e., upper lower and lower middle levels. The median per capita income (interquartile range (*IQR*)) of households in the study sample was 3,750 (2,500–6,667) Indian rupees (INRs). The prevalence of dental caries is represented as an error bar in Fig. 1. The overall prevalence of dental caries was 49.3% (42.5–56.1%). A significantly higher prevalence of dental caries was observed in primary teeth (46.4% (39.8–53.3%)) than in permanent teeth (6.6% (3.95–10.9%)). The median DMFT score (*IQR*) was 1 (1–1.25), and the median deft score was 2 (1–4).

The association of dental caries with sociodemographic factors is presented in Table 2. Although the prevalence was higher among children attending government schools compared to private schools, no significant association was observed. In the study sample, the mother's educational status demonstrated a stronger association with dental caries than the father's educational status. However, none of the sociodemographic factors showed a significant association with dental caries.

The association of dental caries with various risk factors – oral hygiene, breastfeeding, sugar exposure, and ETS exposure – is presented in Table 3. Only 13 individuals (6.2%) in the study sample reported brushing their teeth twice daily. Breastfeeding during sleep time was common during infancy (87.7%; *n* = 185), while bottle feeding was reported by 36% of participants (*n* = 76). Among the bottle-fed children (*n* = 76), 16 (21.0%) used the bottle as a pacifier. Approximately 30% of the children (*n* = 64) had high sugar exposure, with a sugar score >15. During the antenatal period, the respondents exhibited lower levels of ETS exposure (54.5%; *n* = 115) than during the index period (64.9%; *n* = 137). The school neighborhood exposure (46.9%; *n* = 99) was higher than that of restaurants/roadside stalls (42.2%; *n* = 89) or transit (bus or railway) points (59.7%; *n* = 126). However, none of the oral hygiene and dietary factors were significantly associated with dental caries. Environmental tobacco smoke exposure was most often due to smoking by the grandfather (24.2%; *n* = 52), followed by the father (11.8%; *n* = 25). Cigarettes were the most common form of ETS exposure (26.1%; *n* = 55), followed by beedi (17.5%; *n* = 37). Similar results were found for ETS exposure during the index period.

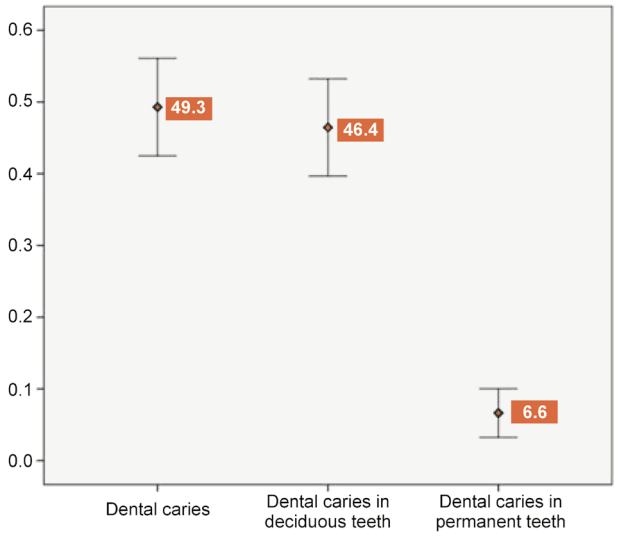

Fig. 1. Prevalence of dental caries in children

Table 2. Association of dental caries with sociodemographic parameters based on the study sample

Sociodemographic characteristics		Size of the sub-group sample *n*	Prevalence of dental caries [%]	*PR* (95% *CI*)	*p*-value*
School type	government	84	53.6	1	0.312
	private	127	46.5	0.87 (0.66–1.14)	
Gender	female	120	51.7	1	0.428
	male	91	46.2	0.89 (0.67–1.18)	
Birth order	1	99	52.5	1	0.377
	2 or more	112	46.4	0.89 (0.67–1.16)	
Mother's education	high school level or below	140	52.9	1	0.145
	graduation or above	71	42.3	0.8 (0.58–1.1)	
Father's education	high school level or below	122	50.8	1	0.603
	graduation or above	89	47.2	0.93 (0.7–1.22)	
Socioeconomic status (modified Kuppuswamy SES 2019[19])	upper lower	65	46.2	1	0.484
	lower middle	51	58.8	1.27 (0.9–1.8)	
	upper middle	71	46.5	1.01 (0.7–1.44)	
	upper	24	45.8	0.99 (0.59–1.65)	
Source of water supply	public tap or well	94	53.2	1	0.309
	mineral water	117	46.2	0.87 (0.66–1.14)	

PR – prevalence ratio; *CI* – confidence interval; * χ^2 test.

Table 3. Association of dental caries with oral hygiene parameters, breastfeeding, sugar exposure, and environmental tobacco smoke (ETS) exposure

Parameter		Size of the sub-group sample *n*	Prevalence of dental caries [%]	*PR* (95% *CI*)	*p*-value**
Brushing by parents	no	183	49.7	1	0.745
	yes	28	46.4	0.93 (0.61–1.42)	
Brushing under parental supervision	no	156	50.6	1	0.508
	yes	55	45.5	0.9 (0.65–1.25)	
Brushing before bedtime	no	199	48.7	1	0.519
	yes	12	58.3	1.2 (0.72–1.97)	
Fluoride toothpaste	no	55	40.0	1	0.109
	yes	156	52.6	1.31 (0.92–1.87)	
Breastfeeding during sleep time	no	26	53.8	1	0.620
	yes	185	48.6	0.90 (0.61–1.32)	
Bottle feeding	no	135	52.6	1	0.201
	yes	76	43.4	0.83 (0.61–1.11)	
Use of the bottle as a pacifier	no	59	44.1	1	0.982
	yes	16	43.8	0.99 (0.53–1.85)	
Sugar exposure*	low	147	46.3	1	0.182
	yes	64	56.3	1.21 (0.92–1.60)	
ETS exposure during the antenatal period	no	96	39.6	1	0.010
	yes	115	57.4	1.44 (1.08–1.94)	
ETS exposure during the index period	no	74	40.5	1	0.062
	yes	137	54.0	1.33 (0.97–1.82)	
ETS exposure in the school neighborhood	no	112	54.5	1	0.110
	yes	99	43.4	0.79 (0.60–1.05)	
ETS exposure in restaurants/roadside stalls	no	122	46.7	1	0.382
	yes	89	52.8	1.13 (0.86–1.48)	
ETS exposure in bus stops/railway stations	no	85	52.9	1	0.383
	yes	126	46.8	0.88 (0.67–1.16)	

* sugar score ≤15 was defined as low sugar exposure and >15 as high sugar exposure; ** χ^2 test.

Antenatal exposure was found to be significantly associated with an increased risk of dental caries (*PR* (95% *CI*): 1.44 (1.08–1.94)). No significant associations with dental caries were observed for other variables.

The prevalence of dental caries among children in school neighborhoods with ETS exposure was lower (43.4%) when compared to those without ETS exposure (54.5%). However, there was no statistically significant association between the two. The variables with a *p*-value <0.2 in the univariate analysis were included in the multivariate analysis (Table 4). The multivariate analysis, conducted using binomial regression, included the mother's educational status, sugar exposure classified as low or high, and antenatal exposure to ETS as factors. Exposure to ETS in the school premises and during the index period were excluded due to high collinearity with ETS exposure during the antenatal period. In the multivariate analysis, only ETS exposure during the antenatal period showed a significant association with dental caries. The prevalence among those exposed to ETS during the antenatal period was 41% higher than among those not exposed. No other factors showed a significant association during the analysis.

Table 4. Independent predictors of dental caries in children

Parameter	Exposure level	*APR* (95% *CI*)	*p*-value[$]
Mother's education	high school level or below	1	0.383
	graduation or above	0.87 (0.64–1.19)	
Sugar exposure	low	1	0.244
	high	1.17 (0.90–1.54)	
ETS exposure during the antenatal period	no	1	0.021
	yes	1.41 (1.05–1.90)	

APR – adjusted prevalence ratio; [$] multivariate log-binomial regression analysis.

Discussion

A cross-sectional analytical study was conducted among schoolchildren aged 5 to 10 years to assess the prevalence of dental caries and determine its association with ETS exposure. The overall prevalence of dental caries was 49.3% (42.5–56.1%), with a significantly higher prevalence in primary teeth (46.4% (39.8–53.3%)) than in permanent teeth (6.6% (3.95–10.9%)). Among the risk

factors evaluated in the study, ETS exposure during the antenatal period was found to be significantly associated with an increased risk of dental caries (adjusted prevalence ratio (*APR*) (1.41 (1.05–1.90)).

The prevalence of dental caries in the present study was comparable to the pooled prevalence (49.6%) reported by Ganesh et al.[4] and Janakiram et al.[22] However, a few studies conducted in South India reported a higher prevalence than the present study.[23–25] This difference could be attributed to geographical variation, epidemiological context and differences in age groups compared to other studies. As previously stated, the prevalence of dental caries in primary teeth was considerably higher in the current study. A systematic review evaluated the variation in childhood dental caries and reported that the prevalence of dental caries in primary and permanent teeth was similar in Asia (53% vs. 58%).[26] However, this similarity was not reported in the 5 to 10 age group. The present study did not find any significant associations between sociodemographic factors and dental caries. A scoping review of risk factors in childhood dental caries reported that male gender, poor maternal education and low family income were commonly associated with dental caries.[5] In the present study, gender and maternal education showed comparable results but were not statistically significant.

The dietary factors assessed in the study had no association with dental caries. Previous studies have consistently reported an association between dental caries and breastfeeding, bottle feeding and sugar exposure.[27–29] There is extensive evidence supporting the role of sugar intake in dental caries. Although the present study did not find a significant association with sugar intake, the evidence is overwhelming and cannot be ignored. The lack of association between sugar intake and dental caries could be due to limitations in its assessment, specifically the use of 24-hour dietary recall which may inaccurately represent past sugar intake. Additionally, recall bias and inadequate sample size may have contributed to the lack of significant results. The present study evaluated various factors including brushing frequency, brushing by parents, brushing under parental supervision, and the use of fluoride toothpaste, but none were found to have a significant association with dental caries. Several studies have reported on the protective effect of oral hygiene on dental caries.[23,30] However, the present study did not find a significant association, which could be due to sampling variation and inadequate sample size. In addition, antenatal exposure to ETS was associated with a considerable increase in the risk of dental caries (*PR*: 1.44 (1.08–1.94)). No other variables showed a significant association with dental caries. When adjusted for maternal education and sugar exposure, antenatal exposure to ETS remained substantial, with an *APR* of 1.41 (1.05–1.90).

The findings of the present study are consistent with those of a systematic review conducted by González-Valero et al.[15] In their meta-analysis, prenatal exposure to secondhand smoke increased the risk of dental caries in primary teeth, with a pooled odds ratio (*OR*) of 1.72 (1.45–2.05). Kellesarian et al.[14] and Hanioka et al.[31] also reported a positive association between antenatal exposure and dental caries in children. The findings of the present study support the hypothesis of previous systematic reviews. Tanaka et al.[32] reported a similar association, with a *PR* of 1.43 (1.07–1.91). Other studies by Iida et al.,[33] Tanaka and Miyake[34] and Majorana et al.[35] reported a comparable increase in the risk of dental caries due to prenatal exposure. Our results differed from those of Shulman,[36] Tanaka et al.[37] and Claudia et al.,[38] who reported an insignificant association between the variables. However, in these studies, the lack of significance was marginal. Exposure to ETS during the antenatal period may occur due to the transfer of harmful chemicals through the placenta. Noakes et al.[39] demonstrated impaired toll-like receptor-mediated immune function in neonates and infants, which increases the susceptibility to several infections. This could be one of the biological mechanisms leading to an increased risk of dental caries. Genetic polymorphisms, such as those found in the *MSX1* gene, could play a mediating role between maternal tobacco exposure and dental susceptibility to caries.[40] It has been reported that *MSX1* can also cause alterations in developing teeth.[41] The effects of tobacco exposure may be similar to those of chemical agents.[42] Maternal exposure to ETS may alter the oral microbiome in a similar way to adult exposure.[7] A systematic review concluded that maternal exposure to disinfectants and antibiotics may also alter the oral microbiome.[43] Prenatal exposure to ETS may continue in the postnatal period, resulting in a cumulative increase in exposure.

In contrast to other studies, exposure to ETS during the index period did not have a significant effect on the prevalence of dental caries in the present study. González-Valero et al. reported a significant association between postnatal smoking and dental caries (pooled *OR:* 1.72 (1.45–2.05)).[15] Hanioka et al.[31] reported a significant association among the studies compiled in their systematic review, but did not provide a summary effect estimate. Based on the available evidence, it can be concluded that exposure to ETS during childhood is a significant risk factor for dental caries. The lack of association observed in the present study may be attributed to the low prevalence of smoking in India compared to other countries and the inadequate sample size.

Parental education is directly associated with family socioeconomic status, and dental caries have also been associated with these 2 factors.[44] The present study examined the education levels of both father and mother. The findings of previous studies on the association between ETS and dental caries are comparable with the results of the present study.[16,31,32] None of the participants in the present study belonged to a lower socioeconomic level. The recent outbreak of the COVID-19 pandemic affected

healthcare professionals, including dentists, and led to the development of numerous innovative strategies in clinical dentistry.[45–48] However, the study was conducted during the first wave of COVID-19 pandemic and since none of the children were affected, the relationship between COVID-19 and dental caries could not be evaluated.[45–48] The study participants had a high prevalence of household smoking (35.1% during the index period) compared to the national average of 19% (GATS-2).[16] There could have been a differential recall bias regarding smoking exposure, as the caregivers of children with dental caries could have reported higher ETS exposure than those without dental caries.

Limitations

The major limitation of this study was the insufficient sample size, which may have contributed to a lack of association with several known factors. Additionally, due to the low prevalence of caries in permanent teeth, the study did not have sufficient power to analyze the association with caries in deciduous and permanent teeth separately. Another limitation was the assessment of ETS based on the participant recall, which did not allow for the assessment of cumulative exposure to ETS. The study also lacked objective measures, such as serum or urine cotinine levels, to validate its findings. To date, few studies in India have demonstrated an association between ETS and dental caries in children.[30] The sample was stratified between government and private schools to ensure representation. The prevalence of dental caries was assessed using the standard WHO form to ensure standardization of assessment. The study also focused on an age group at high risk of dental caries and with mixed dentition. The prevalence of dental caries among schoolchildren in Nellore is comparable to the national average reported by systematic reviews. Further investigation is needed to understand the variation between dental caries in primary and permanent dentition. The Indian population has low awareness of the risk posed by ETS exposure for dental caries. To reduce the risk of dental caries, oral health education campaigns must propagate this message among parents and children.

Conclusions

The prevalence of dental caries among schoolchildren aged 5 to 10 was 49.6%. After adjusting for other factors, antenatal exposure to ETS contributed to a slight but significant increase in the prevalence of dental caries by 41%. However, the role of ETS exposure in dental caries requires further evaluation using cohort studies. The present study observed lower rates of brushing under parental supervision and using fluoride toothpaste. Interventions aimed at controlling these factors can further reduce the prevalence of dental caries.

Ethics approval and consent to participate

Ethics approval was obtained from the Institutional Ethics Committee of Narayana Dental College and Hospital (approval No. NDC/IECC/PEDO/12-18/01). Consent to participate was obtained from the school authorities, parents, and families of the children.

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 between sleep pattern, salivary cariogenic bacteria and fungi populations, pH and buffering capacity in children: A comparative study

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Abstract

Background. Sleep quality has a significant impact on a child's health and is linked to oral and systemic diseases. It affects the circadian rhythm, which plays a crucial role in regulating the balance of the endocrine and hormonal systems. Current research has focused on exploring its role in the development of caries, which is influenced by inherent oral factors such as the composition of the oral microbiome and pH levels.

Objectives. This study aimed to investigate the relationship between bacterial population, pH, and buffering properties of saliva and sleep patterns in 8- to 12-year-old children.

Material and methods. This cross-sectional study was conducted on 85 elementary school children aged 8–12 years. After obtaining written consent, non-stimulating saliva samples were collected using the spitting method. The participants' sleep pattern information was obtained with the use of the Persian version of the Children's Sleep Habits Questionnaire (CSHQ). Based on the results of the CSHQ, the participants were divided into 2 groups: those with appropriate sleep patterns; and those with inappropriate sleep patterns. The study compared the bacterial population of *Streptococcus mutans*, *Lactobacillus* spp. and *Candida albicans*, as well as the buffering capacity and pH of the saliva between the 2 groups. The statistical analysis employed the χ^2 test, the independent samples *t*-test and Spearman's correlation.

Results. The group with inappropriate sleep patterns had significantly lower pH and buffering capacity ($p < 0.001$) and significantly higher colony counts of *Lactobacillus* and *S. mutans* ($p < 0.001$ and $p = 0.012$, respectively). There was no association between *C. albicans* and sleep patterns ($p = 0.121$).

Conclusions. Inappropriate sleep patterns increase the population of caries-causing bacteria and reduce salivary pH and buffering capacity. This can be a significant factor in the development of dental caries in children aged 8–12 years.

Keywords: *Candida albicans*, *Streptococcus mutans*, saliva, circadian rhythm, sleep disorders

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Introduction

Sleep has a profound impact on the health and well-being of both adults and children. It plays a regulatory role in the body's physiological functions, including recovery from physical and mental fatigue, muscle growth and repair, enhancing the immune responses,[1] preserving endocrine and hormonal system balance,[2] and sustaining life. Insufficient sleep, which disrupts the circadian rhythm, has been linked to several systemic diseases, including cancer, diabetes, depression,[3] obesity, cardiovascular disease, periodontal disease, and an increased mortality rate.[4,5] Sleep deficiency hinders immune responses, resulting in elevated levels of inflammatory biomarkers (interleukin-6 (IL-6) and C-reactive protein (CRP)), increased white blood cell count and an increased risk of infectious diseases.[6] In addition, it disturbs the intestinal microflora composition by inducing Paneth cell failure, which controls intestinal flora by the secretion of antimicrobial peptides such as α-defensin and human α-defensin 5.[1] Chronic sleep deficiency may lead to obesity by altering appetite hormone secretion, energy intake and food preferences,[7,8] which in turn may result in the development of type 2 diabetes.[9] Several publications have explored the relationship between insufficient sleep and cancer risk.[10–12]

An individual's sleep pattern is a combination of sleeping behavior, duration and depth. Studies show that there is a growing concern about the consequences of insomnia in contemporary societies. Recent epidemiologic data indicates that a significant portion of the population experiences chronic sleep deficiency.[13] Insufficient sleep or sleeping late alters the quality and composition of saliva, as well as the microbial colony type.[14]

The secretion rate and composition of saliva follow a constant daily pattern. Saliva flow is low in the morning, increases in the afternoon and early evening, and decreases during sleep.[14] Saliva contains different types of electrolytes (sodium, potassium, calcium, chloride, magnesium, bicarbonate, and phosphate), proteins, enzymes, immunoglobulins, and other antimicrobial agents, including mucous glycoproteins, albumin, and other important polypeptides and oligopeptides. In addition to glucose, saliva contains nitrogen compounds such as urea and ammonia.[15,16] These substances are crucial in regulating the oral environment's pH, buffering capacity and microbial composition. Additionally, they play a role in the development of oral diseases such as carious lesions and periodontal diseases. The buffering capacity of saliva is essential in maintaining the pH of saliva and dental remineralization. The amount of saliva flow and pH levels play a significant role in the occurrence and spread of caries.[17,18] The pH of saliva at rest can be used to predict the likelihood of tooth decay and buffering capacity. In a healthy person, the resting saliva pH is approx. 7, indicating low caries activity. However, those with a resting saliva pH ranging between 5.5 and 7 have a higher incidence of caries.[19]

Various factors, including previous caries experience, patient health behaviors, socioeconomic factors, diet, and oral microbial flora, have been considered to predict the risk of tooth decay. Oral bacteria increase acid production, demineralization and tooth decay by metabolizing carbohydrates. The most prevalent strains involved in this process are *Streptococcus mutans* and *Lactobacillus* spp.[20,21] Therapeutic strategies that interfere with their colonization can significantly reduce the incidence of dental caries.[22] Studies have reported varying numbers of *Lactobacillus* spp. and *S. mutans* colonies in the saliva of patients from different age groups and communities.[23] On the other hand, studies show that the prevalence of fungal populations, particularly *Candida albicans*, is significantly higher in children with dental caries compared to those without.[24]

Given that the development of appropriate sleep habits should begin at a young age, few studies have been conducted on the effect of sleep patterns on children's oral and dental health, as well as the relationship between sleeping late, irregular sleep cycles, and sleep duration and oral health.[25] Consequently, the present study aims to examine the potential relationship between the sleep quality of 8- to 12-year-old schoolchildren in the city of Qom, Iran, and the populations of cariogenic bacteria and fungi, pH, and buffering capacity of their saliva. It is recommended that clinicians inquire about their patients' sleep patterns and consider sleep patterns a risk factor for dental and periodontal diseases. This risk factor can be eliminated by providing adequate instructions or referring patients to specialized clinicians.

Material and methods

Study design and participants

This descriptive, comparative, cross-sectional study was conducted in 2021 and 2022 at 3 schools located in downtown Qom, Iran. The Research Ethics Committee of Qom University of Medical Sciences approved the study protocol (approval No. IR.MUQ.REC.1401.143). A total of 40 samples were determined for each group, one with appropriate sleep patterns and the other with inappropriate sleep patterns. The alpha value used was 0.05, with a beta value of 0.2 and a prevalence of sleep disorders of 0.4%. The mean ± standard deviation ($M \pm SD$) values were calculated based on a previous study.[26] The sampling was conducted in 4 schools located in different parts of the city, chosen based on their willingness to participate in the study. The students were selected randomly from each of the 5 grade levels, with an equal number of male and female students in each group. The age and

gender of both groups were matched. The study protocol was explained to the parents and their children, and written consent was obtained.

The study included children between the ages of 8 and 12 who were physically and mentally healthy. The exclusion criteria were chronic systemic disease, sedative or hypnotic drug use, having at least 1 parent with a mental illness, drug abuse by at least 1 parent, congenital oral disease, history of radiotherapy or chemotherapy, and antibiotic use within the previous 2 weeks. Both groups received oral hygiene education 2 weeks before the start of the study to eliminate confounding variables. A questionnaire was employed to record demographic information of the parents and children, as well as the frequency of brushing, flossing and snack consumption. Data was collected by a trained dentist in coordination with school officials.

Measurement

Evaluation of sleep patterns

The sleep patterns of the participants were evaluated using the Persian version of the Children's Sleep Habits Questionnaire (CSHQ). The questionnaire was completed by parents. The CSHQ was designed by Owens et al. and contains 45 criteria that measure a child's sleep quality and habits. Based on the CSHQ results, the participants were divided into 2 groups: those with appropriate sleep patterns; and those with inappropriate sleep patterns.[27] The groups were matched by gender and age. Previous studies have confirmed the reliability and validity of the Persian version of the CSHQ.[28,29]

The questionnaire consists of 45 questions, including diagnostic and therapeutic questions that were not relevant to our research purposes; therefore, we only utilized 33 questions in this study. Each question was assigned a value between 1 and 3 (rarely, occasionally, frequently), with the exception of questions 1, 2, 3, 10, 11, and 26, which were scored inversely. The total score can range from 33 to 99. The score for each subscale was calculated based on the total number of related questions. The primary subscales were "bedtime resistance" (questions 1, 3, 4, 5, and 8), "sleep onset delay" (question 2), "sleep duration" (questions 9, 10 and 11), "sleep anxiety" (questions 5, 7, 8, and 21), "night wakings" (questions 16, 24 and 24), "parasomnias" (questions 12, 13, 14, 15, 17, 22, and 23), "sleep disordered breathing" (questions 18, 19 and 20), and "daytime sleepiness" (questions 26, 27, 28, 29, 30, 31, 32, and 33).

The total score on the CHSQ was calculated as the sum of all the section scores. Parents were given 3 response options for each question: frequently (5 to 7 nights per week); occasionally (2 to 4 nights per week); and rarely (0 to 1 night per week). A higher score on the CHSQ indicates a greater number of sleep issues. Children with a CHSQ score below 41 were considered to have appropriate sleep patterns, while those with a score above 41 were deemed to have inappropriate sleep patterns.[27]

Saliva collection

After completing the questionnaire, participants' unstimulated saliva samples were collected in the morning before eating breakfast, brushing their teeth, or washing their mouths. The sample was obtained by holding the patient's head down for 2–3 min and collecting 2 mL of unstimulated saliva in a sterile container.[30] The samples were stored on dry ice and immediately transferred to the microbiology laboratory of Qom University of Medical Sciences for bacteriological and fungal evaluation.

Salivary *S. mutans* level measurements

We thoroughly homogenized 0.5 mL of saliva with 5 mL of phosphate-buffered saline (PBS) using a shaker. Then, 20 µL of the solution was added to the mitis salivarius agar medium with bacitracin and 10% sucrose. The plates were incubated in an environment containing 5% CO_2 at a temperature of 37° for 48 h. Biochemical tests, including the mannitol, melibiose, sorbitol, raffinose fermentation, and arginine dihydrolase tests, as well as Gram staining, were conducted to isolate *S. mutans* from other species. Finally, the confirmed colonies of *S. mutans* were counted and graded.[31–33]

Salivary *Lactobacillus spp.* level measurements

A portion of the sample was cultured in the MRS Broth liquid medium for 48 h at 37°C under anaerobic conditions. Then, the bacterial growth in the MRS Broth medium was transferred to the MRS Agar medium. *Lactobacillus* spp. is an anaerobic microbe that requires a special environment to grow. The microbes were placed inside an anaerobic jar (Merck Chemicals GmbH, Darmstadt, Germany), which is an impermeable container with no gas exchange with the outside environment and is used to cultivate anaerobic bacteria. A MERCK gas pack (Merck Chemicals GmbH), an oxygen-absorbent chemical kit, was placed inside the jar to achieve these conditions. Next, we soaked it with 6 mL of normal saline and placed it in an incubator at 37°C. After keeping the samples in this environment for 1 day, a suspension of the microbes was prepared using a technique similar to that employed for *S. mutans*. *Lactobacillus* spp. colonies were differentiated and confirmed using morphological tests and Gram staining.[34]

Bacterial colonies were counted using the following criteria:

A – 0 colonies: no growth;
B – 1 colony: 1–10^3 bacteria per mL of saliva,
C – 2 colonies: 10^3–10^5 bacteria per mL of saliva; and
D – 3 colonies: more than 10^5 bacteria per mL of saliva.[35]

Salivary *C. albicans* level measurements

For *Candida* isolation, 0.1 mL of saliva was cultured on the suburban chloramphenicol dextrose agar medium and incubated at 37°C for 24–48 h. The presence of *C. albicans* colonies was confirmed by microscopic examination tests based on the colony color after 48 h.

Colony counting was performed using the following criteria:

A – 0 colonies: no growth;
B – 1 colony: 1–10 *C. albicans* isolates per mL of saliva;
C – 2 colonies: 10–100 *C. albicans* isolates per mL of saliva; and
D – 3 colonies: more than 100 *C. albicans* isolates per mL of saliva.[36]

Salivary pH measurements

To determine the pH of saliva, we analyzed the saliva samples using a pH meter (ISOLAB Laborgeräte GmbH, Wertheim, Germany) calibrated with 2 substances of pH 4 and 7. The device's electrode was washed with distilled water before being inserted into the sample. Salivary pH was expressed to 2 decimal places.

Salivary buffering capacity measurements

To determine the buffering capacity of the saliva, we added 0.1 mL of normal 0.05 hydrochloric acid to each saliva sample and measured the pH using a pH meter. This process was repeated multiple times to ensure consistency and continued until the pH of the saliva dropped sharply and the pH changes were minimal. According to this method, a solution with a greater resistance to acid had a greater buffering capacity, whereas a solution with a lower resistance to acid was considered to have a lower buffering capacity.[37]

Bias

The risk of bias was minimized by providing oral hygiene education 2 weeks before the study and using reliable methods to assess children's sleep patterns, salivary microbiota, pH, and buffering capacity in a dedicated laboratory in the city of Qom.

Statistical analysis

Data analysis was performed using the IBM SPSS Statistics for Windows software, v. 28.0 (IBM Corp., Armonk, USA) and descriptive statistics and percentages. Based on the type of variables, Spearman's correlation, *t*-test or χ^2 test was used. Correlation coefficient values were categorized as small (0.1–0.3), medium (0.3–0.5) and large (0.5–1.0).

Results

A total of 85 children participated in this study, with 41 having sufficient sleep and 44 having insufficient sleep. There was no significant difference in gender ($p = 0.450$) or age group ($p = 0.989$). The child's sleep pattern was not associated with the educational level of the mother or father ($p = 0.122$ and $p = 0.564$, respectively) (Table 1). Sleep patterns were linked to pH, buffering capacity, and colony counts of *Lactobacillus* spp. and *S. mutans*. Children with improper sleep patterns had significantly lower pH and buffering capacity ($p < 0.001$) and significantly higher colony counts of *Lactobacillus* spp. and *S. mutans* ($p < 0.001$ and $p = 0.012$, respectively). However, there was no significant association between sleep patterns and *C. albicans* (CFU/mL) ($p = 0.121$).

All of the subclasses correlated negatively with pH and salivary buffering capacity on medium to large scales (Table 2). There were no significant correlations between the subclasses and *S. mutans* colony counts, except for daytime sleepiness, which had a small positive correlation (correlation coefficient = 0.25, $p = 0.01$). A medium positive correlation was observed between the *Lactobacillus* spp. colony counts and sleep anxiety (correlation coefficient = 0.34, $p = 0.001$), parasomnias (correlation coefficient = 0.35, $p = 0.001$) and daytime sleepiness (correlation coefficient = 0.34, $p = 0.001$).

Table 3 presents the correlation between *Lactobacillus* spp., *S. mutans*, *C. albicans*, and buffering capacity, and the secondary variables recorded in this study. Two small correlations were identified: between daily snack consumption and *Lactobacillus* spp. colonies (correlation coefficient = 0.28, $p = 0.01$); and between daily fruit and vegetable consumption and *S. mutans* colonies (correlation coefficient = 0.27, $p = 0.01$).

Discussion

Sleeping habits have a significant impact on systemic health and play an essential immunoregulatory role in the oral cavity by influencing the flow rate and composition of saliva. Saliva, on the other hand, controls the pH and buffering capacity of the oral environment, as well as the types and abundance of oral microbial colonies,[14] including *C. albicans* fungus and *S. mutans* and *Lactobacillus* spp. These 2 bacteria are inherent in the oral cavity and are the major bacterial strains involved in caries development.[20,21]

The study revealed that children with inappropriate sleep patterns had lower salivary pH levels and higher saliva acidity compared to those with appropriate sleep patterns. Salivary *S. mutans* and *Lactobacillus* spp. loads were significantly higher in children with inappropriate sleep patterns. These 2 bacteria, in conjunction with the lower pH levels, can create an oral environment that is more susceptible to dental caries. Chen et al. found that

Table 1. Association between predictor variables and outcome variables

	Variables	Appropriate sleep pattern	Inappropriate sleep pattern	*p*-value
Participants, *n*		41	44	–
Age group, *n*	8 years	5	5	0.989[&]
	9 years	6	6	
	10 years	11	13	
	11 years	9	11	
	12 years	10	9	
Gender, *n*	male	19	24	0.450[&]
	female	22	20	
Single-parent child, *n*	yes	0	4	0.067[&]
	no	41	40	
Mother's education, *n*	not educated	4	1	0.122[&]
	up to secondary school	10	15	
	diploma	19	25	
	bachelor's and above	8	3	
Father's education, *n*	not educated	3	4	0.564[&]
	up to secondary school	12	18	
	diploma	14	14	
	bachelor's and above	12	8	
Brushing frequency [times/day]		1.02 ±0.68	0.84 ±0.68	0.207[#]
Flossing frequency [times/day]		0.24 ±0.62	0.06 ±0.25	0.133[#]
Daily brushing time [min]		2.19 ±1.72	1.63 ±1.41	0.189[#]
Snack consumption [times/day]		0.85 ±0.57	1.22 ±1.07	0.174[#]
Fruit and vegetable consumption [times/day]		1.75 ±1.01	1.54 ±1.06	0.231[#]
Dairy product consumption [times/day]		1.56 ±0.83	1.36 ±0.80	0.320[#]
pH		7.69 ±0.37	6.99 ±0.34	<0.001*[#]
Buffering capacity		7.46 ±0.37	6.77 ±0.42	<0.001*[#]
Lactobacillus spp. [CFU/mL]		13.04 ±9.50	32.45 ±21.14	<0.001*[#]
Streptococcus mutans [CFU/mL]		17.58 ±10.12	27.54 ±17.23	0.012*[#]
Candida albicans [CFU/mL]		4.17 ±5.83	14.45 ±24.08	0.121[#]

* statistically significant ($p < 0.05$); [&] χ^2 test; [#] independent t-test.

Table 2. Correlation between sleep quality and the average number of *S. mutans*, *Lactobacillus* spp. and *C. albicans* colonies, buffering capacity and pH

Variables	*Lactobacillus* spp.	*Streptococcus mutans*	*Candida albicans*	Buffering capacity	pH
Bedtime resistance	0.24[I] (0.027*)	0.20 (0.061)	0.14 (0.196)	–0.47[II] (<0.001*)	–0.53[III] (<0.001*)
Delayed sleep onset	–0.06 (0.530)	0.11 (0.310)	0.018 (0.090)	–0.20 (0.540)	–0.24[I] (0.020*)
Sleep duration	0.11 (0.287)	0.10 (0.361)	–0.06 (0.546)	–0.19 (0.070)	–0.29[I] (0.010*)
Sleep anxiety	0.34[II] (0.001*)	0.06 (0.537)	0.11 (0.314)	–0.47[II] (<0.001*)	–0.49[II] (<0.001*)
Night waking	0.22[I] (0.042*)	0.04 (0.654)	0.21[I] (0.044*)	–0.40[II] (<0.001*)	–0.42[II] (<0.001*)
Parasomnias	0.35[II] (0.001*)	0.10 (0.325)	0.25[I] (0.017*)	–0.38[II] (<0.001*)	–0.38[II] (<0.001*)
Sleep disordered breathing	0.18 (0.086)	0.08 (0.431)	0.09 (0.401)	–0.18 (0.099)	–0.14 (0.192)
Daytime sleepiness	0.34[II] (0.001*)	0.25[I] (0.017*)	0.10 (0.323)	–0.34[II] (0.001*)	–0.39[II] (<0.001*)

Data presented as Spearman's correlation coefficient (p-value); * statistically significant ($p < 0.05$); [I] small correlation; [II] medium correlation; [III] large correlation.

Table 3. Correlation between secondary variables and the average number of *S. mutans*, *Lactobacillus* spp. and *C. albicans* colonies and buffering capacity

Variables	*Lactobacillus* spp.	*Streptococcus mutans*	*Candida albicans*	Buffering capacity
Brushing frequency [times/day]	−0.06 (0.550)	−0.12 (0.250)	0.06 (0.530)	−0.03 (0.750)
Flossing frequency [times/day]	−0.09 (0.380)	−0.21 (0.060)	−0.11 (0.290)	0.06 (0.550)
Daily brushing time [min]	−0.08 (0.460)	−0.03 (0.730)	−0.06 (0.570)	−0.04 (0.680)
Snack consumption [times/day]	0.28[|] (0.010*)	−0.03 (0.770)	0.19 (0.070)	−0.07 (0.500)
Fruit and vegetable consumption [times/day]	−0.10 (0.320)	−0.27[|] (0.010*)	−0.00 (0.940)	−0.12 (0.260)
Dairy product consumption [times/day]	−0.10 (0.320)	−0.20 (0.060)	0.05 (0.580)	0.01 (0.860)

Data presented as Spearman's correlation coefficient (p-value); * statistically significant ($p < 0.05$); [|] small correlation.

insufficient sleep duration and delayed sleep onset were associated with an increased risk of dental caries in 3-year-old children.[38] In a study conducted by Roestamadji et al. on the risk of blood glucose, saliva levels and tooth decay in night shift workers, the night shift workers demonstrated a greater decrease in saliva pH levels than the control group.[18] Researchers believe that sleep deprivation activates the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis,[39] causing an increase in corticotropin-releasing factor and adrenocorticotropic hormone (ACTH) secretion from the hypothalamus, which in turn leads to cortisol secretion from the adrenal gland. Cortisol is associated with stress and affects saliva pH.[40] A study by Cohen and Khalaila demonstrated that stress can increase sympathetic nerve activity, leading to changes in the pH, acidity and buffering capacity of saliva.[41] This evidence confirms that sleep deprivation increases the acidity of saliva, which is a risk factor for tooth decay. Further research in this area is necessary.

The current study found that individuals with inappropriate sleep patterns had more *Lactobacillus* spp. and *S. mutans* colonies in their saliva; however, there was no significant difference in the number of *C. albicans* colonies between the groups. A study by Arvidsson et al. investigated the relationship between body mass index (BMI), eating habits, sleep, and the number of salivary *S. mutans* colonies in 4- to 11-year-old children in Sweden. The study found that a lack of sleep is associated with an increase in salivary *S. mutans* colonies.[42] Our findings are consistent with those of Alqaderi et al., who discovered a positive relationship between the lack of sleep and an increase in bacterial colonies in Kuwaiti children.[43] Chen et al., who investigated the relationship between insufficient sleep and dental caries in Japanese children, found a correlation between late sleep and elevated levels of IL-6, salivary *S. mutans* colonies, and an increased risk of dental caries in a child's primary and permanent teeth.[38] Sardana et al. investigated the effect of sleep on early childhood development of caries. Lack of sleep was cited as one of the causes of immune system weakness, which can increase bacterial colonies, including those that cause cavities, such as *S. mutans*.[44] The composition and properties of oral fluids play a significant role in the onset of dental caries, given that teeth are in contact with saliva. Saliva prevents caries in multiple ways by cleansing food and exhibiting buffering and antibacterial properties.[45]

In the current study, there was no significant difference in the number of *C. albicans* colonies between the 2 groups. There was only a slight positive correlation between night wakings and the parasomnia subclasses. The lack of differences between the 2 groups may be attributed to the small sample size, given the significant standard deviation in the *C. albicans* colony count values for both groups. In addition, there is no available evidence that evaluates the relationship between sleep patterns and the number of *C. albicans* colonies. This correlation should be investigated in future research.

Based on our study, there was a positive correlation between daily snack consumption and the number of *Lactobacillus* spp. colonies (Table 3), which suggests that snack consumption may increase the likelihood of caries development. In addition, daily consumption of fruits and vegetables was negatively correlated with *S. mutans*, indicating their potential role in preventing the progression of dental caries.

Limitations

Our findings were based on a relatively small number of participants. We focused on children living in 1 region, therefore, the generalizability of the findings to other populations may be limited. One of the limitations of the current study was the inability to match participants based on socioeconomic factors, which could influence a child's sleep, as well as their compliance with health and nutrition recommendations. The study's results should be interpreted with caution because filling out the questionnaires by parents was another limitation that could affect the results. However, this method appeared to be the most reliable, given the young age of the study participants.

Conclusions

There is a significant relationship between sleep patterns and salivary cariogenic bacteria, including *Lactobacillus* spp. and *S. mutans*. Participants with poor sleep had a higher salivary bacterial load. In addition, children with improper sleep patterns had more acidic saliva and a lower buffering capacity compared to children with normal sleep patterns. No correlation was found between sleep patterns and salivary *C. albicans* levels.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The Research Ethics Committee of Qom University of Medical Sciences approved the study protocol (approval No. IR.MUQ.REC.1401.143) All procedures were performed following relevant guidelines and regulations. Informed written consent was obtained from the children or their parents.

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 CD44 antigen in type 2 diabetic patients with periodontitis: An immunohistochemical study

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Abstract

Background. Type 2 diabetes mellitus (DM) is a known systemic risk factor for periodontitis. An increased expression of CD44 has been suggested in type 2 diabetics and periodontitis patients.

Objectives. The present study aimed to assess the expression of CD44 antigen in patients with chronic periodontitis (CP) and type 2 DM in a South Indian urban population. Additionally, the relationships between the expression of CD44 antigen in gingival tissues, periodontal clinical parameters, and the random blood sugar (RBS) and glycated hemoglobin (HbA1c) levels were assessed.

Material and methods. A total of 63 subjects were divided into 3 groups: systemically and periodontally healthy controls (group H); CP patients, otherwise healthy (group CP); and CP patients with type 2 DM (group CP+DM). Periodontal parameters were recorded for all groups, and additionally the RBS and HbA1c levels for group CP+DM. Gingival tissue samples were obtained and subjected to immunohistochemical analysis for CD44.

Results. The expression of CD44 was significantly higher in the diseased groups. Epithelial CD44 expression was significantly stronger in group CP+DM as compared to groups CP and H ($p < 0.001$), whereas connective tissue CD44 expression was similar in groups CP and CP+DM ($p = 0.657$). Furthermore, an inverse relationship was observed between blood glucose parameters and CD44 expression in the epithelium and connective tissue.

Conclusions. The expression of CD44 increased with the severity of periodontal disease. Additionally, glycemic control in patients with CP and type 2 DM had an impact on CD44 expression. Our findings indicate a possible destructive role of CD44 in the pathogenesis of periodontal diseases in individuals with type 2 DM.

Keywords: diabetes mellitus, hyaluronan receptors, immunohistochemistry/methods, periodontitis, etiology

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Introduction

Diabetes mellitus (DM) is a chronic non-communicable metabolic disorder afflicting the global population, characterized by abnormal insulin secretion and activity.[1] The American Diabetic Association (ADA) recognizes chronic periodontitis (CP) as the 6th complication of type 2 DM, along with 5 others, namely retinopathy, neuropathy, nephropathy, macrovascular disease, and altered wound healing.[2,3] These complications are direct consequences of hyperglycemia.[4] The hyperglycemic state activates innate immunity, which leads to an increased release of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor alpha (TNF-α).[4,5] Chronic hyperglycemia facilitates anaerobic infection in tissues by inhibiting the pathways of inflammation resolution, with the inflammation increasing insulin resistance by dysregulating glycemic mechanisms. Hyperglycemia can diminish the synthesis of extracellular matrix (ECM) components and connective tissue remodeling by fibroblasts and osteoblasts. The interaction between advanced glycation-end products (AGEs) and their receptors (RAGEs) leads to the formation of free radicals. This alters the relationship between connective tissue cells and their matrix, as well as capillary integrity.[6,7]

CD44 is a type 1 transmembrane glycoprotein expressed in various cell types, including epithelial, endothelial, lymphoid, and myeloid cells, and fibroblasts. The molecule is responsible for a wide array of functions, including the cell–cell and cell–matrix interactions during inflammatory tissue remodeling and regeneration.[8,9] The glycosaminoglycan hyaluronan (HA) is a key ligand that binds to CD44. The receptor–ligand interaction leads to enhanced immunological events, thus playing a significant role in chronic inflammatory diseases.[10] CD44 is known to be strongly expressed in the epithelium and connective tissue of patients with type 1 and 2 DM and CP.[11]

India has the second largest diabetic population after China. It has been reported that the advancement of pre-diabetes to diabetes is more rapid in urban Indian populations.[12] Given that type 2 DM is a recognized systemic risk factor for CP and periodontitis is a recognized complication of uncontrolled type 2 DM, we hypothesized that the dysregulation of CD44 expression in individuals with type 2 DM plays a substantial role in this bidirectional pathogenesis involving periodontitis patients.[13,14] As such, this study aimed to evaluate the expression of CD44 antigen in patients with CP and type 2 DM in a South Indian urban population. Additionally, we assessed the relationships between the expression of CD44 antigen in gingival tissues, periodontal clinical parameters, and the random blood sugar (RBS) and glycated hemoglobin (HbA1c) levels. The null hypothesis stated that there are no differences in CD44 antigen expression between individuals diagnosed with CP and those with CP and type 2 DM.

Material and methods

This cross-sectional study was conducted at the Department of Periodontics, SRM Dental College, Chennai, India, between October 2011 and January 2013. The study was approved by the Institutional Scientific and Ethical Review Board before commencement (No. SRMU/M&HS/SRMDC/2010-13/M.D.S-PG student/504). All subjects received the explanation of the study purpose and procedures, and provided written informed consent to participate. The study was conducted prior to the release of the new periodontal disease classification in 2018.[15] Hence, we continue using terms such as CP throughout this paper. However, according to the new classification, we would have referred to Stage 3 or 4 and Grade B.[15]

Study population

A total of 63 subjects aged 20–70 years (mean age: 43.1 years) were recruited for the study based on the selection criteria. The study participants were divided into 3 groups: group H – systemically and periodontally healthy control subjects (7 males and 14 females; mean age: 30.90 ±8.98 years); group CP – patients with CP who were otherwise healthy (6 males and 15 females; mean age: 43.90 ±10.22 years); and group CP+DM – patients with CP and type 2 DM (10 males and 11 females; mean age: 54.33 ±10.91 years).

Inclusion criteria

Group H included subjects with no clinical evidence of gingival inflammation, the sulcus depth ≤3 mm and no clinical attachment loss (CAL). Group CP included patients with a diagnosis of CP based on the American Academy of Periodontology (AAP) 1999 Classification of Periodontal Diseases and Conditions[16]; they had at least 20 teeth, with the probing pocket depth (PPD) ≥4mm, CAL ≥ 3mm and bleeding on probing (BOP). Group CP+DM recruited patients with self-reported DM with a minimum duration of 6 months. Additionally, the RBS and HbA1c levels were assessed to include patients with HbA1c ≥ 6% of total hemoglobin.

Exclusion criteria

Patients with known systemic diseases other than DM, smokers, those with a history of periodontal treatment in the last 6 months, those using antibiotics or anti-inflammatory drugs in the past 6 months, and pregnant and lactating women were excluded. In addition, patients with normal HbA1c levels were excluded from group CP+DM.

Clinical protocol

Full-mouth clinical parameters, including the plaque index (PI), the gingival index (GI), PPD, and CAL, were recorded. A single calibrated examiner recorded PPD and CAL using

a UNC 15 periodontal probe. Following the examination, the patients from group CP+DM were evaluated for their blood sugar levels, and the eligible participants had gingival samples collected at the subsequent appointment.

Gingival sample collection

In group H, gingival samples were collected during surgical crown lengthening procedures and tooth extraction for orthodontic purposes. In groups CP and CP+DM, the samples were collected from areas of Grade 3 tooth mobility, resulting from severe periodontitis and indicated for extraction.

Gingival biopsies were performed with blade No. 15 under adequate local anesthesia (2% lignocaine with 1:80,000 adrenaline), using an internal bevel incision. The samples were washed with a sterile saline solution and immediately fixed in 10% neutral buffered formalin (NBF). The biopsy specimens were embedded in paraffin blocks. The blocks were sectioned to a thickness of 4 µm, mounted on poly-L-lysine-coated glass slides, incubated at 37°C for 1 day, and further incubated at 58°C for 1 h before deparaffinization.

The paraffin-embedded sections were deparaffinized, rehydrated and treated with 3% hydrogen peroxide at 37°C for 30 min to block endogenous peroxidase activity. Then, they were rinsed with phosphate-buffered saline (PBS) for 5 min and treated in a microwave oven with Tris-EDTA buffer (pH 6.0) for 10 min for antigen retrieval.[17] The slides were cooled to room temperature for 20 min, rinsed with distilled water for 5 min and washed twice with PBS (pH 7.6) for 5 min. Next, they were placed in 3% hydrogen peroxide for 15 min and washed with PBS for 5 min. To prevent non-specific reactions with other tissue antigens, the slides were treated with Power Block™, which contains casein and proprietary additives, in PBS with sodium azide 15 M for 15 min. The sections were then incubated with the CD44 primary antibody at room temperature for 1 h. After rinsing 3 times with PBS for 5 min, the sections were incubated with the biotinylated secondary antibody at room temperature for 30 min. The specific reaction for each antibody was visualized using 3,3'-diaminobenzidine. The sections were then counterstained with Mayer's hematoxylin, air-dried, cleared in xylene, and mounted on slides with the use of the dibutylphthalate polystyrene xylene (DPX) medium.[18]

The immunodetection of CD44 was performed with the use of BioGenex Super Sensitive™ Detection Systems (BioGenex, Chennai, India). The immunohistochemistry (IHC) procedure was conducted in the Oral Pathology Laboratory, SRM Dental College, Chennai, India.

Immunohistochemistry image analysis

The mounted sections were observed under a light microscope (Olympus BX51; Olympus, Tokyo, Japan) to evaluate immunostaining in epithelial and connective tissue cells. Positivity was determined based on the brown stain of diaminobenzidine. The quantitative estimation involved counting the number of CD44-positive cells in more representative areas under light microscopy at ×400 magnification, using the Image-Pro Plus software, v. 6.3 (Media Cybernetics, Inc., Rockville, USA).[18]

Statistical analysis

Statistical analysis employed SPSS Statistics for Windows, v. 17.0 (SPSS Inc., Chicago, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Since the values were normally distributed, parametric tests were used for further analysis. The parameters in this study were expressed as mean ± standard deviation (*M* ±*SD*). A *p*-value ≤0.05 was considered statistically significant. To compare continuous variables between the groups, the one-way analysis of variance (ANOVA) was used, with Tukey's post hoc test for multiple comparisons. The Pearson correlation coefficient was used to determine correlations between variables.

Results

Demographics and clinical characteristics

The study involved 63 adults aged 20–70 years. Table 1 presents the demographic data and clinical characteristics of the participants. Periodontal parameters and age were higher in periodontitis patients with DM (group CP+DM) as compared to patients with periodontitis alone (group CP).

Table 1. General demographics and clinical characteristics of the study participants

Variables		Group H (*n* = 21)	Group CP (*n* = 21)	Group CP+DM (*n* = 21)
Gender *n*	M	7	6	10
	F	14	15	11
Age [years]		30.90 ±8.98	43.90 ±10.22	54.33 ±10.91
Clinical parameters	PI	0.6 ±0.1	1.9 ±0.5	2.4 ±0.4
	GI	0.5 ±0.1	2.0 ±0.5	2.4 ±0.4
	PPD [mm]	1.8 ±0.3	5.5 ±1.3	6.6 ±0.9
	CAL [mm]	1.1 ±0.2	5.3 ±1.3	7.1 ±1.4
	duration of DM [years]	–	–	4.98 ±4.50
	RBS [mg/dL]	–	–	176.70 ±79.70
	HbA1c [%]	–	–	6.08 ±1.04

Data presented as mean ± standard deviation (*M* ±*SD*). Groups: H – healthy controls; CP – patients with chronic periodontitis (CP); CP+DM – patients with CP and type 2 diabetes mellitus (DM). M – male; F – female; PI – plaque index; GI – gingival index; PPD – probing pocket depth; CAL – clinical attachment loss; RBS – random blood sugar; HbA1c – glycated hemoglobin.

CD44 expression

All groups exhibited CD44 immunopositivity (Table 2). Figure 1 shows representative IHC images of CD44 expression. Positive staining for CD44 was observed in the basal layer of the epithelium. Strong cytoplasmic positivity was evident in basal and parabasal cells of healthy controls (group H) (Fig. 1A,B). In patients with CP but without DM (group CP), strong positive staining for CD44 was observed in the basal layer of the epithelium and the stromal cells of the connective tissue, specifically in lymphocytes (Fig. 1C,D). In patients with both CP and DM (group CP+DM), stronger positive staining for CD44 was observed in most cells of the epithelial layer, suggestive of hyperplasia. Dense positivity was also noted in many cells of the connective tissue, specifically in lymphocytes and endothelial cells (Fig. 1E,F).

Although all groups showed immunopositivity, the diseased groups exhibited a higher CD44 expression (Table 2). There was a significantly stronger epithelial CD44 expression in group CP+DM as compared to group CP ($p < 0.001$), whereas the expression of CD44 in the connective tissue was similar in groups CP and CP+DM ($p = 0.657$) (Table 3).

The relationships between CD44 expression and periodontal parameters are presented in Table 4. There were statistically significant positive correlations between clinical parameters (PI, GI, PPD, and CAL) and CD44 expression in the epithelium and connective tissue ($p < 0.001$).

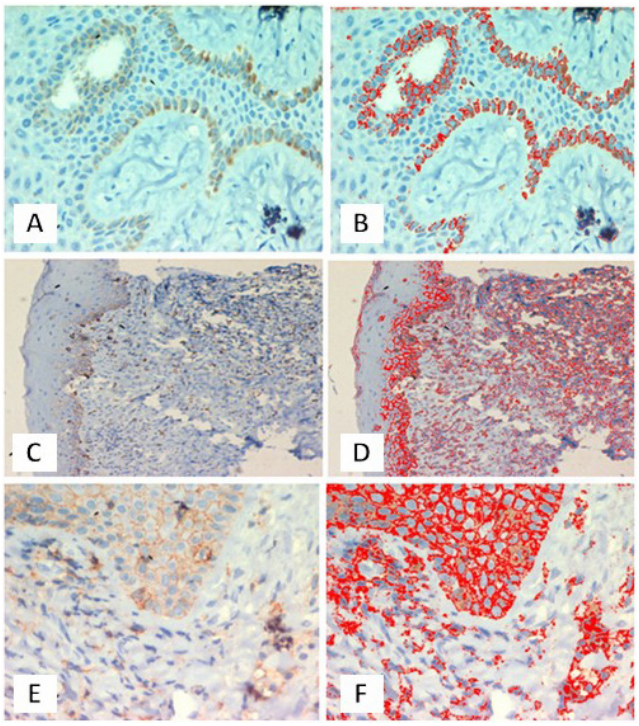

Fig. 1. Immunohistochemical staining for CD44 expression across the groups
A,B – group H; C,D – group CP; E,F – group CP+DM. Pictures B, D and F were used as representative images for counting CD44-positive cells with the use of Image-Pro Plus.

We further observed a statistically significant inverse relationship between connective tissue CD44 expression and blood glucose parameters (RBS and HbA1c) ($p < 0.001$). Epithelial CD44 expression did not show any significant correlation with the RBS and HbA1c levels, although a negative correlation was observed.

Table 2. Comparison of CD44 expression (the number of stained cells) between the groups

CD44 expression	Group H	Group CP	Group CP+DM	*p*-value
Epithelium	20.62 ±5.64	31.43 ±3.44	38.86 ±5.41	<0.001*
Connective tissue	15.76 ±4.02	39.57 ±5.80	41.24 ±15.95	<0.001*

Data presented as *M* ±*SD*. * statistically significant.

Table 3. Comparison of CD44 expression (the number of stained cells) between groups CP and CP+DM

CD44 expression	Group CP	Group CP+DM	*p*-value
Epithelium	31.43 ±3.44	38.86 ±5.41	<0.001*
Connective tissue	39.57 ±5.80	41.24 ±15.95	<0.657

Data presented as *M* ±*SD*. * statistically significant.

Table 4. Correlations between CD44 expression and clinical parameters

CD44 expression		PI	GI	PPD	CAL	RBS	HbA1c
Epithelium	r	0.792	0.745	0.746	0.764	–0.206	–0.146
	p-value	<0.001*	<0.001*	<0.001*	<0.001*	0.370	0.527
Connective tissue	r	0.552	0.546	0.608	0.570	–0.653	–0.877
	p-value	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

r – Pearson correlation coefficient; * statistically significant.

Discussion

This cross-sectional investigation analyzed the expression of CD44 in the gingival tissue samples obtained from CP patients with and without DM, from a South Indian urban population. There is mounting evidence for the rising prevalence of diabetes in both urban and rural populations of India.[19] The largest national study of diabetes, funded by the Indian government, involved 15 states and reported the spread of a diabetes epidemic among those with a lower socioeconomic status within urban populations.[12,19]

The current study used an immunohistochemical technique to assess CD44 expression. The findings showed strong CD44 immunopositivity in periodontal disease groups. There was a significant increase in the expression of CD44 in epithelial cells of CP patients with type 2 DM as compared to CP patients without DM and healthy controls. Furthermore, the expression of CD44 in the stromal connective tissue was higher in the diseased groups as compared to healthy controls. However, there was no significant difference between the diseased groups with and without type 2 DM, although an inverse relationship was observed between CD44 expression and the blood glucose levels.

Our findings are in agreement with previous reports on CD44 expression in gingival tissues of CP patients with type 2 DM.[11] Elevated levels of soluble CD44 have also been reported in the saliva of smokers with periodontitis.[20,21] Another report indicated elevated CD44 in peri-implantitis as compared to peri-implant mucositis, suggesting a strong role of CD44 in the inflammatory response.[22] The current study observed positive staining for CD44 in the basal layer of the epithelium, with strong cytoplasmic positivity evident in basal and parabasal cells of healthy controls, which is in agreement with a previous report.[23] Furthermore, an increased expression of CD44 in the epithelium was noted in group CP+DM as compared to group CP, which could be due to the release of pro-inflammatory mediators, such as TNF-α, in response to AGEs. A previous in vitro study demonstrated an increased CD44v6 expression in human gingival epithelial cell lines when they were stimulated with pro-inflammatory mediators, such as TNF-α and interferon gamma (IFN-γ).[24] The current findings of an increased CD44 epithelial expression contradict a previous report that did not find any difference in epithelial CD44 expression,[11] though this could be attributed to the different populations investigated and methods used.

The current study found an increase in connective tissue CD44 expression among CP patients, indicating that CD44 is involved in the recruitment of inflammatory cells at the site of periodontal inflammation, as reported in a previous study.[25] Additionally, HA is a key ligand for CD44 in ECM. The CD44–HA complex can mediate adhesive interactions between lymphocytes and gingival fibroblasts, and such interactions may provide intracellular cell activation signals that regulate proliferative T cell responses and stimulate the production of pro-inflammatory cytokines. Furthermore, CD44 is involved in healing by mediating the interactions between platelets and the subendothelial tissue; it has been suggested that platelets express CD44 on their surface to facilitate HA binding in the subendothelial tissue during wound healing.[26] The current findings support a possible role for CD44 in the wound healing of tissues affected by inflammatory destruction. A thorough understanding of the role of the CD44–HA complex may help in effective periodontitis management.[27]

Type 2 DM is a metabolic condition known to cause endoplasmic reticulum stress, which further induces the deposition of HA. Furthermore, HA plays a role in retaining inflammatory cells at the site of inflammation via CD44 receptors, which may explain an increased expression of CD44 receptors in type 2 DM patients and excessive inflammatory tissue destruction.[28,29] The present study observed an inverse relationship between the blood glucose levels and CD44 antigen expression among CP patients with type 2 DM, which could be explained by well-controlled diabetes.

Animal experiments have shown that in some autoimmune diseases, such as rheumatoid arthritis and type 1 DM, blocking CD44 receptors can affect downstream adaptive and innate immune interactions, impeding further accumulation of inflammatory cells and worsening of the condition.[30] Our findings suggest that dense CD44 positivity in connective tissue lymphocytes can be attributed to the activated CD44 participation in lymphocyte trafficking to the inflammatory sites, and may indicate impending episodes of hyper-inflammatory or autoimmune-type responses.[8] Based on this premise, it can be speculated that there is an autoimmune-type response in periodontal tissues of diabetic patients due to the excessive expression of these receptors, which may be a potential therapeutic target.[31]

The strengths of this study include reporting the immunolocalization of CD44 in gingival tissues by using IHC, and having adequate power in comparison with previous studies. The findings contribute to a better understanding of the pathogenesis of CP in type 2 DM patients in a South Indian urban population with a high prevalence of DM.

Limitations of the study include the lack of assessment of the principal CD44 ligand, HA, and other CD44 isoforms, which could have provided a better insight into the exact mechanistic links in these patients.

The 2018 classification of periodontal diseases categorizes periodontitis based on staging and grading.[15] The new framework has provided us with the ability to introduce potential validated biomarkers for improved case definition.[32] In this context, it would be interesting to see whether CD44 could be considered a validated biomarker in the future.

India is undergoing a significant shift from communicable diseases to non-communicable diseases, such as DM, with the trend of increasing prevalence demonstrated by the results of several studies conducted in Chennai. The development of diagnostic and prognostic biomarkers for DM in a dental setting will strengthen the ability of the healthcare system to prevent complications associated with the disease.[32] Understanding diabetic patients of an Asian Indian phenotype can promote advancement in preventive and therapeutic strategies in medical and dental settings.

Conclusions

To date, the role of CD44 in the pathogenesis of periodontitis and type 2 DM remains unclear. The current study rejected the null hypothesis, suggesting the possibility of a shift in the role of CD44 from protective to destructive in the host response of CP patients with DM as compared to those with CP alone. CD44 could essentially serve as a diagnostic biomarker and a therapeutic target in the future. However, longitudinal studies with a robust design are necessary in this area. This study adds to the existing evidence and suggests that blocking CD44 with CD44 antagonists might prove beneficial as a novel therapeutic strategy in the management of periodontal diseases, especially in patients with DM.

Ethics approval and consent to participate

The study was approved by the Institutional Scientific and Ethical Review Board before commencement (No. SRMU/M&HS/SRMDC/2010-13/M.D.S-PG student/504). All subjects provided written informed consent to participate 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

Effect of different cone beam computed tomography settings on artifact production in titanium and zirconia dental implants: An in vitro study

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Abstract

Background. The use of dental implants in the treatment of edentulous patients is increasing. Zirconia implants are an alternative to titanium implants, offering advantages in terms of aesthetics and biological compatibility. However, the number of artifacts observed on radiographic images with zirconia implants compared to titanium implants is yet to be determined.

Objectives. The purpose of this study was to evaluate the impact of different cone-beam computed tomography (CBCT) parameters on the production of artifacts in zirconia and titanium implants.

Material and methods. A dry human mandible was coated with wax to simulate human soft tissues and examined. Subsequently, titanium and zirconia implants were placed at the same points in the posterior region of the mandible. The production of artifacts on CBCT scans was evaluated using 2 parameters. The first parameter, the standard deviation within the region of interest (SD_{ROI}), is based on a comparison of the gray levels at implant and control areas. The second parameter was the contrast-to-noise ratio (CNR), which was evaluated for different protocols created by various combinations of the field of view (FOV) area, milliampere [mA] intensity and metal artifact reduction (MAR) programs.

Results. The study found that zirconia implants produced more artifacts than titanium implants. However, the production of artifacts in zirconia implants could be significantly reduced by increasing the mA values, performing CBCT scans with smaller FOV areas, and enabling MAR programs.

Conclusions. The production of artifacts is a disadvantage of zirconia implants, but this drawback can be mitigated by selecting appropriate protocols for the CBCT device.

Keywords: titanium, zirconia, dental implant, tomography, artifact

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Introduction

Radiographic imaging is the diagnostic tool used in oral implantology from pre-treatment planning to post-treatment control.[1] This tool is used to evaluate the alveolar bone in the peri-implant region and to control the passive fit of the cemented restorations that are frequently used in implant prostheses.[1,2] Although panoramic radiographs are the most commonly used imaging method in dental implantology, the use of cone-beam computed tomography (CBCT) is increasing daily as it provides more detailed analysis than orthopantomography (OPG).[3] Recently, there has been concern that CBCT images are prone to metal artifacts that obscure the visualization of the peri-implant region and alveolar bone.[4]

In radiology, an artifact is defined as the presence of visual, reconstructed radiographic data that is not part of the radiographically examined object.[5] Artifact production is related to the technical aspects of CBCT. Some objects can act as filters that change the X-ray spectrum depending on their atomic number and density. Therefore, the object being scanned has importance in artifact production.[6]

The photons emitted by the X-ray source are absorbed as they pass through objects, with low-energy photons being more absorbed than others. This results in an increase in the average energy of the remaining high-energy photons, a phenomenon known as the "beam hardening effect". This effect occurs more frequently in metal objects due to their denser nature and is one of the most common causes of the formation of metal artifacts. Beam hardening results in the formation of 2 types of artifacts: cupping artifacts, which are distortions of metallic structures due to different types of absorption; and linear artifacts, which are lines and dark bands that may appear between 2 dense objects.[7]

In recent years, metal artifact reduction (MAR) programs have been developed for CBCT devices to minimize the effects of artifacts on image quality. These programs define a threshold image representing the average gray values to reduce the variability of gray values and reduce artifacts by moving high or low gray values closer to the threshold value.[8–10]

At present, CBCT devices use various algorithms to reduce the formation of metal artifacts. The most commonly used methods are projection completion techniques and iterative approaches. Projection completion methods identify inconsistencies in the projection data due to incomplete representation of metal objects and accurately reconstruct these deficiencies using various techniques. These approaches typically encompass metal segmentation, projection addition and final image painting reconstruction. On the other hand, iterative reconstruction techniques are typically based on the optimization of selected functions, which leads to a reduction in the formation of artifacts.[11]

Zirconia has recently emerged as an alternative to titanium in dental implants. Its aesthetic advantages include a tooth-like color, high osseointegration potential and a lower microbial dental plaque deposition rate than titanium.[12,13] These properties contribute to the health of the peri-implant tissues, which have a higher inflammatory potential than currently available periodontal tissues.[14,15]

Currently, zirconia material is also used in prosthetic restorations. The advanced mechanical properties of zirconia crowns have yielded promising results in the field of prosthetic restorations, especially in patients diagnosed with TMJ disease or bruxism.[16,17]

Despite the abovementioned advantages of zirconia implants, the zirconium element in zirconia implants is a dense material with a relatively high atomic number (Z = 40), which may result in these implants producing more artifacts on CBCT scans.[18]

This in vitro study aimed to assess the impact of different CBCT settings on the production of artifacts in zirconia and titanium implants.

Material and methods

The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Nuh Naci Yazgan University, Kayseri, Turkey (31.05.2020; decision No. 2021/221). Two different implants were used to analyze the production of artifacts: zirconia implants (NobelPearl® Tapered; Nobel Biocare, Istanbul, Turkey); and titanium implants (NobelActive®; Nobel Biocare). The dimensions of both implants were identical (5.5 mm × 12.5 mm).

Study modeling and implant placement

A dry human mandible coated with wax was used in the study to simulate soft tissue attenuation. A gutta-percha cone was placed on the lingual aspect of the alveolar crest as a reference point to ensure standardization in the selection of a section in implant images prior to all CBCT scans. Initially, CBCT scans were conducted on the mandible before implant placement. Then, zirconia and titanium implants were placed in the dry mandible, which was fixed to the container with impression material to ensure CBCT standardization. Finally, CBCT scans were performed (Fig. 1).

CBCT scans

All CBCT scans were taken using a 90 kilovoltage peak (kVp) and a 0.2-µm voxel size on KaVo ORTHOPANTOMOGRAPH™ OP 3D Pro (KaVo, Tuusula, Finland). First, a zirconia implant was placed in the left posterior region of the dry mandible, and CBCT images were obtained with different field of view (FOV) areas (the milliampere [mA] intensity was fixed

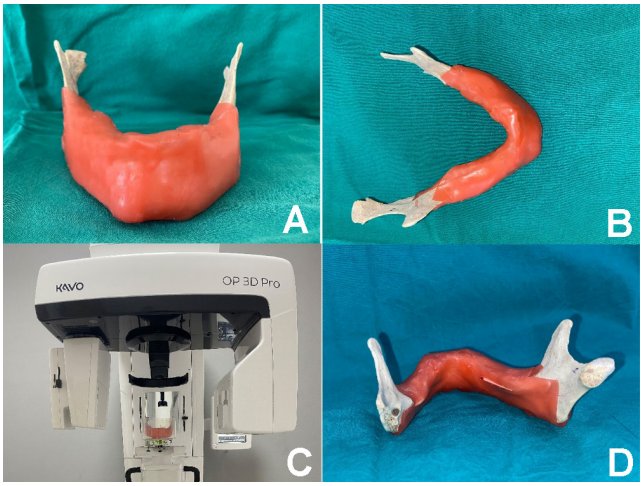

Fig. 1. Study material

A,B. Dry human mandible coated with wax; C. Cone-beam computed tomography (CBCT) procedure; D. Placement of the gutta-percha cone

at 3.2 mA), mA intensity values (FOV field was fixed at 8 × 8) and MAR programs in the on or off state (Table 1). Then, a titanium implant was placed in the same region, and the aforementioned protocol was repeated.

CBCT data evaluation

All CBCT images were evaluated by a radiologist with 4 years of experience. The first axial section at the level where the gutta-percha began to appear in the axial plane towards the mandibular basis was taken as a reference.

In the coronal plane, the measurement of the vertical linear distance was taken as a reference+, specifically the axial section of the first coronal section where the gutta-percha began to appear. All measurements were made on the same axial section, which was equidistant from the axial reference section.

Gutta-percha is a radiopaque material that can be easily identified on CBCT scans. Therefore, we used a gutta-percha cone as a determinant to provide standardization in both coronal and axial sections in our study.[19]

The contrast-to-noise ratio (CNR) was calculated according to Kursun-Cakmak et al. using the following formula (Equation 1)[20]:

$$\mathrm{CNR} = \frac{\left|M_{\mathrm{implant}} - M_{\mathrm{control}}\right|}{\sqrt{SD^2_{\mathrm{implant}} + SD^2_{\mathrm{control}}}} \quad (1)$$

where:
CNR – contrast-to-noise ratio;
M – mean;
SD – standard deviation.

Regions of interest (ROIs) were identified in both the control and implant areas in the first axial section in which the gutta-percha was observed on CBCT scans. A spherical ROI with uniform dimensions was selected (10-mm diameter). This ROI encompassed the entire implant and the surrounding bone tissue area.[21]

The minimum and maximum gray values were determined using the ImageJ histogram tool (https://imagej.net/ij/download.html). These values were then used to calculate the mean (*M*) and standard deviation (*SD*). Histograms were determined using these ROIs. To obtain the minimum and maximum grayscale values used in the determined histograms, the *SD* and *M* values of both the implant ROI and the control ROI were calculated (Fig. 2,3).[21]

Statistical analysis

The statistical analysis was conducted using the IBM SPSS Statistics for Windows software, v. 22.0 (IBM Corp., Armonk, USA). The normal distribution of the groups was determined by the Shapiro–Wilk test and Q–Q plots. As the groups exhibited a normal distribution, an independent *t*-test was used to evaluate the paired groups, and one-way analysis of variance (ANOVA) was employed to evaluate groups of more

Table 1. Cone-beam computed tomography (CBCT) parameters according to different FOV areas, mA intensity values and MAR programs

Protocol No.	FOV	3.2 mA	3.2 mA	3.2 mA	3.2 mA	MAR program
1	13 cm × 15 cm	7	7	7	7	ON
	8 cm × 15 cm	7	7	7	7	
	8 cm × 8 cm	7	7	7	7	
	6 cm × 8 cm	7	7	7	7	
	5 cm × 5 cm	7	7	7	7	
2	13 cm × 15 cm	7	7	7	7	OFF
	8 cm × 15 cm	7	7	7	7	
	8 cm × 8 cm	7	7	7	7	
	6 cm × 8 cm	7	7	7	7	
	5 cm × 5 cm	7	7	7	7	

Protocol No.	FOV	3.2 mA	5 mA	6.3 mA	8 mA	MAR program
3	8 cm × 15 cm	8	8	8	8	ON
	8 cm × 15 cm	8	8	8	8	
	8 cm × 15 cm	8	8	8	8	
	8 cm × 15 cm	8	8	8	8	
4	8 cm × 15 cm	8	8	8	8	OF
	8 cm × 15 cm	8	8	8	8	
	8 cm × 15 cm	8	8	8	8	
	8 cm × 15 cm	8	8	8	8	

FOV – field of view; MAR – metal artifact reduction. Data presented as number (*n*).

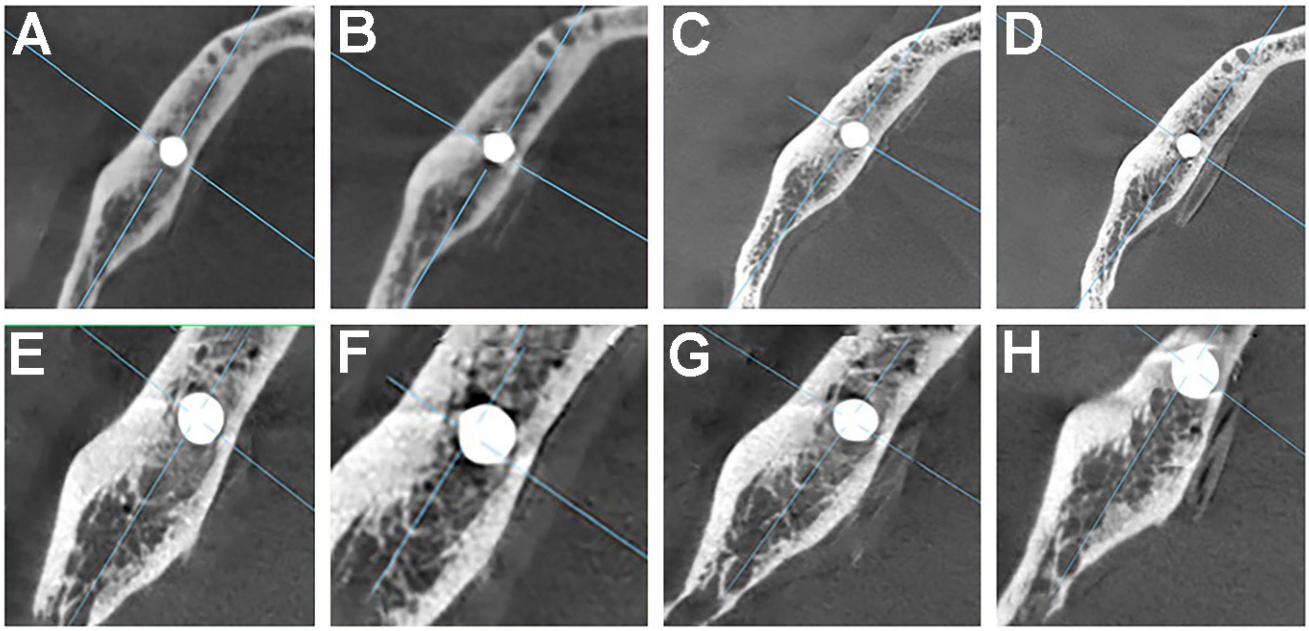

Fig. 2. CBCT sections with different parameters in the axial plane

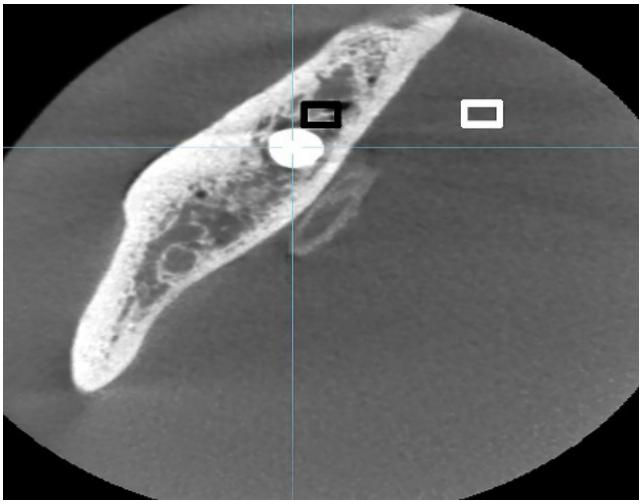

Fig. 3. Axial image representing the regions of interest (ROIs)

than two. The homogeneity of variance in more than 2 groups was determined by the Levene's test. If the variance was homogeneous, Tukey's honestly significant difference (HSD) test was used, and the Games–Howell test was employed as a post hoc test. A p-value <0.05 was considered statistically significant.

The number of artifacts present in the zirconia and titanium implants was quantified using the CNR and the standard deviation within the region of interest (SD_{ROI}) values of the gray areas around the implant. The differences between the 2 implant types with regard to these 2 parameters were evaluated by means of an independent t-test.

One-way ANOVA and post hoc tests were applied to examine the relationship between the CNR and SD_{ROI} values and between the FOV areas and mA values, which represent different parameters of CBCT.

In the independent t-tests, the sample size for each group was 35, with a power of 0.95 and an effect size of 0.8. In one-way ANOVA tests, the total sample size for the FOV areas was 35 (5 FOV area groups, n = 7 per group), and the total sample size for the mA intensity values was 32 (4 groups, n = 8 per group), with a power of 0.95 and an effect size of 0.8.

Results

The zirconia implant generated significantly more artifacts in both parameters than the titanium implant when the MAR program was deactivated (Table 2) ($p < 0.01$). Conversely, no significant difference was observed in either parameter between the zirconia implant and the titanium implant when the MAR program was activated (Table 3) ($p = 0.07$).

For the titanium implants, the post hoc Tukey's test results demonstrated a statistically significant difference between the SD_{ROI} values in the 6 cm × 8 cm and 5 cm × 5 cm FOV area groups (Table 4) ($p < 0.05$).

Table 2. Statistical comparison of the CNR and SD_{IMP} values for both implant types (MAR program deactivated)

Variable	Implant type	n	$M \pm SD$	p-value
CNR	titanium implant	35	1.21 ±0.32	0.000*
	zirconia implant	35	0.62 ±0.39	
SD_{IMP}	titanium implant	35	354.70 ±69.26	0.000*
	zirconia implant	35	696.42 ±48.98	

M – mean; SD – standard deviation; CNR – contrast-to-noise ratio; SD_{IMP} – implant standard deviation. There were statistically significant differences between the CNR and SD_{IMP} parameter groups ($p < 0.05$, independent t-test).

Table 3. Statistical comparison of the CNR and SD_{IMP} values for both implant types (MAR program activated)

Variable	Implant type	*n*	*M* ±*SD*	*p*-value
CNR	titanium implant	35	1.89 ±0.27	0.891
	zirconia implant	35	1.91 ±0.53	
SD_{IMP}	titanium implant	35	283.88 ±67.77	0.445
	zirconia implant	35	304.79 ±79.66	

SD_{ROI} – standard deviation within the region of interest. There were no statistically significant differences between the CNR and SD_{ROI} parameter groups ($p = 0.07$, independent *t*-test).

Table 4. Statistical comparison of the SD_{ROI} values around the titanium implants according to the FOV area and mA groups

Group		*n*	*M* ±*SD*	F	*p*-value
FOV	13 cm × 15 cm	7	393.80 ±44.34	3.618	0.045
	8 cm × 15 cm	7	375.200 ±19.501		
	8 cm × 8 cm	7	341.40 ±86.00		
	6 cm × 8 cm	7	402.43 ±44.47[a]		
	5 cm × 5 cm	7	260.70 ±44.74[b]		
Intensity	8 mA	8	354.85 ±66.23	0.399	0.756
	5 mA	8	383.20 ±42.99		
	3.2 mA	8	368.54 ±44.71		
	6.3 mA	8	323.02 ±111.90		

Different superscript letters show statistical differences between the groups ($p = 0.03$, Tukey's multiple comparison test).

In addition, the results of the post hoc Tukey's test showed a statistically significant difference between CNR values in the 13 cm × 15 cm and 5 cm × 5 cm FOV field groups ($p < 0.05$). However, the differences between the mA groups and CNR values were not statistically significant (Table 5) ($p > 0.05$).

Table 5. Statistical comparison of the CNR values for the titanium implants according to the FOV area and mA groups

Group		*n*	*M* ±*SD*	F	*p*-value
FOV	13 cm × 15 cm	7	1.63 ±0.075[a]	3.788	0.040
	8 cm × 15 cm	7	1.56 ±0.31		
	8 cm × 8 cm	7	1.29 ±0.14		
	6 cm × 8 cm	7	1.08 ±0.40		
	5 cm × 5 cm	7	1.02 ±0.10[b]		
Intensity	8 mA	8	1.25 ±0.24	0.517	0.679
	5 mA	8	1.40 ±0.27		
	3.2 mA	8	1.45 ±0.34		
	6.3 mA	8	1.18 ±0.44		

Different superscript letters show statistical differences between the groups ($p = 0.02$, Tukey's multiple comparison test).

For the zirconia implant, the post hoc Tukey's test revealed a statistically significant difference between the SD_{ROI} values in the 8 cm × 8 cm and 5 cm × 5 cm FOV area groups ($p < 0.05$). However, the differences between the mA groups and SD_{ROI} values were not statistically significant (Table 6) ($p > 0.05$).

Table 6. Statistical comparison of the SD_{ROI} values around the zirconia implants according to the FOV area and mA groups

Group		*n*	*M* ±*SD*	F	*p*-value
FOV	13 cm × 15 cm	7	726.73 ±37.18	3.994	0.034
	8 cm × 15 cm	7	692.20 ±43.82		
	8 cm × 8 cm	7	771.06 ±82.29[a]		
	6 cm × 8 cm	7	663.67 ±36.37		
	5 cm × 5 cm	7	627.80 ±15.13[b]		
Intensity	8 mA	8	727.42 ±66.09	0.634	0.608
	5 mA	8	697.75 ±40.35		
	3.2 mA	8	678.30 ±33.32		
	6.3 mA	8	734.40 ±103.80		

Different superscript letters show statistical differences between the groups ($p = 0.03$, Tukey's multiple comparison test).

Additionally, the results of the post hoc Tukey's test demonstrated a statistically significant difference between the CNR values in the 13 cm × 15 cm and 5 cm × 5 cm FOV area groups as well as between the 8 cm × 15 cm and 5 cm × 5 cm FOV area groups. However, the differences between the mA groups and CNR values were not statistically significant (Table 7) ($p > 0.05$).

Table 7. Statistical comparison of the CNR values for the zirconia implants according to the FOV area and mA groups

Group		*n*	*M* ±*SD*	F	*p*-value
FOV	13 cm × 15 cm	7	1.01 ±0.08[a]	6.671	0.007
	8 cm × 15 cm	7	0.91 ±0.23[a]		
	8 cm × 8 cm	7	0.49 ±0.40		
	6 cm × 8 cm	7	0.62 ±0.23		
	5 cm × 5 cm	7	0.08 ±0.14[b]		
Intensity	8 mA	8	0.70 ±0.38	1.495	0.27
	5 mA	8	0.54 ±0.24		
	3.2 mA	8	0.50 ±0.36		
	6.3 mA	8	0.61 ±0.43		

Different superscript letters show statistical differences between the groups ($p = 0.02$, Tukey's multiple comparison test).

Discussion

The formation of artifacts was evaluated in this study using 2 parameters. The first parameter, the SD_{ROI}, is based on a comparison of the gray levels at the implant and control areas. The second parameter is the CNR. These parameters were determined for an overall estimate of the degree of dark and light areas associated with artifact formation and have been used in previous studies to evaluate artifact formation.[22–25]

Pauwels et al. and Parsa et al. demonstrated the formation of artifacts based on the difference between ROI values of the gray areas in the peri-implant region.[26,27] The authors stated that if, during the CBCT procedure, the *SD* scores of the color values of the gray areas in the relevant

ROI were lower, lower artifact production may occur. The current study observed a reduction in the number of artifacts in regions with lower *SD*s in the gray values. These results are consistent with those previously reported by Pauwels et al. and Parsa et al.[26,27]

Titanium and zirconia are 2 substances with different densities, physical properties and atomic numbers (Z = 22 for titanium and Z = 40 for zirconium). Zirconia exhibits a higher atomic number and density than titanium, which results in a greater propensity for artifact formation compared to titanium.[24]

Demirturk Kocasarac et al. and Sancho-Puchades et al. observed that zirconia implants produced more artifacts than titanium or titanium alloy implants.[28,29] In our study, when the MAR program was not activated, a greater number of artifact products associated with zirconia implants was found, in alignment with the current literature.

The existing literature indicates that the presence of metal artifacts can be minimized by reducing the FOV area and section thickness.[30,31]

The results of our study align with those reported in the literature. As the FOV area increased, the number of artifacts increased, and this rise showed statistically significant differences between some FOV area groups. Conversely, an increase in the mA intensity increased the number of X-ray photons, which reduced the CNR by reducing quantum mottling in the radiograph.[32] Although the increase in the mA intensity decreased the CNR, this difference was not statistically significant.

In our study, it was observed that the MAR program reduced both the CNR and the SD_{ROI}.

Since the evaluation of artifact formation of titanium and zirconia implants of different sizes may have introduced limitations to the study, we used implants of the same size (5.5 mm × 12.5 mm).

A variety of experimental models can be employed to evaluate the production of artifacts around an implant. For example, in the study by Smeets et al., implants were embedded in gelatin and the production of artifacts was investigated.[33] A study by de-Azevedo-Vaz et al. examined the dehiscence around implants where bovine ribs were used for the experimental model, with the implants placed within the bovine ribs.[34] Schulze et al., Benic et al., and Harris et al. evaluated the gray areas around the implant using dental stone and silicone material.[5,35,36] Freire-Maia et al. and Pena de Andrade et al. used a dry human mandible in their study.[37,38]

Similarly, we used a single dry human mandible to standardize the production of artifacts for both implant types. The dry mandible was coated with wax to simulate soft tissue.

Limitations

This study had 2 major limitations. First, it should be noted that this was a cadaveric study. The second major limitation of the described process is that it is only applicable to the mandible. Given the morphological differences, such as bone density and the trabecular structure of the maxilla and mandible, it is uncertain to what extent the results obtained in the mandible represent the maxilla. Additionally, according to the review by Pauwels et al., the CNR may have certain limitations in determining image quality.[39]

Conclusions

Within the limits of the current study, artifact formation in zirconia implants can be reduced by modifying various CBCT parameters, using smaller FOV areas and larger mA values, or by using a MAR program; nevertheless, this problem cannot be solved definitively. However, with the future development of MAR programs for CBCT devices, this issue could be eliminated. The current study provides a potential solution to the artifact problems commonly observed in zirconia implants.

Ethics approval and consent to participate

The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Nuh Naci Yazgan University, Kayseri, Turkey (31.05.2020; decision No. 2021/221).

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 the effects of fluoride varnish containing silver nanoparticles and conventional fluoride varnish on the surface microhardness of tooth enamel

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Abstract

Background. Nano-silver fluoride (NSF) has been introduced to improve enamel lesions. The effective use of varnishes is important in the prevention of dental caries.

Objectives. The study aimed to compare the effect of conventional sodium fluoride varnish with the same varnish containing 1% and 2% silver nanoparticles (AgNP) on the surface microhardness of enamel.

Material and methods. The baseline surface microhardness of 40 premolar teeth was measured using a Vickers microhardness tester. After immersing the samples in a demineralizing agent for 24 h, the microhardness was measured again. In group B, a layer of conventional fluoride varnish was applied to the tooth surfaces using a microbrush with soft bristles, following the manufacturer's instructions. Groups C and D were treated with 1% and 2% NSF varnishes, respectively, while group A received no varnish. Surface microhardness tests were conducted on all specimens, including those previously tested.

Results. The microhardness of the enamel surface increased significantly in all 3 test groups compared to the microhardness after demineralization ($p < 0.05$).

Conclusions. Conventional fluoride varnish and fluoride varnishes containing 1% and 2% AgNP are equally effective in remineralizing initial caries.

Keywords: dental enamel, dental caries, fluorides, silver, varnish

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Introduction

Dental caries is one of the most common chronic diseases that varies in severity among the population.[1] Recent studies have reported an increase in the incidence and prevalence of dental caries in deciduous and permanent teeth.[2] This medical condition is a dynamic process, with intermittent demineralization and remineralization. Repeated exposure to cariogenic challenges result in the formation of incipient enamel lesions that may progress, remain unchanged or remineralize over time.[3]

Prevention is crucial in the context of dental caries, especially in children, given the necessity for high dexterity on the part of the dentist and the potential for general anesthesia, which can result in considerable costs.[1] Additionally, treatments to arrest caries have some advantages, such as minimal discomfort, minimal caregiver education requirements, ease of application, low costs, and non-invasiveness compared to restorative procedures for carious lesions.[4]

Fluoride is one of the materials applied topically in dental offices to prevent lesions. It is available in different forms, including solutions, gels, varnishes, foams, and prophylactic pastes.[5] Among these, dentists tend to prefer 5% fluoride varnish due to its ease of use, fast application, low risk of ingestion, and patient acceptance.[6] Fluoride varnish is a standard remineralizing agent that increases the contact time between the fluoride and the tooth surface and serves as a reservoir for slow fluoride release.[7,8] Fluoride prevents dental caries by inhibiting the dissolution of the mineral content of the tooth by adsorption to the crystalline surfaces, inducing remineralization of the crystalline surfaces by forming a fluorapatite layer that is highly resistant to acid attacks, and inhibiting bacterial metabolism by inhibiting the activity of necessary enzymes.[9] A 5% sodium fluoride varnish contains 226,000 ppm of fluoride and is used to inhibit dental caries.[10]

Several studies have evaluated the incorporation of silver nanoparticles (AgNP) into materials used in dentistry and have shown that these particles can enhance the properties of dental materials. For example, Haghgoo et al. suggested the use of nano-silver fluoride (NSF) under amalgam restorations to reduce microbial counts and prevent recurrent caries.[11] In a study conducted by Nozari et al., NSF was very useful in the remineralization of the enamel of primary teeth.[12] However, Akyildiz and Sönmez reported that NSF was not as effective as sodium fluoride varnish and silver diamine fluoride (SDF) on enamel carious lesions.[13]

Considering the abovementioned discrepancies and the importance of more effective use of varnishes in the prevention of dental caries, this study aimed to compare the effect of conventional sodium fluoride varnish and the same varnish containing 1% and 2% AgNP on the microhardness of the enamel surface.

Material and methods

This in vitro experimental study was conducted in the dental material laboratory of Shahid Beheshti University of Medical Sciences (Tehran, Iran) and the protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (approval No. IR.SBMU.RIDS.REC.1396.486). The study included 40 premolar teeth that had been extracted for orthodontic reasons within the previous 6 months and were free of caries and fissures. The extracted teeth were stored in deionized water containing 0.1% thymol to prevent dehydration and microbial growth until testing.

Before testing, the teeth were cleaned with fluoride-free pumice paste (Nupro Prophylaxis Paste; Dentsply Sirona, Charlotte, USA) and distilled water to remove any calculi, plaque and soft tissue remnants, using a slow-speed handpiece for 10 s. Then, paper stickers, measuring 3 × 3 mm, were cut with the use of a mm-graduated ruler and a sharp scalpel blade, and affixed to the buccal surfaces of the samples. All other areas were covered with anti-acid nail polish (MODA Cosmetics, Instanbul, Turkey) in 2 stages. The teeth were mounted in transparent self-cured acrylic resins (Acropars; Marlic Medical Ind. Co., Tehran, Iran) inside a cylindrical plastic mold, with their buccal windows exposed. Each enamel block was polished to achieve a smooth surface using 1,000- and 1,200-grit silicon carbide abrasive paper (MATADOR GmbH & Co.KG, Remscheid, Germany).

To prepare fluoride varnish containing 1% and 2% AgNP, 40-nm AgNP was added to fluoride varnish in the amount of 1% and 2%, respectively, and manually mixed in a plastic container using a mixer with a plastic head for 1 min to achieve a uniform consistency. Then, the enamel blocks were randomly assigned to 4 groups: group A (no treatment); group B (conventional fluoride varnish); group C (fluoride varnish with 1% AgNP); and group D (fluoride varnish with 2% AgNP).

The enamel blocks were immersed in 15 mL of a demineralizing solution (2.2 mM $CaCl_2$, 2.2 mM NaH_2PO_4 and 0.05 M acetic acid; pH: 4–4.5 adjusted with NaOH and HCl) for 24 h to simulate dental caries. After demineralization, the surface microhardness of all samples was measured using a Vickers hardness tester (Zwick Roell, Worcester, England) with a 50-gr force applied for 10 s. The microhardness of each sample was determined at 3 points within the enamel block window. Finally, the mean value was calculated. After determining the baseline microhardness of each sample, the samples were stored in distilled water until the next stage of the study.

In the next stage, group B's tooth surfaces were covered with a thin layer of conventional fluoride varnish using a small microbrush with soft bristles, according to the manufacturer's instructions. In the same manner,

1% and 2% AgNP-containing fluoride varnishes were applied to the tooth surfaces in groups C and D, respectively. No treatment was administered to group A.

After the varnish dried, the samples were placed in separate containers with distilled water and incubated at 37°C for 24 h. Then, the teeth underwent a pH cycling procedure to simulate the caries process. First, the samples in each group were immersed in a demineralizing solution in separate containers for 3 h, followed by a mild rinse in distilled water. The samples were then immersed in distilled water for 30 min. Next, the samples were immersed in a remineralizing agent (15 mM $CaCl_2$, 0.9 mM $NaHPO_4$ and 0.15 mM KCl; pH: 6.5–7) without sodium fluoride, at 15 mL/tooth. Then, the samples were briefly rinsed in distilled water and immersed in distilled water for 30 min. The 24-hour cycles were repeated for 7 days. The demineralizing and remineralizing solutions were refreshed daily, and all procedures were carried out in an incubator at 37 ±2°C.

At the end of the 7th day, if the remnant layer of varnishes remained after washing, it was removed with a scalpel. The microhardness of the teeth in all 4 groups was reassessed by an operator who was blinded to the groups. The Vickers microhardness tester was used with a 50-gr force for 10 s at 3 points in each sample, and the mean values were calculated.

Statistical analysis

The data was analyzed using the IBM SPSS Statistics for Windows software, v. 22.0 (IBM Corp., Armonk, USA). The mean and standard deviation surface microhardness values in different study groups were calculated before treatment, after the first demineralization cycle, after the application of varnish, and after pH cycling at the end of the 7th day. The normality of data was confirmed using the Shapiro–Wilk test. Analysis of variance (ANOVA) and post hoc Tukey's tests were used to compare the surface microhardness at different intervals in each group and between the groups. The statistical significance level was set at $p < 0.05$.

Results

The present study analyzed 40 extracted human premolar teeth, which were divided into different treatment groups (no treatment, conventional fluoride varnish, fluoride varnish containing 1% AgNP, and fluoride varnish containing 2% AgNP). Table 1 displays the mean and standard deviation values as well as changes in the enamel surface microhardness for each study group at different time intervals.

Vickers microhardness images of the selected samples before and after demineralization are shown in Fig. 1 and Fig. 2.

The study found significant differences in the surface microhardness between the 3 time intervals in the control group ($p < 0.0001$), as confirmed by ANOVA. The results of Tukey's test demonstrated significant differences in the surface microhardness before demineralization, after demineralization and after treatment. However, there was no significant difference in the surface microhardness between 2 intervals, after demineralization and after treatment in the control group ($p = 0.12$). Figure 3 presents the Vickers image of a sample from the control group after the application of the study cycles.

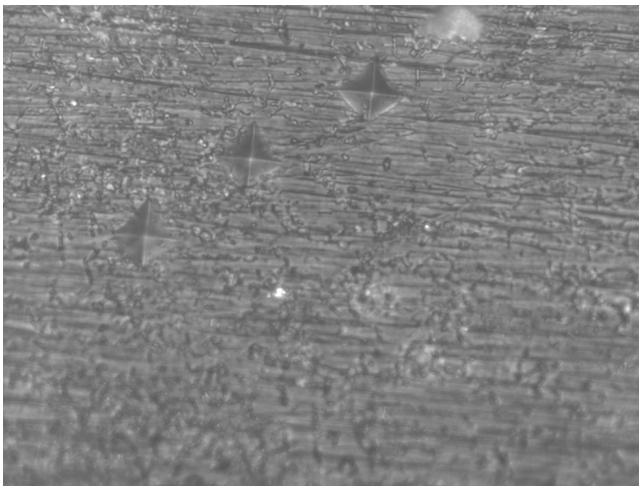

Fig. 1. Selected sample before demineralization (×10; Vickers microhardness tester). The sample shows uniformity

Table 1. Changes in the enamel surface microhardness at different time intervals for each study group

Group	Baseline *M* ±*SD*	After lesion induction *M* ±*SD*	After treatment *M* ±*SD*	*p*-value	Changes between the 2 intervals, after demineralization and after treatment	
					change *M* ±*SD*	*p*-value
Control	340.66 ±14.22	59.38 ±17.6	76.04 ±23.2	<0.0001*	16.66 ±17.53 (↑)	0.12
Conventional fluoride varnish	351.66 ±18.17	48.26 ±19.2	107.5 ±27.6	<0.0001*	59.24 ±24.94 (↑)	<0.0001*
Fluoride varnish with 1% AgNP	355.66 ±26.52	64.5 ±74.9	126.9 ±57.1	<0.0001*	62.47 ±43.53 (↑)	<0.0001*
Fluoride varnish with 2% AgNP	334.99 ±13.3	48.4 ±45.3	106.3 ±52.8	<0.0001*	57.84 ±27.88 (↑)	<0.0001*

M – mean; *SD* – standard deviation; AgNP – silver nanoparticles; * statistically significant ($p < 0.05$).

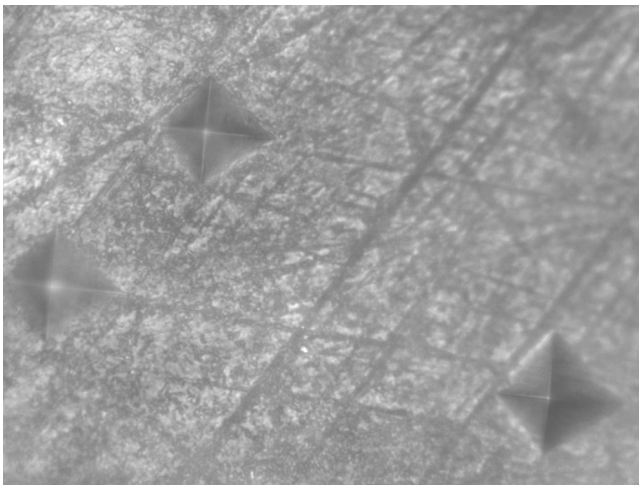

Fig. 2. Selected sample after demineralization (×40; Vickers microhardness tester). The surface of the sample has been partially demineralized compared to its state before demineralization

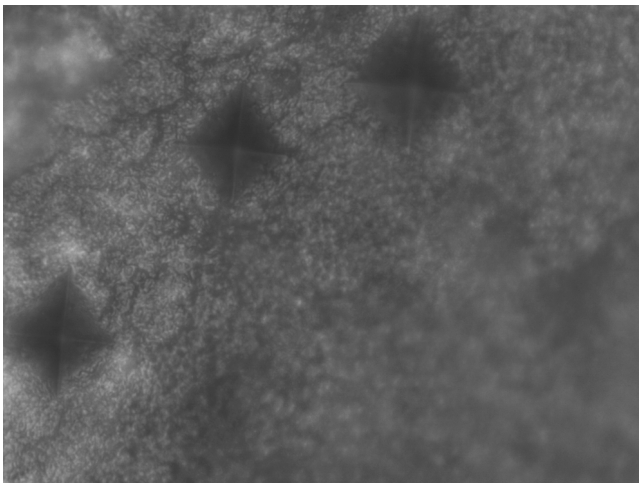

Fig. 3. Sample in the control group after the application of the study cycles (×40; Vickers microhardness tester). Demineralization is visible at the porous surface of the samples

In the conventional fluoride varnish group, significant differences in the surface microhardness were found between the 3 time intervals ($p < 0.0001$), as confirmed by ANOVA. The results of post hoc Tukey's test indicated significant pairwise differences between the 3 time intervals ($p < 0.0001$). Figure 4 presents the Vickers image of one of the samples from this group after treatment.

In the fluoride varnish group with 1% AgNP, ANOVA showed significant differences in the surface microhardness values between the 3 time intervals ($p < 0.0001$). The results of post hoc Tukey's test indicated significant pairwise differences between the 3 time intervals. Figure 5 presents the Vickers image of a sample from this group after treatment.

In the fluoride varnish group with 2% AgNP, ANOVA revealed significant differences in the enamel surface microhardness between the 3 time intervals ($p < 0.0001$). The results of post hoc Tukey's test indicated significant pairwise differences between all 3 time intervals. Figure 6 presents the Vickers image of a sample from this group after treatment.

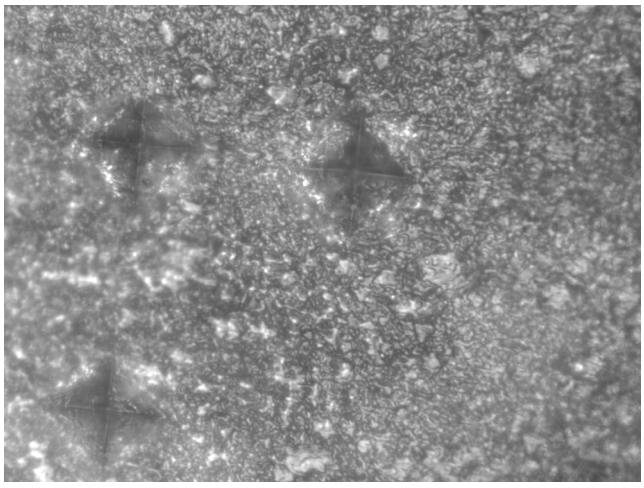

Fig. 4. Selected sample in the conventional fluoride group after treatment (×40; Vickers microhardness tester). The sample exhibits less demineralization and porosity compared to the control group

Fig. 5. Selected sample in the fluoride varnish group with 1% AgNP after treatment (×40; Vickers microhardness tester). The sample exhibits less demineralization and porosity compared to the control group

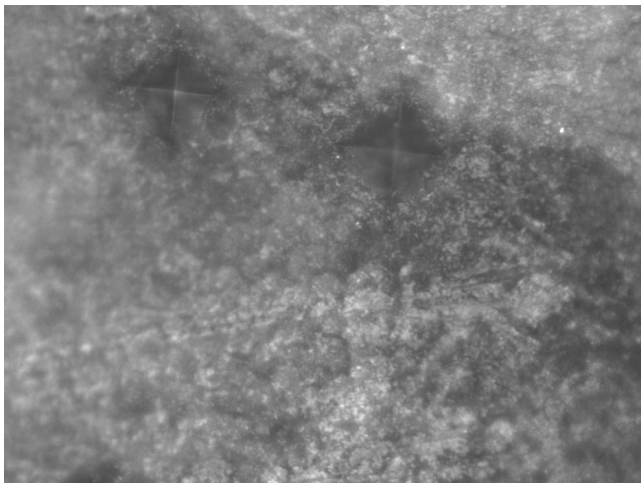

Fig. 6. Selected sample in the fluoride varnish group with 2% AgNP after treatment (×40; Vickers microhardness tester). The sample exhibits less demineralization and porosity compared to the control group

Table 2. Pairwise comparisons of changes in the enamel surface microhardness between the study groups

Group	Control	Conventional fluoride varnish	Fluoride varnish with 1% AgNP	Fluoride varnish with 2% AgNP
Control	–	0.016*	0.008*	0.02*
Conventional fluoride varnish	0.016*	–	0.995	1.000
Fluoride varnish with 1% AgNP	0.008*	0.995	–	0.986
Fluoride varnish with 2% AgNP	0.02*	1.000	0.986	–

Data presented as *p*-value. * statistically significant ($p < 0.05$).

Table 2 presents pairwise comparisons of changes in the enamel surface microhardness between the study groups, along with the relevant *p*-values. The results of ANOVA indicated significant differences in these changes between the 4 study groups ($p = 0.004$), after confirming the normal distribution of data. The results of post hoc Tukey's test revealed significant differences in these changes between the control group and all the other groups. However, no significant differences were found regarding these changes between the 3 study groups.

The evaluation of Vickers images revealed that the severity of demineralization and the porosities formed in the control group were higher than in the other groups.

Discussion

Despite recent advances in orodental care, dental caries remains a significant health problem.[14,15] Research is currently underway to develop higher quality remineralizing agents for carious lesions. One of the new materials that has been introduced for this purpose is AgNP. Therefore, this study aimed to evaluate the effect of incorporating AgNP at 1 and 2 wt% in fluoride varnish on the remineralization of enamel lesions. The enamel surface microhardness was determined in different groups to compare the effects of different varnish products on the remineralization of enamel lesions. The surface microhardness is a reliable index for evaluating fluoride effects and overall tooth mineralization.[16–18]

The 5% fluoride varnish is one of the most effective agents for remineralizing incipient enamel caries.[14,19,20] In order to improve its efficacy, several agents, including calcium phosphate salts and xylitol, have been incorporated into it. Fluoride varnish used in the present study contained 5% sodium fluoride, tricalcium phosphate and xylitol at a fluoride concentration of 22,600 ppm. Rirattanapong et al. demonstrated the effectiveness of fluoride varnishes containing tricalcium phosphate in inhibiting the progression of incipient enamel lesions.[21]

Recently, a study evaluated the effect of adding silver compounds to fluoride for the improvement of enamel lesions. For this purpose, 2 forms of silver particles are available.[22] One form is the silver ion, which is used in commercial SDF solutions and is directly applied to carious lesions. Clinical studies have shown that it is successful in inhibiting and preventing dental caries through 2 mechanisms.[23] First, SDF has a direct antibacterial effect. Second, it reacts with hydroxyapatite and forms fluorapatite.[24] However, a study by Mohammadi and Farahmand Far showed that although there was a decrease in the enamel surface microhardness after the use of SDF solution compared to fluoride varnish, the difference was not significant. Both were equally effective in preventing demineralization of the enamel in anterior primary teeth.[10] Besides, the use of SDF has been associated with certain disadvantages, such as dark discoloration of the teeth, painful lesions that may appear within 48 h and a metallic taste.[24–26]

Another form of silver particles, AgNP, has recently attracted a great deal of attention.[27] These nanoparticles are as effective as the SDF solution and do not cause brown discoloration of teeth. In addition, they can penetrate the bacterial matrix and disrupt some cellular processes, such as DNA transcription, especially in gram-negative bacteria.[22]

In the present study, 1 and 2 wt% of AgNP were added to conventional fluoride varnish to evaluate their effect on the enamel surface microhardness. The use of these nanoparticles in combination with fluoride varnish significantly increased the enamel surface microhardness after demineralization.

Based on the study results, the null hypothesis stating the lack of effect of adding AgNP to fluoride varnish on the enamel surface microhardness was rejected. All 3 fluoride varnish products were equally effective in remineralizing incipient enamel lesions.

Mares-Garcia et al. reported that remineralization with fluoride varnish containing AgNP was more effective than with fluoride varnish without AgNP for treating white spot lesions in trisomy 21 patients.[28] Nozari et al. also found that the enamel surface microhardness was significantly higher after the application of NSF compared to fluoride varnish and nano-hydroxyapatite.[12] However, Akyildiz and Sönmez reported that the enamel surface microhardness was higher after demineralization in the sodium fluoride varnish and SDF groups compared to the fluoride–AgNP group. They concluded that fluoride varnish with AgNP was not as effective as sodium fluoride varnish and SDF in treating enamel carious lesions.[13]

Additionally, in our study, there were no significant differences between fluoride varnishes with and without AgNP. Differences in the results of the studies may be attributed to differences in the structure of the evaluated enamel. For example, Nozari et al. evaluated primary anterior teeth,[12] while Akyildiz and Sönmez[13] and the present study evaluated permanent third molar and premolar teeth, respectively. Primary teeth have more unstructured enamel compared to permanent teeth.[6] Therefore, AgNP can penetrate the enamel structure more efficiently and increase the surface microhardness by precipitating within the lesions.[4,12] It appears that the use of AgNP for the remineralization of enamel lesions in permanent teeth is less effective than in primary teeth due to the higher mineral content of permanent teeth.

We examined the effect of NSF on enamel initial caries by evaluating its impact on the surface microhardness. The treated samples exhibited higher surface microhardness values compared to the control group. This finding is consistent with the results of studies by Teixeira et al. and El-Desouky et al., who showed that NSF was more effective in increasing remineralization after pH cycling than the negative control samples.[29,30]

El-Desouky et al. concluded that NSF and fluoride varnish are equally effective anticariogenic materials in limiting enamel demineralization caused by cariogenic challenges.[30] This is in agreement with our results and proves both NSF and fluoride varnish effective in enhancing remineralization of enamel with no significant differences.

Similarly, Teixeira et al. found no statistically significant difference between a NSF-containing dentifrice and a sodium fluoride dentifrice in preventing demineralization. However, the study did show that sodium fluoride resulted in a lower percentage of microhardness variation.[29] These results can be explained by the different pH cycling protocols used and the repeated application of dentifrice slurries before each pH cycle, which could have accentuated the effects of the materials used.

The results of the present in vitro study may be different when carried out in the presence of the dynamic interactions occurring at the tooth surface in the oral cavity, such as the presence of the biofilm and oral flora, variations in salivary components, individuals eating habits, and oral hygiene practices. In addition, the present study was limited to a period of 7 days, while demineralization and remineralization are long-term processes.

Conclusions

Based on the results of this in vitro study, conventional fluoride varnish and fluoride varnish containing 1 and 2 wt% of AgNP are equally effective in remineralizing initial caries. However, the results of this study are based solely on surface microhardness readings and need to be clinically validated.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (approval No. IR.SBMU.RIDS.REC.1396.486).

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 different surface roughening treatment on polyether ether ketone and acrylic resin bonding: A pilot study

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

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Abstract

Background. As polyether ether ketone (PEEK) is a relatively new material in dentistry, its bonding properties with regard to dental acrylic base materials are not fully known. To ensure the long-term success of removable dentures with a PEEK framework, the base materials must be well bonded to each other.

Objectives. The study aimed to investigate the effects of different kinds of surface roughening treatment on PEEK and acrylic resin bonding.

Material and methods. Eighty PEEK specimens ($N = 80$) were randomly divided into 5 groups ($n = 16$ per group) and subjected to various surface roughening treatment (control, grinding, sandblasting, tribochemical silica coating (CoJet), and sulfuric acid etching). Heat-polymerized acrylic resin was applied to the treated surfaces of the PEEK specimens. The shear bond strength (SBS) test, environmental scanning electron microscopy (ESEM) analysis and three-dimensional (3D) surface topography analysis were performed. The statistical analysis of the data was conducted using the analysis of variance (ANOVA) and Tukey's multiple comparison test.

Results. The one-way ANOVA showed significant differences in the SBS values between the groups ($p = 0.001$). Sandblasting, tribochemical silica coating and sulfuric acid etching resulted in high SBS values ($p = 0.001$). The highest SBS values were observed in the sulfuric acid etching group (8.83 ±3.63 MPa), while the lowest SBS values were observed in the control group (3.33 ±2.50 MPa).

Conclusions. The additional roughening treatment applied to the PEEK surface increases the bond strength with heat-polymerized acrylic resin.

Keywords: surface morphology, sulfuric acid, CoJet, polyether ether ketone, sandblasting

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Introduction

Polyether ether ketone (PEEK) is a high-performance semicrystalline thermoplastic that belongs to the polyaryl ether ketone (PAEK) family. It consists of a triple aromatic ring unit bonded with 2 ether groups and a carbonyl group.[1] Polyether ether ketone is stable against almost all organic and inorganic chemicals, has a high melting point, high hardness, and good dimensional stability. It is also easy to process.[2] In addition to these properties, the polymer shows superior properties, such as high fracture strength and low water absorption.[3] Due to its mechanical characteristics, such as excellent electrical insulation, it has been used in many sectors, including aviation, automotive industry, electronics, and medical equipment production.[4,5] Its application in the medical field has increased since the 1990s with the use of high-performance thermoplastic polymers for implants and metal components, particularly in orthopedic and trauma cases.[6–8] Polyether ether ketone is compatible with all imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI),[9] and its radiolucency enables the examination, diagnosis and treatment of clinical conditions without the need for dismantling or changing the framework.[10] In dental treatment, PEEK has been used as an implant material due to its near-bone modulus of elasticity.[11] Additionally, it has been used in the production of temporary abutments, bars for implant-supported prostheses, as a framework material in fixed dentures, and for major connectors and clasps in removable dentures.[12–14] Polyether ether ketone can be also used as a denture base material in complete dentures[15] and implant-supported overdentures.[16] With a wide range of applications in terms of prosthetics, PEEK is a promising material for the future due to its advantages, including lightness, low probability of corrosion, low fatigue, low plaque affinity, and high biocompatibility. It is also an alternative to metal-supported systems.[12] Since PEEK-related allergy and hypersensitivity cases have not been observed,[17] the material can be used as an alternative to titanium (Ti) and cobalt-chromium (Co-Cr). It may be preferred as a major connector and base material in the production of removable dentures, especially for patients with metal allergies.

Notwithstanding the abovementioned advantages, it is recommended to coat the material with an esthetic layer due to its grayish-brown or opaque color. If used as a base or major connector material in removable dentures, it should form a strong bond with acrylic resin. The chemical aromatic structure of PEEK, along with ketone and other components, provides low bond strength. Therefore, surface treatment, including acidification with acids such as sulfuric acid,[18] piranha solution (a mixture of hydrogen peroxide and sulfuric acid)[19] and hydrofluoric acid,[10] and processes such as plasma or laser application and sandblasting may be required to achieve a better bond.[20,21]

However, the bonding mechanisms are changing and are still not fully understood. Data on the bonding of PEEK to dental materials is insufficient. Although the conducted research investigates PEEK and composite bonding, there are not enough studies on PEEK–acrylic resin bonding. Acrylic resin is used as a repair and dental base material in removable dentures.[22] It can be polymerized in different ways, using heat, autopolymerization, light, and microwave.[23] When PEEK is used as a component of a dental prosthesis, it must be firmly fixed to acrylic resin. A strong bond between PEEK and acrylic resin significantly reduces the possibility of denture fractures.[24] The shear bond strength (SBS) test is a commonly used mechanical test for evaluating the performance and bonding properties of adhesive systems in a laboratory environment.[25] In addition to mechanical tests, scanning electron microscopes (SEMs) and three-dimensional (3D) optical profilometers are used to examine changes on the surface of the material and the surface topography. Environmental scanning electron microscopy (ESEM) analysis is a method used to examine the natural states and microscopic properties of materials without the need for any coating on the surface of the material.[26]

Polyether ether ketone is also used as a framework material, so its compatibility with prosthetic materials is of great importance. Improving bonding between PEEK and acrylic resin positively affects the long-term use of PEEK framework prostheses.

The present study aims to evaluate the effects of different kinds of surface roughening treatment on bonding between PEEK and acrylic resin. The null hypothesis of the study is that all kinds of surface treatment applied to the material will increase the PEEK–acrylic resin bond. The other hypothesis is that 98% sulfuric acid etching will result in the highest SBS values.

Material and methods

Specimen preparation

The power analysis was carried out to obtain the highest power level with the smallest sample size, using the G*Power software program (v. 3.0.10; https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower). The analysis revealed that at least 16 specimens were required to achieve the highest power level (power = 80, $\alpha = 0.05$). A total of 80 specimens ($N = 80$) were used in this study. The specimens were milled using a computer-aided design/computer-aided manufacturing (CAD/CAM) unit from PEEK blocks (CopraPEEK; Whitepeaks Dental Solutions, Essen, Germany), provided by the manufacturer in the form of cylinders

measuring 10 mm in diameter and 2 mm in height. After verifying the compatibility of the obtained specimens with the initial dimensions, the surfaces of the specimens were ground with P600 and P800 grit silicon carbide paper (English Abrasives & Chemicals Ltd., London, UK) for 60 s, and polished with a fine pumice stone (Ernst Hinrichs Dental, Goslar, Germany) and Jiffy™ goat hair brushes (Ultradent Products, Inc., South Jordan, USA) for 60 s in an automatic polishing machine (PM Super, series 2300; Reco Dental, Wiesbaden, Germany) with a vertical force of 25 N to produce a standard surface. Then, the specimens were cleaned in an ultrasonic machine (CD-4800; Jeken, Dongguan, China) for 10 min. After the polishing process, they were stored in distilled water at 4°C until used in the surface roughening procedures.

Surface treatment and imagining

The obtained specimens were randomly divided into 5 groups (n = 16 per group), and each specimen was numbered. The groups were as follows:

Control group: no surface treatment was applied to the specimens;

Grinding group: grinding was performed under water cooling with cylindrical diamond burs (837LF.FG.014, 27–76 µm; Hager & Meisinger, Neuss, Germany) and a multiplier handpiece (a contra-angle handpiece up to 160,000 rpm, Synea Vision TK-100L; W&H, Bürmoss, Austria), using an average finger pressure of approx. 1 N for 10 s. A new bur was used for each specimen to ensure standardization;

Sandblasting group: the surfaces of the specimens were sandblasted with 50-micrometer Al_2O_3 particles in various directions, at a distance of 10 mm, for 15 s, under a pressure of 4 bars, using the Airsonic® Mini Sandblaster (Hager & Werken, Duisburg, Germany). After sandblasting, the surfaces were washed for 60 s and dried;

Tribochemical silica coating (CoJet) group: the surfaces of the specimens were sandblasted with 30-micrometer silanized Al_2O_3 particles (CoJet™ Sand; 3M Deutschland, Neuss, Germany) in various directions, at a distance of 10 mm, for 15 s, under a pressure of 2.8 bars, using a pencil-point intraoral sandblasting device (CoJet Prep; 3M Deutschland, Seefeld, Germany). No washing was applied to the surfaces of the specimens to not disrupt the silanization formed after the applied process;

Sulfuric acid etching group: the surfaces of the specimens were treated with 98% sulfuric acid (Fluka buffer solution; Honeywell Deutschland Holding, Offenbach, Germany) for 60 s at room temperature. After the treatment, the surfaces were washed for 60 s and dried.

After the surface roughening procedures were completed, the ESEM and 3D optical profilometry images of randomly selected specimens were taken for each group. The surface imaging was performed using an ESEM (Quanta™ 250 FEG; FEI Company, Hillsboro, USA) without any coating applied to the surfaces of the specimens. The images were recorded at ×3,000 magnification. After the ESEM analysis, the surface topography of the specimens was analyzed using a 3D optical profilometer device (Contour GT-K 3D; Bruker, Mannheim, Germany).

Shear bond strength test

After the surface imaging procedures, the preparation of the specimen surfaces for the SBS test was initiated. All specimens were embedded in cylindrical, transparent, auto-polymerized acrylic resin blocks (Integra; BG Dental, Ankara, Turkey), 25 mm × 20 mm in size, with the treated surfaces exposed for placement in the test device. Afterward, metal molds (thickness: 2 mm; diameter: 6 mm) were placed in the center of the exposed surfaces, and acrylic resin (Meliodent HC; Heraeus Kulzer, Newbury, UK) was inserted through these spaces and heat-polymerized according to the manufacturer's instructions. The polymerized specimens were placed in a special SBS mold. Force was then applied to the PEEK–acrylic resin junction point at a crosshead speed of 0.5 mm/min in the shear mode of the universal testing machine (2519-106; Instron, Norwood, USA). The SBS values obtained in newtons were converted to megapascals.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows software, v. 20.0 (IBM Corp., Armonk, USA). The Kolmogorov–Smirnov test for data distribution normality and the analysis of variance (ANOVA) were conducted. Tukey's multiple comparison test was used for intergroup comparisons.

Results

SBS test results

The ANOVA revealed that different surface treatment applied to the PEEK specimens significantly affected the bond strength of PEEK with acrylic resin (p = 0.001). The highest SBS values were observed in the sulfuric acid etching group (8.83 ±3.63 MPa), while the lowest SBS values were observed in the control group (3.33 ±2.50 MPa). Based on the results of Tukey's multiple comparison test, there were no statistically significant differences between the sandblasting, CoJet and sulfuric acid etching groups ($p > 0.05$). However, these groups showed a statistically significant difference when compared to the control and grinding groups ($p < 0.05$). The SBS values for each group are shown in Table 1 and Fig. 1.

Table 1. Shear bond strength (SBS) values for all groups tested

Group	Number of specimens	SBS [MPa]		
		M ±*SD*	min	max
Control	16	3.33 ±2.50[a]	1.99	4.17
Grinding	16	3.95 ±1.36[a]	2.72	4.66
Sandblasting	16	8.81 ±4.26[b]	6.54	11.08
Tribochemical silica coating (CoJet)	16	8.76 ±3.34[b]	6.97	10.54
Sulfuric acid etching	16	8.83 ±3.63[b]	6.89	10.96

M – mean; *SD* – standard deviation; min – minimum; max – maximum. Different uppercase letters show statistical differences between the groups according to Tukey's multiple comparison test.

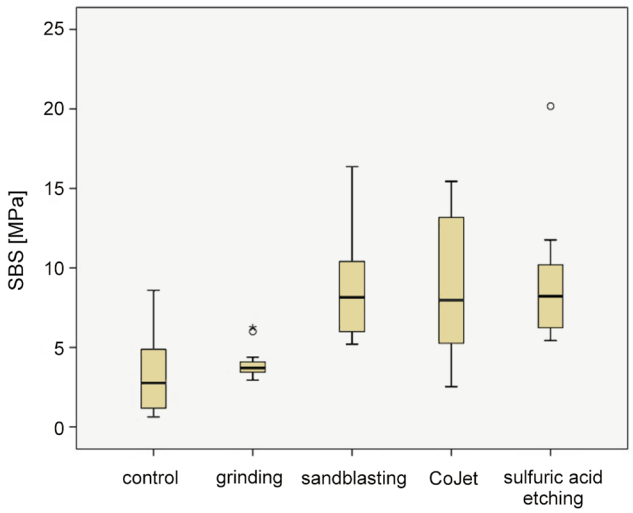

Fig. 1. Box plot of the shear bond strength (SBS) test results

ESEM results

Based on the ESEM examination of the specimens at ×3,000 magnification, it was observed that even though the surface of the specimens in the control group was smooth, it had hollows and micro gaps in some areas. The specimens in the grinding group showed a similar image to the control group despite significant traces of burs on the entire surface. The images of the sandblasting and CoJet group specimens were similar, and the surface structure varied with regard to the specimens in the control group. The applied sands covered the entire surface and created an intense and complex texture. In contrast, the sulfuric acid-treated specimens had a smoother surface covered with a thin layer of scarce micro gaps as compared to the control group (Fig. 2A–E).

3D profilometry results

Upon the examination of the 3D profilometry images, rough areas were observed on the entire surfaces of the control and grinding group specimens. These areas were peripheral rather than central in the sulfuric acid etching group. The surfaces in the sandblasting and CoJet groups were similar and had more dense areas (Fig. 3A–E).

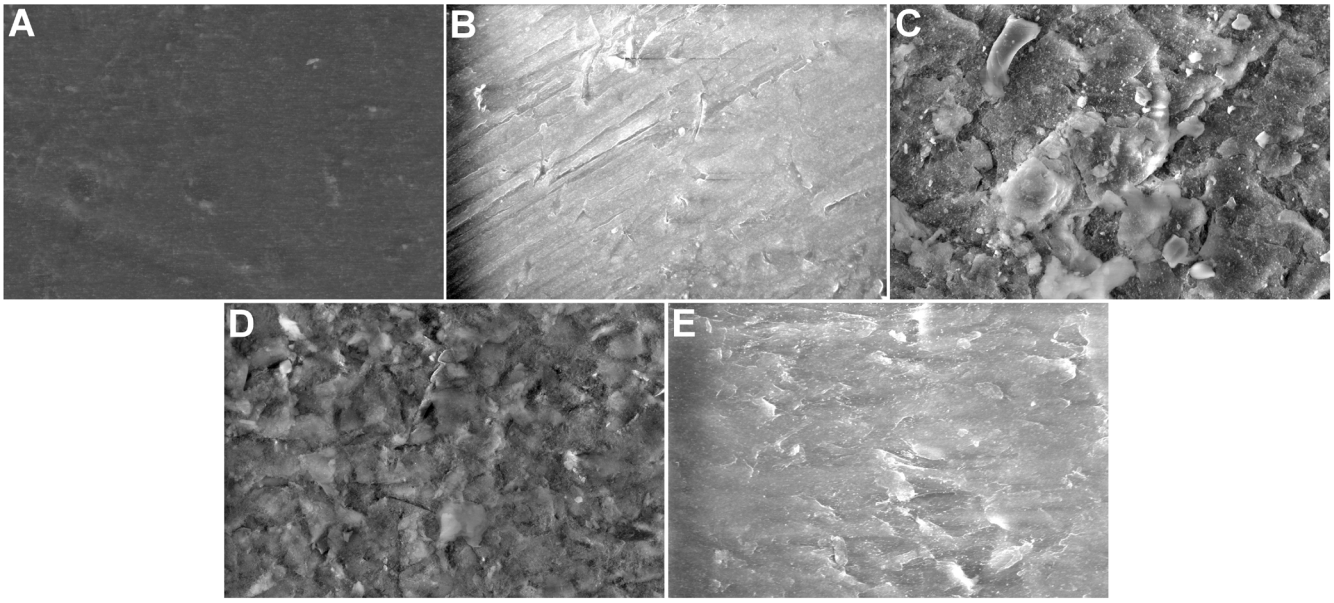

Fig. 2. Environmental scanning electron microscopy (ESEM) images of the specimens at ×3,000 magnification

A – control group; B – grinding group; C – sandblasting group; D – tribochemical silica coating (CoJet) group; E – sulfuric acid etching group.

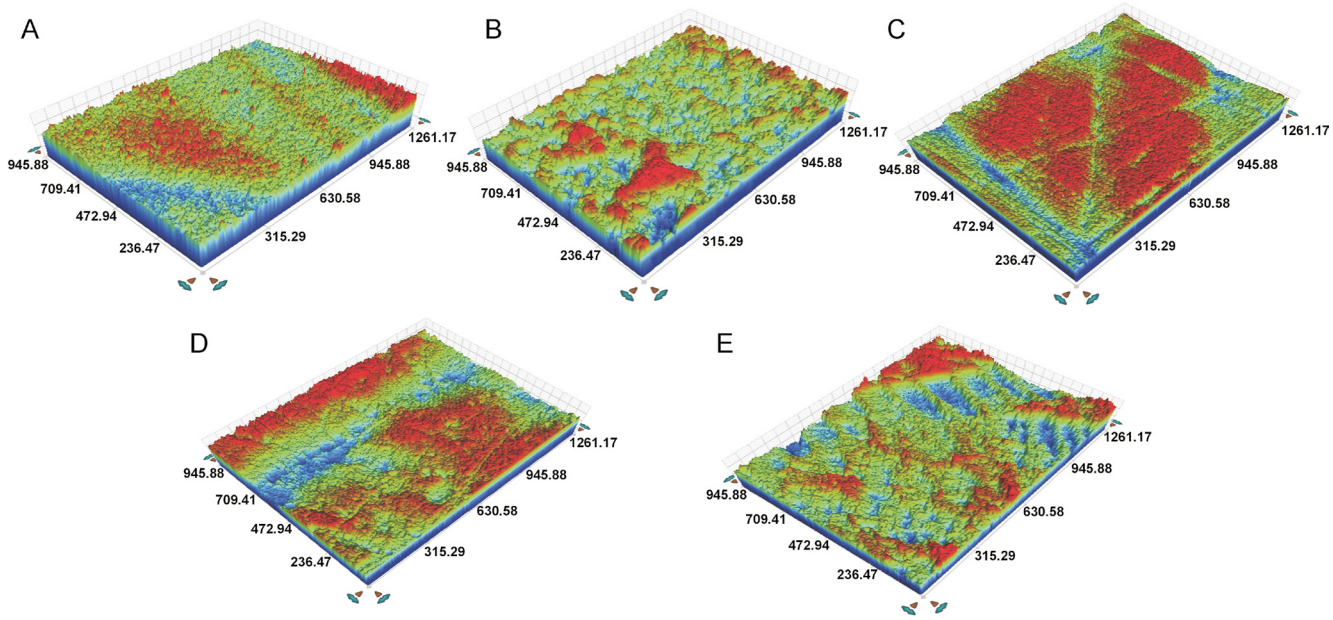

Fig. 3. Three-dimensional (3D) surface topography images of the specimens

A – control group; B – grinding group; C – sandblasting group; D – tribochemical silica coating (CoJet) group; E – sulfuric acid etching group. The presented values are provided in micrometers.

Discussion

This study aimed to investigate the effects of different surface roughening methods on PEEK–acrylic resin bonding. The results showed that while sandblasting, CoJet and sulfuric acid etching increased the SBS values of the materials as compared to the control group, the null hypothesis was rejected, since the grinding process did not show a significant effect. However, the highest SBS values were observed in the sulfuric acid etching group, supporting the second hypothesis of the study.

Although PEEK is used in many different areas of dental treatment, it can also be used as an alternative base material in removable partial dentures due to its positive properties, such as light weight, no metal content and the lack of allergic responses.[27] When used as a base material or a major connector, it should form a strong bond with the acrylic resin it will be paired with. The surface roughening processes play an essential role in enhancing the bonding by creating a rough area on the material surface.[28] In this study, different treatment types were used to roughen the surface of the PEEK material. Studies have reported that 98% sulfuric acid etching creates a highly porous and permeable PEEK surface, which is effective for bonding.[10,21] Some studies indicate that sandblasting is an effective and easily applicable method that enhances bonding by changing the surface morphology of PEEK–composite resin.[29] In addition, the tribochemical silica coating process was reported to improve bonding between PEEK and veneer composites.[19] Based on the available literature, this study used sulfuric acid etching, sandblasting and tribochemical silica coating as surface roughening procedures, as well as the grinding process, which provides micromechanical retention.[30–32]

Studies on the clinical properties of PEEK, a new material used in dental treatment, have recently begun. In addition to research aimed at increasing the bond strength of the material, studies have focused on PEEK–composite resin bonding.[10,18,19,33–35] However, there are few studies on PEEK–acrylic resin bonding. In their study, Kurahashi et al. examined PEEK and auto-polymerized acrylic resin bonding, and reported that the highest bond strength values were observed when the Rocatec treatment was applied in combination with a ceramic primer (Clearfil™ Ceramic Primer Plus; Kuraray Noritake, Tokyo, Japan).[24] In the same study, it was reported that the sandblasting process with 50-micrometer Al_2O_3 particles increased the SBS values as compared to the control group, where no treatment was applied.[24] Similarly, in the present study, the sandblasting process with 50-micrometer Al_2O_3 particles significantly increased the SBS values as compared to the control group ($p = 0.001$). The formation of a layer on the material surface as a result of sandblasting made it ideal for micromechanical retention and may be considered a reason for this situation. According to the results of the study, the CoJet application significantly increased the SBS values as compared to the control group ($p = 0.001$). The absence of a statistically significant difference between sandblasting and the CoJet application ($p > 0.05$) suggests that silica particles were not effective in bonding, and that the CoJet group bound to PEEK specimens through micromechanical retention, similar to the sandblasting group. Additionally, the application of 98% sulfuric acid significantly increased the SBS values as compared to the control group ($p = 0.001$). The possible reason for this situation is that 98% sulfuric acid may have penetrated

into PEEK, creating fibrous micromechanical retention[35] and acting as a solvent on the PEEK surface, thereby increasing the bonding.[36] The ESEM and 3D profilometer images taken for the specimens also support these assumptions. It was observed that changes on the surfaces treated with sandblasting, CoJet and sulfuric acid etching made the bonding more ideal as compared to the surfaces of the control group specimens. The SBS values obtained from the grinding process carried out with burs were similar to those of the control group, suggesting that the grinding process does not significantly affect the PEEK material. Studies on the acrylic resin–metal framework have shown that mechanical pretreatments (sandblasting and laser irradiation) increase the SBS results as compared to the no-treatment groups.[37,38] It was reported that combined methods applied together with adhesive agents (the primer) further increase these values.[38] The values obtained in the present study indicate that surface treatment improves PEEK–acrylic resin bonding. The values were close to those of metal–acrylic resin bonding. Thus, surface treatment is an effective method to achieve the long-term clinical success of PEEK framework dentures.

Limitations

One of the limitations of this study was the evaluation of PEEK–acrylic resin bonding without thermal cycling. Additionally, there could have been more kinds of surface treatment applied in different combinations, and thus more study groups.

Conclusions

Within the limitations of this study, it was concluded that sandblasting, tribochemical silica coating (CoJet) and the 98% sulfuric acid application significantly increased PEEK and heat-polymerized acrylic resin bonding, while the grinding process did not cause any changes. Sandblasting, CoJet and 98% sulfuric acid etching can be safely used to increase bonding between PEEK and acrylic resin, especially in the PEEK frameworks used in removable partial dentures. This will positively affect the durability and efficacy of PEEK-containing removable dentures for patient use.

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

Screw-retrievable cement-retained implant restorations: A scoping review of fracture strength and clinical performance

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

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Conflict of interest
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Abstract

Background. The screw-retrievable cement-retained (SRCR) design combines the benefits of both screw- and cement-retained implant-supported restorations. This concept has sparked interest in implant dentistry. However, there is a lack of research on fracture behaviors and clinical performance of such restorations.

Objectives. The aim of the present article was to review the current literature on the fracture loads and fracture modes of SRCR implant restorations – in vitro studies, and also studies demonstrating the clinical performance of such design.

Material and methods. A literature search was conducted from January 2000 to June 2022, using 6 databases to identify studies on fracture load and clinical performance that fulfilled the eligibility criteria. Thirty-eight studies met the inclusion criteria (22 in vitro and16 in vivo). The in vivo studies comprised case reports/series/letters (9), clinical techniques (2), retrospective/prospective studies (3), and randomized controlled trials (RCTs) (2).

Results. The reviewed articles reported the effects of the SRCR design on the fracture risk if screw access channels were filled or unfilled, with regard to their diameter, and the preparation before or after glazing. The effect of the type of material used in the construction on the fracture modes SRCR restorations was also reported. The long-term clinical data was mainly retrospective and referred to metal–ceramic constructions. Limited long-term clinical data was available for all-ceramic materials and high-performance polymers (HPPs).

Conclusions. Screw-retrievable cement-retained implant restorations appear to have potential in the monolithic design. If the SRCR construction is metal–ceramic or made of a veneered material, special design and abutment selection should be considered. High-performance polymers may be recommended as a substitute for posterior implant restoration.

Keywords: cement-retained, fracture load, screw-retained, screw-retrievable, monolithic screw hole implant

Introduction

The quest for optimal implant restoration with a high success and survival rate has grown by leaps and bounds over the past 5 decades.[1,2] Aside from osseointegration, the form of retention between the crown, the abutment and the implant fixture has the greatest impact on the predictability of the success and survival rate of implant therapy.[3,4] Classically, this type of connection for implant-supported fixed prostheses can be either screw- or cement-retained. The advantages of the cement-retained approach are the passive fit, simple laboratory constructions and favorable esthetics, as the screw access channels traversing the implant crown can be avoided.[5] Despite these benefits, it is well-established that cement-retained restorations are irretrievable and the removal of excess cement can be difficult, possibly resulting in peri-implantitis.[4] Furthermore, in the event of technical issues caused by screw loosening, the abutment in a cement-retained restoration is not accessible and may cause damage to the prosthesis if drilling is needed on the intact crown.[4] Managing complications is less complicated with screw-retained restorations, since they are retrievable for easier maintenance. They also eliminate biological complications caused by the inherently risky cementation process.[6] However, inferior esthetics, more complex laboratory procedures and the lack of passive fit, which may create mechanical strain on the prosthesis, are the main limitations of screw-retained restorations as compared to cemented restorations.[4,7]

To address these limitations and features of implant restoration, the combination of cement- and screw-retained retention has been introduced in the form of screw-retrievable cement-retained (SRCR) restorations. This combination approach eliminates the risk of excess subgingival cement, as the components are cemented extraorally.[8–10] The design also enables the cement layer to act as an interface for the distribution of forces, while the screw access channels facilitate retrieval.[11,12] Furthermore, the cost of fabrication is substantially reduced when the superstructure is connected to prefabricated titanium (Ti) by using luting cement instead of a cast high noble abutment for screw-retained restorations.[13–15] However, the presence of screw access channels itself may interrupt the structural ceramic continuity and interfere with the occlusal morphology, thereby negatively affecting the fracture resistance and longevity of the prostheses.[11,16]

To improve the mechanical and physical properties of SRCR restorations, a few studies have recommended a protocol for their preparation, size, and the filling material of the screw access channels.[17,18] These should be prepared in the blue phase prior to crystallization and glazing to avoid microcracks.[19] In addition, preparation with high-speed burs after zirconia sintering should be avoided to prevent cracks within the restoration.[20] A screw diameter of less than 1 mm and not exceeding half of the occlusal area is also recommended.[17] Filling the screw access with inlay ceramic or bulk-fill composite should be considered to minimize wear and polymerization shrinkage in SRCR implant restoration.[21,22] The location of the screw access channel appears to not affect the fracture risk of SRCR restorations, a finding that warrants further investigation.[23]

Besides optimizing the design of the access channels, the selection of appropriate implant restoration materials and methods may also contribute to the durability of the SRCR design. A variety of computer-aided manufacturing (CAM) materials, including zirconia, lithium disilicate, high-performance polymers (HPPs), and block composite resins, are used to construct SRCR restorations. These may be fabricated as monolithic or veneered constructions, or with predesigned screw access channels (Fig. 1).[8,24,25] Zirconia and lithium disilicate are usually preferred because of their excellent esthetics and high strength.[16,23] However, these materials are often unyielding and prone to excessive occlusal loading, resulting in the chipping and fracture of implant-retained prostheses due to the lack of proprioceptive feedback from periodontal ligaments.[25,26] Furthermore, the wear of the opposing natural dentition caused by ceramics has initiated the manufacturing of implant restorations utilizing HPPs.[25,27] High-performance polymers have a lower elastic modulus than ceramics, more like human bone, and are believed to have a shock-absorbing effect within the implant prosthesis complex.[24,26] Additionally, the low elastic modulus of HPPs has been shown to lessen the pressure on the implant, hence reducing peri-implant bone resorption.[25,28] However, the fracture strength and clinical performance of this material in the SRCR design have been questioned. Poor prognoses have been recorded for the restorations designed as a hybrid or veneered with a lower-strength material.[29,30] Therefore, it is critical to understand and screen relevant literature on the types of designs and materials that have an optimum mechanical strength, which would enhance SRCR performance.[26,30,31]

To that end, this scoping review is structured in 3 parts to evaluate the concept of SRCR restorations. Firstly, a summary is provided of the various designs of screw access channels and to what extent these may affect the fracture resistance of SRCR restorations. Secondly, the various types of materials from which SRCR restorations are fabricated are described, including metal–ceramics, all-ceramics and HPPs, and how these materials affect the fracture mode and loading of SRCR restorations. Finally, the clinical performance of SRCR restorations is reviewed, and the implications of this retention system for the long-term success of implant prostheses are discussed.

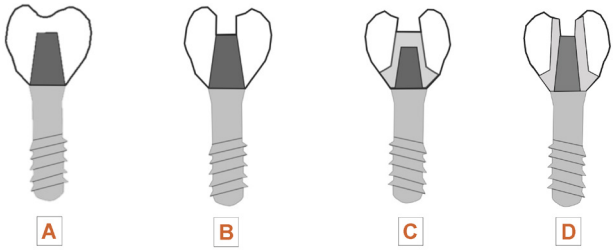

Fig. 1. Conventional cement-retained implant-supported prosthesis (A), monolithic screw-retrievable cement-retained (SRCR) restoration (B), veneered type SRCR restoration (C), and veneered type SRCR restoration with a predesigned zirconia wall (D)

Material and methods

Search strategy

The PICO framework (P = patient problem/population, I = Intervention, C = Comparison, O = Outcome) was used for this review. The research question to be answered was: In cases where implant-supported prostheses are used, do SRCR restorations have a higher mechanical strength and better clinical performance than conventional cement- or screw-retained restorations?

Scopus, Google Scholar, PubMed, SpringerLink, ClinicalKey, and the Web of Science (WOS) were used to search for relevant literature from January 2000 to March 2022. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was used in this study.[32]

A manual search of the reference lists for all full-text publications from the following journals was also conducted: "Journal of Prosthetic Dentistry"; "Journal of Oral Implantology"; "European Journal of Oral Implantology"; Journal of Osseointegration"; "International Journal of Oral and Maxillofacial Implants"; "International Journal of Prosthodontics"; "Clinical Implant Dentistry and Related Research"; and "Clinical Oral Implant Research". The following search terms were used: "screw retrievable"; "implant hybrid crown"; "monolithic screw channel implant"; "layered screw channel implant"; "screw cement-retained"; "screw access channel implant crown"; "combination screw cement implant crown"; and "screw retained access channel".

Inclusion and exclusion criteria

Studies were included if the following criteria were met:
– articles in English;
– articles related to the fracture load and mode of the SRCR concept;
– clinical studies using prospective or retrospective designs to evaluate clinical outcomes; and
– clinical case series, technical reports and case reports with at least 12 months of follow-up.

The exclusion criteria were:
– studies related to implant surgery; and
– articles that referred only to cement-retained implant-supported restorations.

Study selection

A total of 457 articles were found in the electronic databases from the initial search: 120 in WOS, 125 in PubMed, 93 in Scopus, 43 in SpringerLink, 37 in Google Scholar, 32 in ClinicalKey, and 7 by hand searching. After initial screening, 263 articles were removed due to duplication or for reasons. Only 71 publications remained after 87 were eliminated based on the title and abstract. Twenty-two in vitro and 16 in vivo full-text publications met the eligibility criteria after a thorough review by two independent reviewers (Fig. 2).

Data extraction and statistical analysis

A meta-analysis was not possible due to the small number of studies included and the heterogeneity of the study designs. Consequently, a descriptive scoping review was used to summarize the influence of the various designs and materials used in SRCR restorations on fracture loads, fracture modes, and also on the clinical performance of SRCR restorations.

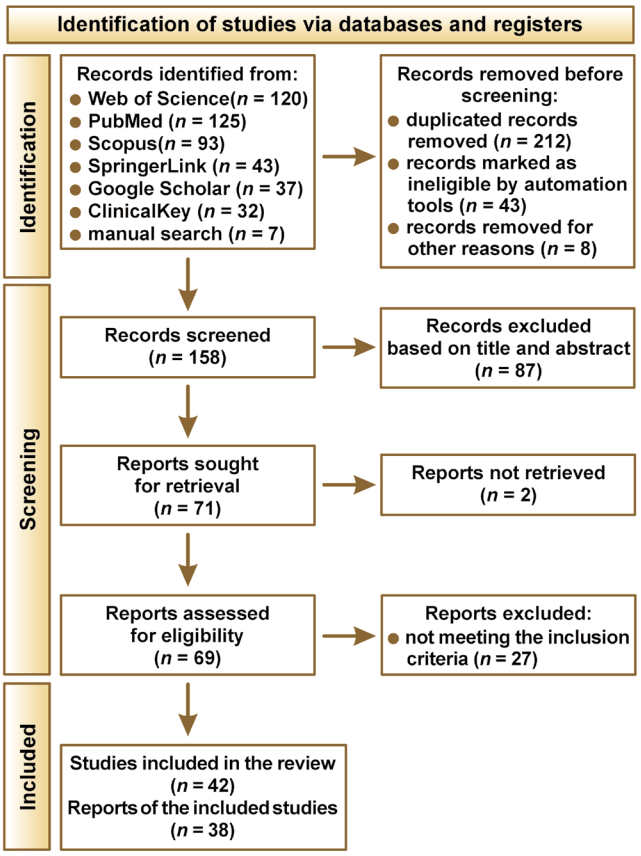

Fig. 2. Flow chart of the study

Results

Influence of various SRCR designs on fracture resistance

The design of the SRCR restorations has been shown in vitro to affect their fracture resistance, and the results are presented in Table 1.[17,19,20,33,34] The most important factor that increases the chipping risk and compromises fracture resistance is the design of the screw access channel.[34] The filled or unfilled screw access channel,[35] its diameter,[17,36] if the preparation was performed before or after sintering,[19,20] and if the screw access channel was specially designed or not[34] were assessed for possible significant effects on the risk of chipping and the fracture resistance values. In an earlier study by Karl et al., more chipping fractures were recorded in cases with the unfilled occlusal screw access channels of screw-retained restorations during dynamic loading.[35] Although in clinical practice, the screw access hole is never left unfilled, this pioneer finding has led to the development of a few protocols for the stability of the occlusal table and the prevention of the chipping of ceramic veneering.[35] Regarding the size of the screw access channel in the SRCR design, a finite element analysis-based study showed that a diameter up to 4 mm received a more vertical bite force before fracture, while a diameter of less than 3 mm received a lower stress force, thus protecting the screw.[17] Al-Omari et al. compared screw-retained, screw-retained offset and cement-retained specimens, and found that the diameter of the screw access channel, which could occupy nearly half of the occlusal table, was the main cause of reduced fracture strength.[33] Interestingly, fracture resistance is unaffected when the screw opening is placed 1 mm offset from the center of the occlusal surface.[33] Though a 1-millimeter diameter has been recommended for the screw access channel, the clinical application is limited, as most screw shanks and heads exceed 1 mm.

Mokhtarpour et al. found that the fracture resistance of the anterior veneered zirconia restoration was reduced when the screw access channel was manually prepared with a handpiece and a diamond bur after sintering.[20] Similarly, the fracture resistance of glass implant-supported restorations in monolithic lithium disilicate and hybrid abutments was reduced by the screw access channel prepared after firing.[19,37] By contrast, with monolithic zirconia, no significant differences in the fracture load values were recorded, no matter if the screw access channel was prepared before or after sintering; however, failure or crack initiation might be due to the heat produced during manual preparation after sintering or re-sintering.[38] On the other hand, specially designed, reinforced metal framework walls of screw access channels have higher fracture resistance than conventionally designed screw access channels for cement-retained metal–ceramic restorations.[18] Similarly, Saboury et al. investigated the influence of reinforcing the framework wall with zirconia before the pre-sintering of the SRCR design.[34] Their reinforcement design had a height of 0.8 mm and a width of 1 mm to avoid interfering with occlusal contacts in the veneered type. As expected, the predesigned zirconia walls supporting screw access channels exhibited higher fracture resistance as compared to screw access channels that were not specially designed, which may be an alternative design for veneered restorations.[34] Nonetheless, since the abutments and the implant analogs were used multiple times, and only vertical compressive load was applied during testing, some of the in vitro results should be interpreted with caution.[34]

Influence of various SRCR materials on fracture resistance

In an earlier test of the fracture load of metal–ceramic restorations, there was a discernible difference between cement-retained and screw-retained restorations (Table 2).[39] Scanning electrographic analysis identified that microcracks were frequently generated in screw-retained restorations, depending on the level of the screw access channel.[39] With metal–ceramic restorations, a significant difference was also recorded in the fracture load values for cement-retained and SRCR restorations using non-adhesive cement.[40] Although the different types of cement used do not affect fracture load in cement-retained restorations, the screw access channel may compromise the fracture load value of SRCR restorations. Since the abovementioned study used non-adhesive cement, future research using adhesive cement when analyzing the performance of SRCR restorations should be conducted. A more recent study compared the effect of using a 15-degree angulated abutment to simulate a tilted implant for cement-retained SRCR with a screw-retained gold cast abutment.[41] In this study, the highest fracture load values were recorded for the cement-retained designs, followed by the SRCR design. Both designs were cemented to prefabricated tilted Ti abutments using self-adhesive cement. The screw-retained design with a castable abutment showed the lowest fracture load value, with the cohesive types of failure occurring within the ceramic veneering.[41] Similarly, Rosa et al. recorded the lowest fracture load values for SRCR restorations on customized computer-aided design (CAD) Ti abutments with self-adhesive cement.[42] In addition, for SRCR restorations fabricated with Ti, chipping fractures were more frequently recorded near the screw access channels than were catastrophic failures, which is similar to a previous study.[35,42] Hence, most studies concluded that cement-retained metal–ceramic restorations frequently have higher fracture load values than implant restorations with screw access channels.[39–42] Screw access channels in SRCR restorations affect the structural continuity of the ceramic by reducing

Table 1. Influence of various designs of screw-retrievable cement-retained (SRCR) restorations on the chipping risk and the fracture resistance values

No.	Study	Type of abutment	Crown materials	Implant manufacturers	Thermocycling (Y/N)	Retention system	Fracture load (Lf) value [N]		Fracture type			Comments
							no SAH	SAH	catastrophic	cohesive		
										within the porcelain	reaching the framework	
1.	Karl et al.[35] 2007	precious metal alloy (Degudent)	MC	ITI solid screw implants; Straumann AG	Y	5-unit FDP	NA	NA	NA	Y	NA	chipping in the unfilled SAH
2.	Al Omari et al.[33] 2010	UCLA cast with Co-Cr alloy	MC	3i LTX external hexagon implants	Y	CR SR SRO	CR: 3,707 ±1,086	SRO:1,885 ±491 SR: 1,721 ±593	load until failure	NA	NA	the diameter occupied half of the occlusal table, reduced Lf
3.	Du et al.[17] 2018	Ti (Bego)	MZ, MC	Semados S Line, Bego	N	SRCR	NA	NA	NA	NA	NA	the diameter reached 4 mm, received more stress
4.	Mokhtarpour et al.[20] 2016	15° esthetic (Nobel Biocare)	VZ	implant analogs tri-channel (Nobel Biocare)	Y	CR SRCR (Hbs) SRCR (Has)	888.3 ±228.9	Hbs: 610.4 ±125 Has: 496.7 ±104.1	load until failure	NA	NA	Lf reduced in manually prepared restorations
5.	Cabrera et al.[19] 2021	Ti (Nobel)	MLD	implant replicas (Nobel Replace)	Y	CR SRCR	1,086 ±144	1,054 ±168 880 ±153*	load until failure	NA	NA	*SAC created after firing reduced Lf
6.	Roberts et al.[37] 2018	Ti bases (hybrid (LD, Z))	MLD	implant (Certain 4.1 mm; Biomet 3i)	Y	CR SRCR	4,714.7 ±594.5	2,892.3 ±451.8*	Y	NA	NA	*SAC created with a tapered diamond bur had the lowest Lf
7.	Zhang et al.[38] 2022	Ti (GuangCi M.D. China)	MZ	Ti implants (ZZT-SP, China)	N	CR SRCR	4,476.46 ±1,023.94	4,467.00 ±415.00 MP: 4,139.00 ±600.59* RS: 4,048.44 ±565.45**	NA	Y	NA	*SAC manually prepared (MP), **SAC resintering (RS) affected Lf (result insignificant)
8	Derafshi et al.[18] 2015	straight prefabricated abutment	MC	implant analog (Dio Corp)	Y	CR CR (stain) SRCR	1,947 1,928 (stain)	2190	load until failure	NA	NA	designed holes with a metal framework wall – higher Lf
9	Saboury et al.[34] 2018	Ti (BioPilar)	VZ	implant analog (Biotechnology Institute, Spain)	Y	CR SRCR (S,W)	5,794.85	2,691.48 (S) 3,878.06 (W)	NA	Y	NA	designed holes with a zirconia wall (W) – higher Lf

Y – yes; N – no; SAH – screw access hole; Co – cobalt; Cr – chromium; Ti – titanium; MC – metal-ceramic; MZ – monolithic zirconia; VZ – veneered zirconia; MLD – monolithic lithium disilicate; FDP – fixed dental prosthesis; CR – cement retained; SR – screw-retained; SRO – screw-retained offset; SAC – screw access channel; Hbs – SAC before sintering; Has – SAC after sintering; SRCR(S) – normal SAC; SRCR(W) – SAC with a designed wall; MP – SAC manually prepared; RS – SAC manually prepared then resintering; NA – data not available.

Table 2. Summary of the influence of metal–ceramic on the fracture resistance of SRCR restorations

No.	Study	Type of abutment	Crown materials	Implant manufacturers	Thermocycling (Y/N)	Retention system	Fracture load (Lf) value [N]		Fracture type			Comments
							no SAH	SAH	catastrophic	cohesive		
										within the porcelain	reaching the framework	
1.	Zarone et al.[39] 2007	Gold Coping (Argedent 75)	MC	NA	N	CR SR	1,657 ±725	1,281 ±747	NA		Y	microcracks in the SAC of SR
2.	Shadid et al.[40] 2011	UCLA cast with Co-Cr alloy	MC	3i external hexagon (Biomet)	Y	CR (Znp) CR (Zoe) SRCR (Znp)	CR: 3,707 ±1,086 (Znp) CR: 3,169 ±867 (Zoe)	1,700 ± 526	load until failure	NA	NA	the cement type did not affect fracture resistance in CR
3.	Malpartida et al.[41] 2020	UCLA (Ni–Cr alloy, vs a 15°-angled abutment)	MC	Super Line Implant (Dentium)	N	CR SR SRCR	2,718.00 ±266.25	SRCR: 2,508 ±153.59 SR: 2,125.10 ±293.82	NA	Y	N	SRCR (angled abutment) had no effect on fracture load
4.	Rosa et al.[42] 2019	Ti (Conexao)	MC	4 × 11.5 mm; AR morse NP (Conexao)	Y	CR SRCR	2,522 ±40	967 ±560 (Ms) 833 ±195 (Msa)	NA	NA	Y	CR had higher fracture resistance than SRCR
5.	DuVall et al.[43] 2021	UCLA abutment noble metal alloy (Olympia)	MC	Full Osseotite Tapered Certain (Biomet 3i)	Y	CR SRCR	1,155 ±300	3,380 ±530	Y	NA	Y	SRCR layered with pressed ceramic had high fracture load

Ni – nickel; Znp – zinc phosphate; Zoe – zinc oxide eugenol; Ms – metal screw; Msa – metal screw aging.

Table 3. Summary of the influence of all-ceramic SRCR restorations on fracture resistance

No.	Study	Type of abutment	Crown materials	Implant manufacturers	Thermocycling (Y/N)	Retention system	Fracture load (Lf) value [N]		Fracture type			Comments
							no SAH	SAH	catastrophic	cohesive		
										within the porcelain	reaching the framework	
1.	Honda et al.[16] 2017	Ti GingiHue Post	MZ VZ ILZ	Osseotite Implant (Biomet 3i)	N	SRCR	NA	MZ: 7.54 kN VZ, ILZ: 1.45–1.96 kN	Y (MZ)	NA	Y (VZ, ILZ)	the highest Lf for MZ
2.	Hussien et al.[44] 2016	Ti (TiXos; Leader Italia)	MZ, MLD VZ	internal hexagon implants (Tixos; Leader Italia)	Y	CR SRCR	MZ: 2,028.7 ±104.5 MLD: 615.3 ±76.6 VZ: 461.2 ±72.7	MZ: 2,047.8 ±83.2 MLD: 605.4 ±37.9 VZ: 411 ±34.4	load until failure	NA	NA	The highest Lf for MZ (SRCR), a different fracture pattern on the crown with SAC and without SAC
3.	Yazigi et al.[24] 2020	Ti (Bredent)	MZ, MLD	implants (BlueSKY; Bredent)	Y	SRCR	NA	MZ: 2,645 MLD: 1,070	NA	Y	NA	the highest Lf for MZ
4.	DuVall et al.[43] 2021	TiBase abutments (Dentsply Sirona)	VLD MLD VZ PMMA	Full Osseotite Tapered Certain, (Biomet 3i)	Y	CR SRCR	VLD: 2,520 ±400 VZ: 2,330 ±410	PMMA: 3,280 ± 370 MLD: 2,670 ±345	Y	Y	Y	the highest Lf for MLD vs. the veneered type
5.	Mallmann et al.[45] 2018	Ti (Speed; Conexão)	VZ	Implants (Morse AR NP; Conexão)	Y	3-unit FDPt CR SRCR	VZc: 3,803 ±1,038	VZs:2,601 ±830 VZsa: 446 ±575	Y (50% on VZs)	Y (VZc, VZsa)	NA	for SRCR VZ, lower Lf than for cemented, aging reduced Lf
6.	Rosa et al.[42] 2019	Ti (Conexão Sistemas)	VZ	Morse taper (Conexão Sistemas)	Y	CR SRCR	MC: 2,522 ±406	VZ: 932 ±309 VZa: 817 ±282	Y	NA	NA	VZa showed lower Lf

PMMA – polymethylmetaacrylate; VZc – veneered zirconia cement-retained; VZs – veneered zirconia screw-retained; VZsa – screw-retained aging; VZa – veneered zirconia aging; ILZ – indirect composite-layered zirconia.

the metal–ceramic bond strength. This decreases the fracture load value and increases the risk of chipping in a way not observed in cemented restorations.[33,35,39,42] Interestingly, when metal–ceramic layered with pressed ceramic was used, higher fracture resistance was recorded for SRCR restorations as compared to cemented restorations.[43] This finding could be due to the steps involved in the protocol for surface treatment, the application of self-adhesive cement and pressed ceramic material.

Given the ongoing interest in selecting the optimal material for an implant prosthesis, a few studies have reported an intriguing finding regarding the SRCR concept on all-ceramic materials utilizing Ti-base abutments (Table 3).[16,19,44,45] After load testing, the monolithic zirconia of SRCR restorations frequently survived and was found to withstand the highest fracture loads.[16,24,44] Other materials, such as monolithic lithium disilicate, also showed high fracture loads, with the fatigue fracture resistance being unaffected by screw access channels.[24,43] Scanning electrographic analysis showed that the fracture patterns were different from those in metal–ceramics in that they started in the cervical area and continued occlusally; this seems to be due to the greater stress transmitted at the abutment–implant junction, caused by the high fracture load value.[16,24,38,44] Meanwhile, veneered SRCR restorations showed a significant reduction in the fracture load values as compared to monolithic and veneered cemented restorations.[16,42,44,45] Cracks in veneered materials vary with regard to cracks from the internal surface of the framework and chipping within the ceramic on the feldspathic veneer.[42,43,45] Additionally, increased porcelain chipping and a decrease in fracture loads were observed following thermal cycling, implying a slow crack propagation in aged porcelain.[42,45] Therefore, special designs with special screw access channels, using finite element analysis, fractographic analysis and video recordings should be further investigated.

Aside from ceramics, several studies have studied the fracture resistance of implant crowns made of CAD/CAM composites and HPPs, such as resin nano-ceramic, polyetheretherketone (PEEK) and polymer-reinforced ceramics (Table 4).[24,25,30,46] Joda et al. investigated the monolithic designs of resin nano-ceramic (Lava™ Ultimate) bonded to Ti, and found no detectable fractures after quasi-static loading, regardless of the abutment type.[25] Tribst et al. confirmed that the use of the SRCR design did not affect the survival of a monolithic perforated crown made from VITA Enamic, a polymer-reinforced ceramic bonded to TiBase®.[47] Yazigi et al. found that fracture load was the highest for PEEK (BioHPP) fabricated as a monolithic implant SRCR, followed by CAD/CAM composites blocks, Grandio blocs and polymer-reinforced ceramics (VITA Enamic).[24] Nonetheless, the monolithic polymer-reinforced ceramic, the weakest of the 3 materials, has a lower fracture load than normal physiological loading of the posterior molars and should be used with caution.[24] In contrast to the monolithic design, the SRCR design had a negative impact on

Table 4. Summary of the influence of high-performance polymers (HPPs) of SRCR on its fracture resistance

No.	Study	Type of abutment	Crown materials	Implant manufacturers	Thermocycling (Y/N)	Retention system	Fracture load (Lf) value [N]		Fracture type		Comments
							no SAH	SAH	catastrophic	cohesive	
1.	Joda and Brägger[58] 2014	Ti (synOcta, CADCAM CARES, Variobase (VB))	RNC (Lava)	implant (Straumann)	N	SRCR	NA	1,100–1,500 (S) 1,300–1,500 (C) 1,100–1,200 (VB)	NA	Y	monolithic implant crowns made of RNC are stable prosthetic reconstructions under laboratory testing
2.	Tribst et al.[47] 2020	Ti (Conexão Sistemas)	PIC (VITA Enamic)	Morse taper implants (Conexão Sistemas)	Y	CR SRCR	NA	NA	Y	Y	fracture was commonly observed on the emergence profile
3.	Yazigi et al.[24] 2020	Ti (CEREC; Bredent)	PEEK (P) composites (C/Grandio blocs) PIC (E/VITA Enamic)	implants (Bremen, Germany)	Y	SRCR	NA	2,030 (P) 915 (C) 670 (E)	NA	Y	fracture load was the highest on PEEK
4.	Preis et al.[30] 2017	Ti	PEEK (BioHPP) RNC (Lava) CADCAM composites	implant analogs (Straumann)	Y	CR SRCR	PMV: 921.3 PPV: 1,329.8 CO: 1,667.6	PMV: 964.3 PPV: 978.0 CO: 1,526.8	NA	Y	layered resin-based were weakened with SAH

RNC – resin nano-ceramic; PIC – polymer-reinforced ceramic; PMV – polyetheretherketone + milled composite veneer; PPV – polyetheretherketone + composite paste veneer; CO – composites.

fracture loads when implant crowns made of the PEEK (BioHPP) substructure and a layered with CAD/CAM milled composite were used.[30] The SRCR design also resulted in the failure of PEEK (BioHPP) layered with conventional composite paste.[30] In terms of the biomechanical behavior of HPPs, a high prevalence of fracture was observed at the emergence profile and in the cervical area in the monolithic design, as well as in the screw access channel in the veneered design.[47] With an increasing fracture load, a higher concentration of stress was transmitted to the implant–abutment junction, resulting in cracks near the emergence profile.[16,24,38,44]

Clinical performance of SRCR restorations fabricated from various materials

Few authors have applied the SRCR design to implant restorations in clinical settings (Table 5). Rajan and Gunaseelan described a protocol for fabricating the SRCR concept for metal–ceramic restorations.[48] The ceramic superstructure was cemented on metal cast abutments and excess cement was removed extraorally.[48] Three other studies documented how SRCRs were used to restore fully edentulous maxillae and mandibles.[49–51] In addition to casting gold abutments, SRCRs were milled from Ti as a cost-effective solution for the multi-unit fixed partial denture.[49] In a retrospective analysis of edentulous patients restored with SRCRs, porcelain chipping occurred in only 10.9% of cases, indicating a low rate of complications.[50] AlHelal et al. developed a protocol for a cementation technique that avoided the use of die spacers at the cervical finish line, thereby preventing the excess cement complications.[9] Based on this clinical report and technique, SRCRs using metal–ceramics have improved implant restoration survival rates by preventing damage to the porcelain when the screw loosens, as well as reduced the cost of maintenance.[52]

Regarding all-ceramic SRCR restorations, Proussaefs et al. recommended a digital workflow for monolithic zirconia bonded to a custom Ti abutment, using the SRCR technique.[10] The prostheses were cemented while positioned intraorally. After extrication from the mouth, the cement was removed extraorally after polymerization.[10] With a similar technique, Wasiluk et al. assessed the incidence of undetected cement by using custom Ti cement abutments fabricated for SRCR restorations.[53] Excess cement was recorded on the distal (17.9%), mesial (15.0%), palatal (8.8%), and buccal surfaces (3.4%).[53] Therefore, with these procedures, the risk of undetected cement residue was reduced when polishing and cleaning were possible for SRCR restorations. The SRCR design with monolithic zirconia and an angulated screw channel (ASC) revealed no difference in crestal bone loss.[54] Joda and Ferrari evaluated an SRCR implant crown made of monolithic lithium disilicate bonded to a Ti base, and reported no complications after 1 year.[55] In a randomized split-mouth trial, a monolithic lithium disilicate implant crown fabricated as an SRCR was reported to have a 100% survival rate.[23] Cicero et al. reported no complications following a 3-year follow-up using a hybrid approach (a zirconia coping layered with pressed lithium disilicate luted to a Ti base).[56] Using a similar veneered approach, fractographic analysis revealed premature failures and cracks near the screw access channel.[57] However, with the exception of 2 studies, there were limitations, i.e., the majority of them were clinical techniques and case reports.[10,23,54–57]

Screw-retrievable cement-retained implant restorations using HPPs have been reported in a few studies. When bonded to a prefabricated abutment, monolithic resin nano-ceramic (Lava Ultimate) fabricated using a digital method demonstrated a more favorable esthetic outcome (Variobase®).[58] Monolithic SRCRs with polymer-reinforced ceramics (VITA Enamic) have been shown to have an excellent outcome, with no prosthetic or biological complications.[59] However, when zirconia abutments were used, 80% of bonding failures occurred within the 1st year of service in the monolithic type fabricated from resin nano-ceramic.[29] As a result, researchers have emphasized the contraindication for resin nano-ceramic bonded to a zirconia abutment as an implant restoration material. Nonetheless, limited information is available on the application and clinical studies of PEEK and block CAD/CAM composites as an alternative for implant restoration.

Discussion

In restoring dental implants with monolithic or veneered ceramic crowns, SRCR incorporates the advantages of both the traditional screw and cement techniques.[12] The different fracture load values, and crack initiation and propagation mechanisms were all influenced by different SRCR implant restoration designs and materials. The size and design of the screw access channel, and whether its preparation is performed before or after sintering are all relevant elements that influence the ultimate performance of the SRCR design. Oversized diameters of screw access channels not only contribute to the fracture risk, but also influence stress concentration at the margin of the channel, which makes the restorations vulnerable to failure, particularly in patients with excessive bite force.[17] Furthermore, grinding an intact lithium disilicate restoration after crystallization and glazing should be avoided, as more cracks occur than when grinding the crown while still in its pre-glazing or blue phase. After crystallization and glazing, the strength of the crown increases from 130–150 MPa to 350–450 MPa.[23] Regarding zirconia, diamond bur grinding rather than tungsten carbide is recommended before sintering to avoid phase transformation in the zirconia microstructure.[59] To improve the fracture resistance of SRCRs, screw access channels with surrounding zirconia walls should be used for the reinforcement of the restoration.[34]

Table 5. Summary of the clinical performance of SRCR fabricated with various types of materials

	No.	Study	Study period	Study design	Type of implant	Number/site	Retention system	Superstructure material	Abutment	Implant survival	Prosthesis complications	Comments
Metal–ceramic restoration	1.	Rajan et al.[48] 2004	NA	clinical report	NA	1/molar	SRCR	MC	–	Y	NA	the use of provisional cements is not indicated in SRCR
	2.	Uludag et al.[49] 2006	NA	case report	Swissplus, Zimmer Dental, San Diego, California	9 units	SRCR (FPD)	MC	–	Y	NA	milled abutment as alternative to cast abutment for SRCR
	3.	Al Amri[51] 2016	NA	clinical report	Standard plus ITI: SLA	maxilla	SRCR	MC	–	Y	survived after 5 years	peri-implant crestal bone levels were stable in SRCR multi-unit restoration
	4.	Lixin et al.[50] 2010	22–62 months	retrospective	Camlog RootLine, Camlog	234/maxilla 119/mandible	SRCR	MC	–	99.15%	10.91% ceramic chip-off	–
	5.	Nissan et al.[52] 2016	12 years	retrospective	Nobel, Zimmer, 3i, MIS	148/maxilla 245/mandible	CR SRCR (SAH created after firing)	MC	NA	Y	ceramic fracture, screw loosening	adding SAC on the metal framework decreased the need for refabrication
	6.	AlHelal et al.[9] 2017	NA	clinical technique	NA	premolar, molar	SRCR	MC	custom Ti	NA	none	–
All-ceramic restorations	1.	Proussaefs and AlHelal[10] 2018	NA	clinical technique	NA	premolar, molar	SRCR	MZ	custom Ti	NA	none	–
	2.	Wasiluk et al.[53] 2017	NA	prospective case series clinical trial	Osseospeed TX (Denstply)	premolar, molar	SRCR	MZ	custom abutment	Y	none	the majority of cement residue was on the distal(17.9%) and mesial (15%) site
	3.	Di Fiore et al.[54] 2023	36 months	prospective clinical study	Nobel Parallel (CC)	molar	SRCR	MZ	ASC TiBase	96%	96%	–
	4.	Joda and Ferrari[55] 2018	NA	case report	NA	molar	SRCR	MLD	TiBase	Y	none	–
	5.	Khamis and Zakaria[23] 2022	12 months	randomized controlled split-mouth trial	SuperLine (Dentium)	molar	CR SRCR	MLD	Tibase (preparable)	None	none	no significant differences between both groups
	6.	Cicero et al.[56] 2021	3 years	case report	NA	premolar, molar	SRCR	hybrid, MZ	TiBase	Y	none	–
	7.	Juica et al.[57] 2022	NA	case report	Tapered Internal (BioHorizons)	premolar	SRCR	hybrid	TiBase	Y	Y	catastropic failure due to overloading, poorly designed material
Resin nano-ceramic restorations	1.	Joda and Brägger[58] 2014	NA	case series	tissue level (Straumann)	premolar, molar	SRCR	RNC	TiBase (prefabricated vs. custom)	Y	none	favourable esthetic outcome for the prefabricated bonding bases
	2.	Schepke et al.[29] 2016	1 year	randomized controlled trial	ASTRA TECH implant system	premolars	SRCR	RNC	stock vs. custom zirconia	Y	Y	poor prognosis of RNC luted to zirconia abutment
	3.	Lambert and Mainjot[59] 2017	1 year	case letter	tissue level (Straumann)	premolar, molar	SRCR	PIC	TiBase	Y	none	–

ASC – angulated screw channel.

These modifications have only been evaluated using in vitro testing with standardized parameters, and therefore, clinical studies are timely and highly needed to validate these in vitro findings.

In terms of the influence of materials, the majority of studies concluded that screw access channels in metal–ceramic restorations weakened the porcelain and reduced fracture load in SRCR.[33,39,40,42] Screw-retrievable cement-retained restorations may harm the geometrical variations of the framework, resulting in porcelain cracking.[33,41] Such cracks were found to be distributed in areas of higher mechanical resistance near the screw access channels, whereas jagged lines were discovered in areas of low-stress concentration.[35,39] Furthermore, cracks formed during thermocycling led to failure after aging.[33] There were conflicting reports on the fracture loads of cement-retained and SRCR restorations.[18,41] These could be attributed to the use of different implant systems, cement types, screw access channel diameters, filling materials, number of loadings, fatigue cycles used, and thermocycling effects.[11,18,43] As a result, additional standardization methods are required to prevent bias in future clinical studies.

Differences in screw access channels, on the other hand, do not affect the fracture load value of SRCRs constructed entirely from monolithic ceramics. Screw-retrievable cement-retained restorations fabricated with monolithic zirconia and monolithic lithium disilicate had a high fracture load, which exceeded masticatory forces of 900 N in the posterior region during load testing, indicating the suitability of these materials for posterior molar restorations.[16,19,24,60] Catastrophic fractures occurred only when the load was increased to 2400–4500 N.[16,19,45] High fracture loads in monolithic ceramics have raised clinical concerns about stress concentration in the cervical peri-implant bone area.[60,61] To alleviate this concern, zirconia crowns have been veneered with lithium disilicate or composite resins. This veneering also improves shade matching and occlusal wear on the opposing teeth, as monolithic zirconia is relatively opaque and hard.[56] However, the presence of screw access channels in veneered restorations has increased tension near the channels while decreasing fracture loads.[16,34] The fracture mode ranged from catastrophic to chipping within the porcelain, but the veneered type is able to withstand physiological masticatory forces in the molar region.[16,45,62] The diameter of the screw access channel, occlusal contact, and the quality of bonding between the layering materials must be investigated further to avoid premature failure.[57]

High-performance polymers have been recommended to compensate for the absence of periodontal ligaments through absorbing forces and withstand a greater load to avoid stress being transmitted to the surrounding bone.[30] High-performance polymers have a high modulus of elasticity, allowing them to deform before cracking.[24,46] They also exhibit distinct mechanical behavior depending on the underlying abutment or the monolithic/veneered design of the structure.[24] The load capacity causes their failure mode to originate from the cervical part to the top of the restoration. The presence of screw access channels for SRCRs in these materials also causes no stress and performs similarly to the cemented type. High-performance polymers can withstand forces greater than those occurring on a natural posterior molar, except for SRCRs fabricated with polymer-reinforced ceramics, which failed catastrophically at a load of 600 N. These materials create a grey zone that compromises esthetics when monolithic designs are used. To address this esthetic issue, a hybrid abutment or veneered abutment has been proposed,[46] but this deteriorates physical properties and fracture load performance.[30] Consequently, when selecting materials for HPPs, especially for the veneered type and hybrid abutments, caution should be exercised. In general, to avoid failure at the emergence profile and cervical area, there should be a minimum thickness for this material. For posterior implant restorations, materials with a low modulus of elasticity that absorb energy and have comparable fracture resistance, are preferable.

Few authors have used SRCRs in clinical studies regarding implant-supported restorations. Only clinical techniques and retrospective clinical studies have been reported, although the use of metal–ceramic SRCRs is considered to be simple and as effective as cemented restorations.[9,48,50] For all-ceramic restorations and monolithic HPPs, no damage and mechanical complications were observed at the interface of the Ti base abutment, suggesting that this was a suitable clinical method for implant-supported prostheses.[19,44,54,55] Further clinical trials and studies with a longer follow-up are required before recommending routine application of this method, especially of the veneered type.[8,54] Selecting suitable abutments and material types is fundamental to ensure the satisfactory clinical performance of SRCRs.

Conclusions

Metal–ceramic SRCRs have a generally lower fracture load value than cemented implant-supported restorations, although the differences may vary considerably. Cracks start mostly at the screw access channels. There is no significant difference in the fracture load values between SRCRs fabricated as monolithic ceramics and cement-retained restorations. The adhesive bonding between Ti abutments and monolithic ceramic frameworks showed no damage at the interface and did not affect the fracture risk. For the veneered type, the presence of screw access channels in zirconia and lithium disilicate significantly reduces fracture load as compared to cemented restorations, but is sufficient to withstand molar masticatory forces. Among HPPs, monolithic forms of ceramic-reinforced PEEK and resin nano-ceramic demonstrated higher fracture resistance than those occurring clinically.

However, monolithic polymer-reinforced ceramic networks and veneered restorations had lower fracture resistance and should be used with caution.

Regarding the clinical performance of SRCRs fabricated with metal–ceramics, the clinical data is mainly retrospective and contains case reports. However, no controlled randomized clinical trials RCTs) have been conducted. Monolithic SRCRs fabricated with all-ceramic restorations have shown good short-term clinical performance within 1–3 years post-loading. For veneered SRCR restorations, clinical data demonstrating the predictability of this approach is lacking. High-performance polymers may be recommended as a substitute for posterior implant restorations, but clinical data is scarce; hence, further investigations are needed.

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

Factors influencing NiTi endodontic file separation: A thematic review

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Abstract

Nickel-titanium (NiTi) file separation during endodontic treatment is an undesirable event. This phenomenon needs to be understood by knowing the factors influencing fracture in endodontic files. There is a large amount of literature where these factors and their influence have been studied, increasing the knowledge about the mechanisms involved, mainly related to wire technology, file shapes and geometry, operator manipulation, the anatomy of the root canal, and the irrigation and sterilization processes. As many factors are involved, the complexity of the fracture phenomena increases and the isolated correlation of one factor with the file fracture becomes a small part of comprehending the separation phenomena. This thematic review aims to compile important reports from 2014 to 2022 on the factors influencing NiTi file separation. The information obtained was classified into wire technology, file geometry, operational aspects, irrigation and sterilization, and anatomy. For this purpose, the Scopus, Web of Science and ScienceDirect databases were consulted using a search string. Filters were applied to consolidate the final set of relevant papers covering the subject of factors influencing endodontic file separation. It was found that the fracture of NiTi files incorporates different mechanisms that operate simultaneously during the endodontic procedure and strongly affect the instrument performance. The collected information promotes good practices to prevent file separation.

Keywords: endodontics, nickel-titanium alloy, dental instrument separation, thematic review

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Introduction

Nickel-titanium (NiTi) files are motorized instruments used for root canal preparation in endodontic procedures. NiTi is an alloy with superelasticity (SE) features, allowing the instrument to adapt to the anatomy of the root canal and avoid irregularities such as zipping, ledging, and perforation.[1,2] Aspects such as motorized operation and procedural times have improved due to the SE properties of NiTi.[3] However, the relationship between cutting efficiency, heat treatment, rotary motion, cross-section, and tapper design, is complex and needs to be studied and more thoroughly understood.[4]

Even though NiTi files have shown outstanding properties superior to stainless steel and other materials, there are still some issues that need to be solved to improve NiTi file reliability in endodontic practice. The superelastic behavior is caused by deformation that induces phase transformations. The material goes from austenite (A) to the R-phase (R) and martensite (M). Martensite gives the material superior strain properties. Once the effect causing the initial deformation (stress) is reversed, a reverse M–A transformation of the alloy and the original shape can be achieved depending on the amount of M-phase developed in the material.[5]

One of the most critical issues in NiTi file use is separation, which entails instrument fracture inside the root canal, causing severe health and economic complications for patients and ethical problems for professionals. Some file manufacturers and professionals consider that using one file per root canal or tooth can ensure instrument structural integrity during an endodontic procedure.[6] The consequence of this approach is an increase in costs, which can affect access to treatment. Also, in the literature, instrument separation has been reported in the first file usage.[7]

Another proposed approach is improving the material properties to promote better performance. There has been a relevant development in NiTi wire technology obtained through machining and heat treatments.[8] Resistance to fracture was improved, allowing the instrument to be used repeatedly. However, the dentist still does not know when a file will fracture.[9] Also, the lack of adequate diagnostic techniques to determine the instrument's condition for further use and if continuing to use the file is safe indicates the need to understand the failure mechanism and predict when the file separation may occur. Many efforts are being made to develop systems to evaluate the usability of endodontics files.[10–13]

Table 1. Representative papers about endodontic file separation

Study	Year	Review subject	Article type
Çapar and Arslan[15]	2016	Presents an overview of the advancements in instrumentation kinematics and the effect of instrumentation kinematics on the root canal shaping procedures and instrument performance.	review
Ya et al.[19]	2016	To evaluate the defects and their frequency of occurrence in WaveOne files after being used in patients.	in vivo
Ahn et al.[20]	2016	The comparison of the kinematic effect of NiTi instruments with a reciprocating and continuous motion for cyclic fatigue resistance, shaping ability, apical debris extrusion, and dentinal defects or cracks.	review
Alsilani et al.[21]	2016	The comparison of the available reciprocating systems – Reciproc and WaveOne.	review
Ferreira et al.[16]	2017	The correlation between different movement kinematics and the cyclic fatigue resistance of NiTi rotary endodontic instruments.	review
Peláez Acosta et al.[22]	2017	To verify the torsional strength of files manufactured with CM-wire and compare them with the values presented by files manufactured with superelastic (SE) alloy.	in vivo
Gavini et al.[23]	2018	Characteristics of NiTi alloys. Influence of metallurgical and mechanical properties of these instruments. Movement types.	review
Cassimiro et al.[24]	2018	To verify the generation of defects in dentin, generated by root canal instrumentation.	ex vivo
Tabassum et al.[5]	2019	Discusses different phase transformations and heat treatment that NiTi instruments undergo.	review
Hülsmann et al.[14]	2019	Summarizes the currently available evidence to point out the different outcomes from static vs. dynamic tests, and to assess whether cyclic fatigue tests provide valuable data and information for clinical practice.	review
Leal Siva et al.[25]	2020	The evaluation of the influence of the autoclave sterilization procedures on the cyclic fatigue resistance of heat-treated NiTi instruments.	review
Leal Siva et al.[26]	2020	Comparison of cyclic fatigue resistance. Different techniques were used to check the design and composition of the files, and transformation temperature similarities.	ex vivo
Kermeoglu and Abduljalil[27]	2022	To examine the impact of irrigants, with and without sterilization, in ProTaper, Wave One Gold and Reciproc files on cyclic fatigue resistance.	in vitro
Orozco-Ocampo et al.[28]	2022	To identify typical failure mechanisms for rotatory and reciprocating files. To summarize the standard mechanical tests for endodontic files and the characteristics of their assembly.	review
Avcil et al.[29]	2022	Martensitic transformation temperature. Wear mechanism and friction coefficient monitoring.	other
Dragoni and Scirè Mammano[30]	2022	To study the high-performance shape memory effect of NiTi wires under constant stress loading. Linear stress–strain variation.	other

Computational simulation and experiments have been essential research tools for determining the mechanical properties of the NiTi alloy. Using these tools, optimizing endodontic variables such as the axial movement of the instrument,[14] types of rotational motion,[15,16] the instrument geometry (size, taper, pitch, cross-section, among others),[17] rotational speed,[18] duration of usage,[19] among others, have been attempted. However, factors that cannot be controlled, like root canal curvature and the human operator's axial movements, can affect the predictability of the model.

Several literature review articles were identified through a search on fracture mechanisms and factors that influence endodontic file separation. Some are shown in Table 1.

This paper presents a compendium of factors reported from 2014 to 2022 that influence the fracture of NiTi endodontic files during root canal instrumentation through a search of relevant literature. The papers reviewed were focused on describing and analyzing the effects of metallurgical and mechanical features of the alloy used for files on instrument fracture.[5,27] Features included rotational movements (kinematics) during instrumentation,[15] comparison between files with the same kinematics but different manufacturers,[20] static vs. dynamic root canal instrumentation,[14,14,31] and autoclave sterilization.[32] For the total number of papers consulted, we found 4 reported as in-vivo experimentation, 60 as in-vitro, and 8 ex-vivo studies. The remaining papers are reviews, computational simulation results, and other studies. Factors related to file separation were classified into wire technology, file geometry, operational factors, irrigation and sterilization, and the root canal anatomic factor.

This thematic review process is based on the need to contribute to the understanding of endodontic file fracture by identifying factors related to this phenomenon. It also aims to provide the reader with a document that summarizes and discusses, in a holistic approach, the factors that influence the separation of endodontic files so that it can be used as a base document for future research on the subject.

Methodology

Some questions were formulated to focus the search for scientific information and subsequently filter the documents found according to the topics of interest of this review.

Q1: Which factors are involved in the fracture of NiTi endodontic files?

Q2: What information is found in the literature to prevent failure?

The Scopus, Web of Science and ScienceDirect databases were consulted to find the most relevant work reports on endodontic file separation. The methodology followed for the literature review includes steps proposed by Kitchenham and Charters.[33] Initially, the search term "endodontic file" was used in all fields, resulting in high results. For that reason, other terms related to file separation were added to narrow the search. The search string and document selection process are shown in Fig. 1.

The search was limited to research articles and conference papers from 2014 to 2022. Some databases did not allow a unique search for the entire search string; for those cases, the search had to be performed separately. Next, all data was combined from each database and repeated results were removed. This search yielded 851 unique results. The paper titles were scrutinized to verify that the documents were related to fatigue, failure, and separation of NiTi endodontic files. From this process, 245 items remained. Next, the abstracts, discussions, and conclusions were reviewed. Comparative studies and articles focused only on a descriptive approach to the performance of one manufacturer compared to others were excluded, resulting in 151 remaining research papers. After reading the complete articles, 100 of the most representative documents for the identified factors were used.

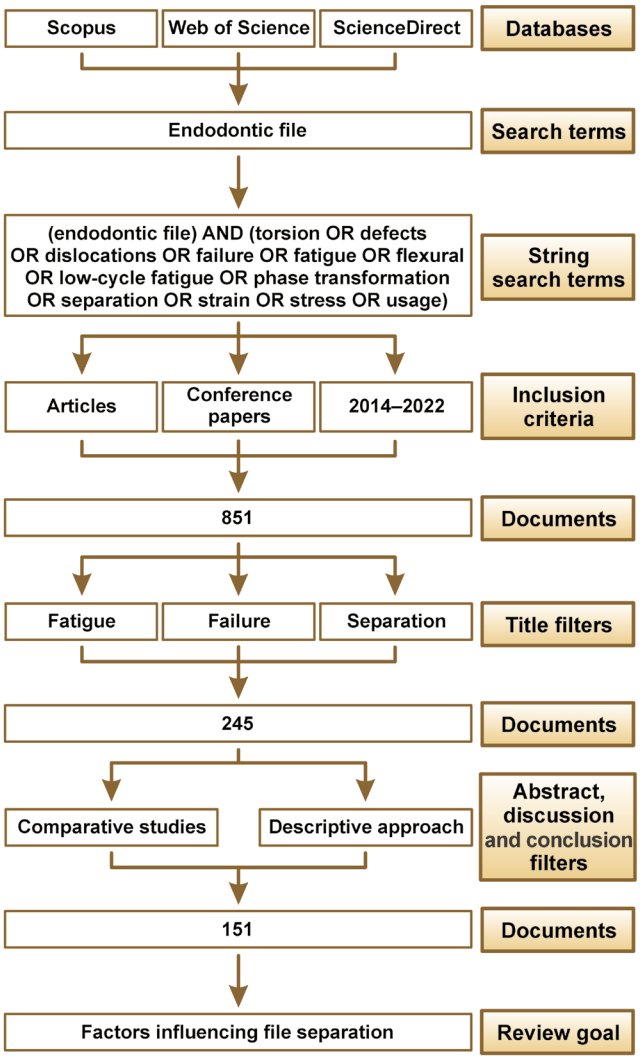

Fig. 1. Flow chart for the document search and selection

Fracture of NiTi endodontic files

File fracture inside the root canal during an endodontic procedure is related to two failure mechanisms: torsional fracture and fatigue fracture. The first mechanism presents when the file tip becomes locked in the canal wall, and the torsional strength of the instrument is exceeded.[34,35] Torsional stress can lead to plastic deformation of the file, which, depending on axial movements, will result in unwinding in the most affected section of file.[32] The second mechanism is due to the flexion–compression cycles. This may occur when file rotation in a curved canal causes one section to simultaneously be in tension while the other is in compression. Repeated cycles of the NiTi files will lead to fatigue failure by work hardening-softening of the material's microstructure by internal stress accumulation. This hardening-softening leads to a loss in flexibility and increased brittleness.[36,37] The number of cracks generated on the surface where the stress concentration is higher than the cohesion forces during flexion causes crack propagation.[38–41]

The files are subjected to torsional and fatigue forces during endodontic procedures. From the fatigue contribution to failure, Braz Fernandes et al.[8] found that independent of the geometry, sections near the midpoint of the curved section of the file inserted in the root canal were subjected to higher stress levels during instrumentation due to the occurrence of maximum deformation amplitude.[40,42] Finally, file fracture can be caused by the accumulation of effects, which have been reported to occur at this file segment.[43,44]

Several studies have focused on establishing each fracture mechanism's role (torsion and/or fatigue) in file separation.[4] Jamleh et al.[45] found that fatigue impacts the hardness and elastic moduli of endodontic files, reducing these properties by 17% and 13% during torsion, respectively, showing the dominant effect of fatigue on file separation, as has been reported by other authors.[19,46] Sattapan et al. found that in 378 NiTi endodontic files analyzed after clinical use, 50% showed visible defects; of these files, 21% were fractured.[47] They also identified that 55.7% of these separations were due to torsional loads and the remainder to bending loads. Torsional failure was associated with apical forces and bending fatigue with canal curvature.[47] Others have reported that torsional stress affects the fatigue resistance of the materials and vice versa.[34,44,48] Several studies have concluded that crack nucleation occurs at the blade surface and propagates to the inner region, exhibiting an opening crack propagation Mode-I (tensile), revealing the capital importance of rotational bending versus torsional loads in crack propagation.[18,49]

Separation during an endodontic procedure primarily depends on the different NiTi phases present in the material. As previously mentioned, NiTi files exhibit 3 phases,[5,50] and the R-phase is an intermediate or a pre-martensitic phase preserving the features of its SE behavior.[8,51] Also, in A-R-M transformations, the austenite elastic properties are promoted at low deformations but the strain increases.[48,52] From the microstructural perspective, the NiTi phase transitions lead to the formation of a branched morphology attributable to martensite.[51] Crack propagation occurs through the interfaces of this branched structure, resulting in crack propagation. A higher dissipation of energy and a slowdown of the speed at which cracks grow at equal stress intensity levels is related to the austenite phase.[50,53,54]

This behavior implies that when the file is in the martensite phase, it is more resistant to fatigue failure, as has already been reported.[50,55,56] Joviano Pereira et al. found that file separation occurs at ultimate tensile strength in the martensite phase.[57] These authors were implying complete transformation to the martensite phase during deformation.[57] Cyclic phase transitions (A-R-M and M-R-A) may be accompanied by residual stress accumulation through dislocations and internal stresses, which entails a reduction of stress required for martensite transformation, resulting in work softening.[58–60] Even though deformed NiTi files exhibit good fatigue resistance, other types of loads (e.g., torsion), cracks, or plastic deformations, can also cause fractures.[32,56] The highly-stabilized martensite SE is limited by plastic deformation. The plated structure is promoted, and further strains lead to fractures.[56,61]

Table 2 presents the 5 principal factors that affect the separation of endodontic files.

Figure 2 shows the number of papers reviewed on file separation factors. In this case, the most studied factors are operational factors and loads. Additionally, it is observed that the factor on which the least literature has been generated is related to anatomical factors.

Wire technology

It is widely accepted that the properties of the material are directly related to its performance. Specifically, endodontic instrument fracture depends primarily on the mechanical properties exhibited by the elements that the tool is comprised of and on the crystalline state (phase) of the NiTi file. NiTi alloy endodontic files performed better than those fabricated with stainless steel because of the superelastic behavior of the NiTi austenitic phase. This property is associated with high deformation of the material through the strain-induced transformation from the austenite to the martensite phase and the recoverable form by reverse phase transition.[50,52] Superelastic behaviors are attributed to the conventional NiTi (austenitic) alloy. At room temperature, austenite NiTi files exhibit low flexural fatigue resistance compared to martensite files due to their high hardness.[40,41,93] It has also been discovered that files with a high martensite phase content exhibit increased flexibility, crack growth reduction (energy dissipation in a branched structure), and better fatigue resistance.[26,40,53,93]

Table 2. References per factor from the literature review

Factors influencing file separation	References
Related to wire technology: – NiTi phase transformations; – types of wire	16,30,32,36,37,39,43,45–47,49,51,52,57,62,63,65–70,71
Related to file geometry: – cross-sectional area; – core mass; – pitch length; – helical angle; – taper	8,17,34,51,53,57,60–63,69–78
Related to operational factors and loads: – types of movement (continuous rotation and a reciprocating motion) – handling (dynamic (pecking) and static immersion movements) – flexural fatigue – torsional fracture – fracture mechanisms	16,17,18,29,32,36,46,60,65,69,81–83 8,18,32,34–37,40–42,44,48–54,56,57,59–61,68–70,82,83,87–89
Related to irrigation and sterilization: – corrosion effects of the irrigant – thermal effects of sterilization	25,27,36,41,61,64,72,73,77,88–92
Related to the anatomic factors: – root canal shape and size	37,40,59,75,92

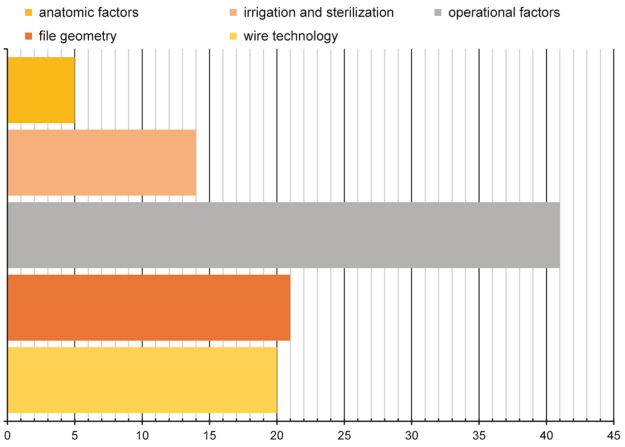

Fig. 2. Documents per factor related to file separation

Even though endodontic instrument manufacturers have secret treatment procedures, wire technology has evolved through the years from conventional NiTi wires to M-wire® and Controlled Memory or CM-wire, among other similar technologies. NiTi wires with total R- or martensite phases enhanced with thermo-mechanical treatments, are an excellent material to fabricate endodontic files.[34] Regarding the thermo-mechanical treatment, the austenite finish temperature (A_f) is shifted to higher values, inducing the presence of stable R- and martensite phases in NiTi files at room (RT) and body temperatures (BT), thus causing improved flexibility and resistance to cyclic fatigue during use.[52,62,69,94] As A_f is higher than RT and operational BT, the performance of the endodontic file is improved due to the martensite and R-phases. The closer A_f is to RT and BT, the file exhibits higher stiffness and less fatigue resistance when used in root canal instrumentation because of the contribution of the austenitic portion in material.[38]

The differences between wire technologies are attributed to the amount of stable R-phase (or martensite) induced during thermomechanical pre- and post-treatment. This is related to the A_f and machining techniques, considering that endodontic files with M-wire technology have an austenite phase with a small R-phase content.[50] Pirani et al. conducted studies to compare WaveOne (M-wire) to ProTaper F2 files (conventional NiTi).[51] The metallographic analysis showed that M-wire technology consists of a high portion of symmetrically twinned martensitic phases (microcrystalline grains) compared to conventional NiTi files.[54] Also, multiple initiation cracks were found in the WaveOne instrument, which was not the case for the ProTaper F2 file. The R-phase and crack initiation were assumed to be responsible for the incremental fatigue of the WaveOne file.

M-wire files have also revealed a high ultimate torsional strength due to their ductility[48,63] as compared to RaCe, ProTaper F2 (both conventional NiTi), and Twisted files (R-phase). Here, it is important to note that R-phase content in M-wire instruments can vary among manufacturers. Some files will exhibit properties more similar to conventional NiTi than others, depending on this R-phase/austenite ratio. R-phase endodontic instruments, compared to conventional NiTi and M-wire technologies, were studied by De Arruda Santos et al.[50] In this study, the uniaxial tensile test revealed that the R-phase had the lowest elastic modulus and plateau stress among all measured samples, which can be beneficial during root canal instrumentation as the instrument will not exhibit resistance to following canal geometry and hence prevent shaping defects like flanges and zipping. A consequence of this capability is that the original shape cannot be recovered, which could be achievable by post-thermal treatment. Finally, this study reported that the R-phase file also showed low bending stress and improved fatigue resistance.

Regarding austenite transformation temperatures, CM technology wires generally have the highest A_s and A_f temperatures.[50,52] CM-wires have exhibited similar properties of R-phase materials, like the remaining deformed shape and the subsequent recovery after thermal treatment,[50] pre-bending capability,[42] and a superior proportion of martensite microstructure.[37] These properties lead to a predominance of martensitic behavior, such as high flexibility, low bending resistance, and higher resistance to fatigue over conventional NiTi and M-wires.[38,66,69] Even though the martensite phases improved fatigue resistance, CM-wire files have shown low torsional resistance compared to those fabricated with M-wire.[17] Pedullá et al. compared the torsional strength and the number of cycles to fatigue (NCF) of ProTaper Next (M-wire) and HyFlex CM (CM-wire).[44] They concluded that while HyFlex CM files had higher NCF than ProTaper Next, torsional resistance was higher for the M-wire technology files.[44] This behavior was also found by Peláez Acosta et al., who found that even if crack ramification in a branched martensitic-like structure can be beneficial for energy dissipation and, hence, fatigue resistance, different types of loading applied to these multiple cracks could weaken the material.[22]

Alcalde et al. found that ProDesign R files (CM-wire) exhibited an evident angular distortion (plastic deformation), indicating that the instrument is close to fracturing.[17] Finally, manufacturers have developed different machining methods to conventional grinding, like electro-discharge machining (EDM) of CM-wires. Files manufactured by the EDM method are composed of martensite and a predominance of R-phase, enhancing flexibility and ductility and improving fatigue resistance.[95] Different studies have shown improvement in NCF of EDM compared to CM-wires of around 700%,[67,70] regardless of geometrical effects like cross-sectional shape and area. HDM files have also exhibited higher independence to temperatures than CM files, allowing their performance in a broader range of temperatures than seen in root canals.[38]

File geometry

Endodontic instruments possess highly complex geometrical features. It is well known that variations in shapes are highly diverse between manufacturers. File properties such as flexibility,[37,73] torsional strength[77,79,96] and fatigue resistance[17,65,97] are dependent on file size, taper, flute depth, pitch length, cross-section, helical angle, thread size, and cross-sectional shape. Regarding their size, in general, those files with a lower cross-sectional area at the maximum curvature point presented low stress levels and hence higher resistance to fatigue due to improved flexibility.[81,98] This factor can even be more crucial than wire technology for specific files.[60] On the other hand, smaller areas lead to low torsional strength values.[19,66] Regarding the shape of the cross-section, those with lower mass content in the core area also had improved fatigue resistance, as reported by Bhatt et al.[54] and supported by other authors.[41,62]

The cross-sectional shape and axial off-centering influence the times the file touches the root walls. High contact can lead to dentinal defects,[24,99] stress distributions along and across the file,[8,60,74,75] and influence cutting efficiency.[76] Also, the number of threads, commonly proportional to helical angle and inversely to pitch length, has been shown to influence endodontic file performance.[77,80] Peláez Acosta et al. reported that the shortest pitch (high number of threads) exhibited higher torsional resistance in files with a triangular convex cross-sectional area.[22] This effect was also reported by Oh et al. in V2H and NRT files.[77] Al Raeesi et al. explained improving cutting efficiency, relating a decreased pitch length with incrementing cutting edges.[80]

Operational factors

Regarding the dependence of endodontic file fractures on how the canal instrumentation is executed, two main factors can influence the instrument durability. First, two types of motor movements can be used in an endodontic procedure: a rotary and reciprocating motion. Over the last decade, reciprocating movements have been widely demonstrated to have notable advantages over rotary movements in avoiding severe damage to the files. Reciprocating movements avoid engaging the tip. This reduces torsional stress,[51] decreases the frequency of occurrence of one cycle during rotation,[84] releases accumulated stress,[62] and reduces torsional strength.[83] Since endodontic instruments have spiral geometrical configurations, the pull-in effect (screw-in effect or taper lock) can lead to plastic deformations as the endodontist applies a contrary force to counter it. In this sense, reciprocating motion eliminates taper lock as it does not rotate continuously as the instrument is inserted into the canal.[37,66] Pirani et al. claimed that this type of movement is suitable for specific wire technologies.[51] However, other works have not found any relationship between the type of movement and fracture resistance of endodontic files, nor in cutting ability.[76]

Second, the device engages in static and dynamic motions during instrumentation. Dynamic methodologies (such as the widely known pecking motion) refer to the in-and-out motion (at a specific amplitude). This methodology allows the distribution of stress to be generated along the file length instead of concentrating it on a limited section, avoiding stress levels that can cause plastic deformation (unwinding) or fracture. This stress distribution is through flexion in the curved segments or contact between the device and dentine surface.[8,37,86]. At the same time, the file is inserted into the root canal, which exhib-

its benefits over static motion (the file is inserted with zero amplitude) to prevent file fracture during operation. Concerning the frequency of the pecking motion, Zubizarreta-Macho et al. found that a low-frequency pecking motion increases fatigue resistance compared to a high-frequency motion.[85]

Regarding the amplitude of the pecking motion, two effects compete when the pecking amplitude is varied. On the one hand, a large pecking amplitude is recommended as it allows for stress distribution along a greater possible length of the file.[84] However, this large amplitude also increases screw-in forces during instrumentation, causing possible unwanted penetration beyond the apical foramen.[35,86] On the other hand, small amplitudes will concentrate torsional and flexural stress on specific file segments, reducing screw-in forces. In this sense, the pecking amplitude must be such that it does not allow the concentration of stress or high screw-in forces.

Further research must be carried out to determine optimal amplitude values. High forces when the file is inserted into the canal can produce high torque, leading to root dentin damage and instrument fracture.[35,37] Also, significant diameter differences between sequential files can severely affect the instrument's integrity and generate high-stress accumulation.[79] Finally, highlighting the critical role of the specialist when making decisions to ensure the instrument's suitability during the endodontic procedure is essential.[19]

Irrigation and sterilization

During canal root instrumentation, irrigation with NaOCl is widely used to achieve tissue dissolution and disinfection. The exposure of the endodontic file to this solution is well known to induce micro-pitting by removing Nickel from the surface in a corrosion process by the aggressive Cl-O ions.[72,88,90] This process has a detrimental effect on the instrument, reducing its fatigue resistance when highly stressed parts of the file and crack initiation zones on the surface are corroded.[41,91]

Many endodontists reuse endodontic files as a common practice, but sterilization procedures are implemented to eliminate cross-contamination between patients. Sterilization involves (among other aspects) the application of thermal treatment to the instrument, which strongly affects its composition and structural and morphological features. For this reason, it is essential to know how these changes can affect the instrument performance and, ultimately, its failure. As a favorable factor, it has been found that sterilization at certain temperatures and certain wire technologies have been found to improve flexibility/ductility and strength by rearrangement of the crystalline structure and by releasing crystalline defects and strain hardening.[77,89,98,100] However, repeated sterilization cycles can produce unfavorable effects on endodontic files, such as alteration of their chemical composition at the surface by oxidation and micro-pitting, inducing changes in morphological features, and reducing its cutting efficiency by 50%.[88] In this respect, after conducting studies on the sterilization of endodontic files, some authors have concluded that there is a strong correlation between sterilization processes and fracture resistance.[101,102] However, considered that few endodontic NiTi file manufacturers suggest the possibility of repeated use of the instrument. A single file must be developed, facilitating timesaving and possible use without adverse consequences.

Anatomic factors

As has been established, the endodontist can manipulate or modify certain factors to prevent file separation during root canal instrumentation. However, one factor that cannot be controlled by the professional and strongly influences instrument fracture. Root canals possess essential parameters such as curvature angles and radius, which have been found to influence an instrument's lifespan.[37,59,75,92] As the angle of curvature or the radii of curvature increases, the time before file fracture also increases, which is related to deformation amplitudes in the zone of maximum deformation.[40,75] In this sense, when considering the size, shape, and number of root canals, endodontists must determine suitable tools and methodologies to perform the procedure and prevent file separation.

Conclusions

Several aspects of file separation are related to mechanical causes of file fracture, such as the shape and dimensions of the file, loads applied during the operation on the endodontic instrument, and the manipulation of the instrument. Other significant factors are irrigant solutions, sterilization by autoclaving, anatomical features, and the alloys used for the files.

Research continues to improve the properties of the alloys, mainly the interaction between hyper-elastici y and fatigue strength, file geometry, and unique designs offering particular characteristics that reduce friction loading during the cutting process. Concentration limits have been established for irrigants, as their effect on files is known. More studies have yet to be performed on the thermal effects on the strength of materials during sterilization.

Material compliance and stiffness, operational temperatures, cutting efficiency, stress distribution in the file, surface modifications, corrosion, and recrystallization processes in post-heat treatments all contribute to the final performance of the file, implying a high complexity of failure and difficult predictability of the instrument.

Another factor to be considered is the selection of ap-

propriate files. Various options, such as wire technology, type, size, and shape of the files, manipulation techniques, exposure to corrosive environments, and sterilization processes, should be based on the specific anatomical features of the root canal.

What properties of endodontic files and work conditions that preclude file separation, including how many times the files can safely be reused while maintaining appropriate properties, has been the subject of significant research in the dental literature. However, the causes of instrument fracture remain incomplete and further research is needed. To avoid unexpected file separation, the use of the endodontic file must follow the manufacturer's indications regarding the permissible number of sterilizations.

Many of the articles reviewed were laboratory studies focused on determining the performance of files subjected to different factors that can cause a fracture. The clinical relevance of these studies is difficult to assess because the experiments were done under conditions significantly different from those in the oral cavity.

It seems necessary to standardize different methodologies to compare the factors that statistically cause fracture failures of files.

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

Epoxy resin-based root canal sealers: An integrative literature review

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Abstract

The correct obturation of the root canal system achieved by means of a core and a cement is essential for the success of endodontic treatment. There are several root canal cements (RCCs) on the market; however, because of their excellent characteristics, epoxy resin-based sealers (ERBSs) have been widely used. The main aim of this review was to analyze and integrate the available information on different ERBSs. An electronic search was performed in the PubMed and Scopus databases, using "epoxy resin" AND "root canal treatment", and "epoxy resin" AND "endodontics" as search terms. In general, ERBSs have good flow properties, film thickness, solubility, dimensional stability, sealing capacity, and radiopacity. They are also able to adhere to dentin while exhibiting low toxicity and some antibacterial effects. However, their main disadvantage is the lack of bioactivity and biomineralization capability. A large number of ERBSs are available on the market, and AH Plus keeps being the gold standard RCC. Yet, information on many of them is limited or non-existent, which could be due to the fact that some of them are relatively new. The latter emphasizes the need for relevant research on the physicochemical and biological properties of some ERBSs, with the aim of supporting their clinical use with sufficient evidence via prospective and long-term studies.

Keywords: root canal sealants, root canal filling materials, AH Plus, epoxy resin-based root canal sealer

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Introduction

Three-dimensional obturation of the root space is essential for the long-term success of endodontic treatment. There are various materials and techniques available for obturation of the root space, with most techniques using a central core material and root canal cement (RCC). Regardless of the central core, the use of RCC is essential for hermetic sealing and fluid tightness.[1] Currently, there are several types of endodontic sealers available on the market with different compositions, the most common being RCCs consisting of zinc oxide eugenol, calcium hydroxide ($Ca(OH)_2$), glass ionomers, silicone sealers, calcium silicates, methacrylate resins, and epoxy resins,[2–4] even though they do not comply with all the requirements described by Grossman.[5] Epoxy resin-based sealers (ERBSs) can be considered the RCC of choice[6,7] for obturation of the root canal system because of their adequate physicochemical properties.[7,8] Most recent studies deal with ERBSs on a general basis[2,9] or approach their properties separately,[6,7,10–16] but notably, the present study analyzes, discusses, and integrates the properties of several of these types of RCCs available on the international market, and is the first one to approach their formulation-behavior relationship. This review aimed to analyze and integrate the available data on the different ERBSs, compiling information on the physical, chemical, and biological properties, formulations, and other areas of clinical interest of these RCCs.

Methods

In November 2020, a preliminary search was carried out for literature reviews related to the physicochemical properties of ERBS, and no studies were found that presented an extensive and updated overview of these sealers. In April 2021, an electronic literature search was performed utilizing the PubMed and Scopus databases and the search terms "epoxy resin" AND "root canal treatment", as well as "epoxy resin" AND "endodontics", to find studies that contained these search terms that had been published within the last 10 years. A second search was performed in August 2022, to analyze the information pertaining to the ERBS formulation components.

Only original works published in English were included. A total of 604 and 264 manuscripts were found in PubMed and Scopus, respectively. The search was limited to clinical trials, in vitro studies, literature reviews, systematic reviews, and textbook chapters. Interim reports, abstracts only, letters, brief communications, studies that did not focus on ERBSs, and duplicated works were excluded. Additionally, agar diffusion studies and sealability studies, including linear and volumetric dye penetration assessment methodologies, autoradiographic detection of isotope penetration, radionuclide detection, culture techniques to detect bacterial penetration, salivary penetration models, fluid filtration techniques, fluorometry, intracanal reservoir techniques, and electrochemical techniques were also excluded because such studies have not been considered useful since reliable and reproducible evaluation methods related to clinical outcomes are required.[17] Subsequently, the titles and abstracts of relevant articles were reviewed and a manual search of the references of each selected article was performed to complement the electronic search. Finally, 91 articles and 6 textbook chapters were considered relevant and included in this review.

Since we only searched two electronic databases, this decision could have limited the results with regard to the inclusion of relevant literature in our review, e.g., grey literature was excluded during the literature search stage. Additionally, being an integrative literature review, the present study has inherent limitations, i.e., the complexity of using diverse selected studies, which apply different methods, has the potential to contribute bias and might, therefore, complicate data evaluation and analysis. However, at the same time, this type of review is the broadest of its kind and has the potential to resolve the complexities brought about by varied perspectives.[18]

General characteristics and formulations of ERBSs

Epoxy resin was patented by P. Casta, a Swiss chemist from DeTrey (Zurich, Switzerland), in 1938.[9] ERBSs were introduced into endodontics by Schroeder in 1950, with the market launch of AH 26® (Dentsply Maillefer).[19] Due to its release of formaldehyde, which causes cytotoxicity in periapical tissues, this sealer has been modified to what is now marketed as AH Plus® (Dentsply Sirona).[10,20] This RCC has been extensively evaluated and compared to other alternatives and, based on its physicochemical properties and biological response, is currently considered the gold standard (Fig. 1).[21–24] However, there are other commercially available ERBSs, with different compositions, according to the manufacturer, and are included in Table 1. Based on our performed search, there is no review that integrates information on the characteristics as well as the physicochemical and biological properties of these types of sealers. A compilation of the information on ERBS physical, chemical, and biological properties with highlights of clinical interest is presented in detail below in different sections.

With regard to Table 1, it must be emphasized that all of the listed ERBSs shall finally form an epoxy resin; however, one should take into consideration that the structure of a material results in the formation of its properties, and the latter determines the behavior of the material. In this regard, most commercially available epoxy resins are based on diglycidyl ethers of bisphenol-A, bisphenol-F,

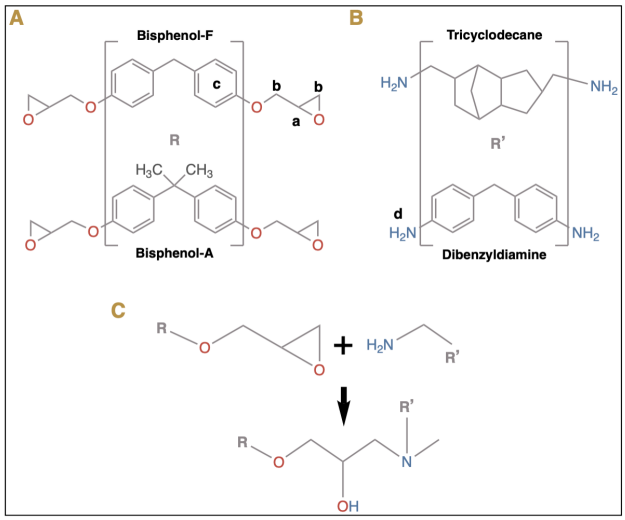

Fig. 1. Molecular structure of the main chemical components of epoxy resin–based endodontic sealer (ERBS) AH Plus

or other phenolic compounds,[25] which react with curing agents. However, almost none of the ERBSs have the same formulation; thus, in the next paragraphs of this section, we will discuss some relevant compounds in the formulations described in Table 1, alongside various other compounds in subsequent sections.

As for the curing agents listed in Table 1 (which are aliphatic and aromatic amines), epoxy resins may be cured with any of them, because they have a labile hydrogen atom or hydroxyl group that reacts with the epoxy rings and initiates the polymerization process, even at room temperature. However, aliphatic amines are strong skin irritants, while aromatic amines impart higher temperature stabilities.[25] AH-26, Sealer 26, Sealer Plus, and Acroseal contain methenamine (hexamethylenetetramine), which releases formaldehyde during the polymerization process, being an inherent disadvantage of these sealers due to its toxicity[26], although the released quantity is considered negligible.[27] Poly(aminobenzoate) is contained in Adseal, MM-Seal, Sicura Seal, and SimpliSeal and is effective in applications where long working times, substrate wettability, and lower heat-build are required,[28] thereby improving the performance in these ERBS. On the other hand, methenamine (which decomposes into formaldehyde and ammonia in an acidic environment) is curiously also used as a food preservative or fraudulently in dairy products.[29] Additionally, formaldehyde is a natural by-product of amino acid metabolism in almost all cells, with the endogenous level known to be 3–12 ng/g in tissues[30] and 2.5 ppm in plasma.[31]

On the other hand, Sealer Plus has silicone and siloxanes (the –Si–O–Si–O– backbone of silicones is referred to as siloxane) added to its composition. In this regard, this backbone confers silicones with a very high thermal stability[25] and results in the enhancement of flexibility, toughness, durability, and chemical and weather resistance.[32] These could be the reasons for their addition to this sealer. AH Plus, Thermaseal Plus, Topseal, Sealer Plus, and 2Seal have silicone oil (polydimethylsiloxane) in their composition, which is hydrophobic in nature, resistant to bacterial degradation, has an extremely low surface tension, and adsorbs strongly to solid surfaces.[33] Additionally, it possesses high heat resistance and lubricant properties.[34] All these properties would certainly favor the clinical behavior of these sealers.

It has been stated that the most important additive in an adhesive composition is the filler (improving thermal stability, bond strength, and flow properties).[25] However, ERBS manufacturers do not specify it in their formulations. In this regard, some sealers (AH Plus, Thermaseal Plus, Topseal, Sealer Plus, 2Seal, and Obturys) contain silica – also defined as silicon dioxide[35] – in their formulations. This is an inorganic filler that has exhibited pivotal effects in relation to reducing shrinkage during curing as well as conferring thixotropic properties and improving the bond strength of epoxy adhesives[25]; it also stimulates osteogenesis by inducing biomineralization.[36] Finally, titanium dioxide is a filler in AH26 and Sealer 26 and is widely used to produce a white color in numerous products.[37]

Acroseal is the only ERBS that contains (three) plant-derived ingredients, i.e., hydrogenated rosin, Venice turpentine, and enoxolone. Hydrogenated rosin (colophony) and Venice turpentine are diterpenic resins with very similar compositions (complex mixtures of resinous acids)[38] that enable cross-linking and polymerization in the polymer matrix.[39] Both of them possess excellent adhesive properties and are often included as additives in adhesive formulations to increase adhesion, brightness, and toughness.[38] Recently, rosin has attracted attention in the formulation of biobased epoxy resins from renewable resources.[40] Furthermore, enoxolone (glycyrrhetinic acid) is a bioactive triterpenoid compound of licorice (*Glycyrrhiza glabra*) that exhibits anti-inflammatory, antioxidant, and anti-nociceptive properties,[41] which are ideal for an endodontic sealer formulation.

Oxyranes – also known as epoxides[42] – are described in Obturys formulation. They represent one of the new monomers that have been developed to substitute bisphenol A-containing BisGMA dental composites.[43] Oxyranes are cyclic ether compounds that are more hydrophobic than methacrylates, and they polymerize via cationic ring-opening processes, which reduces polymerization shrinkage stress.[42] Although the latter would benefit the clinical behavior of the ERBS, there are no published studies that have evaluated such issues.

Perma Evolution contains poly(hexamethylenebiguanide)-hydrochloride, which is considered an antibacterial agent[44] and could improve the antibacterial properties of this sealer. However, there are no published studies that have evaluated this property. Other ERBS-containing antibacterial agents are described below in the antibacterial section, and those containing $Ca(OH)_2$ are described in the biocompatibility and bioactivity sections.

Table 1. Epoxy resin-based sealers (ERBSs) available on the international market

Sealer	Composition*		Manufacturer
AH Plus	paste A: bisphenol A epoxy resin, bisphenol F epoxy resin, calcium tungstate, zirconium oxide, silica and iron oxide pigments	paste B: bibenzyldiamine, aminoadamantane, tricyclodecane-diamine, calcium tungstate, zirconium oxide, silica and silicone oil	Dentsply Maillefer, DeTrey, Germany
Thermaseal Plus			Dentsply Sirona, Becht, Germany
Topseal			Dentsply Maillefer, Ballaigues, Switzerland
AH-26	resin paste: epoxy resin	powder: bismuth oxide, methenamine, silver, titanium dioxide	Dentsply Maillefer, DeTrey, Germany
Acroseal	base: hexamethylene tetramine, bismuth subcarbonate, hydrogenated rosin, paraffin oil, venice terpentine, enoxolone	catalyst: bismuth carbonate, calcium hydroxide, diglycidyl ether bisphenol A, yellow iron oxide	Specialités-Septodont, Saint Maur-des-Fossés, France
Adseal	base: epoxy oligomer resin, ethylene glycol salicylate, calcium phosphate, zirconium oxide, bismuth subcarbonate	catalyst: polyaminobenzoate, triethanolamine, calcium phosphate, bismuth subcarbonate, zirconium oxide, calcium oxide	Meta Biomed Co, Cheongju, Korea
DiaProSeal	paste A: epoxy resin, zirconium oxide, calcium hydroxide	paste B: calcium tungstate, zirconium oxide, calcium hydroxide	Diadent, Cheongju, Korea
EasySeal	diethylenetriamine, amine-epoxy-based no further information		Komet Dental, Lemgo, Germany
Epoxidin	epoxide resin, amine hardening agents, zirconium oxide as a radioopaque filler, a lime component, and a plasticizing agent		TehnoDent, Severnyi, Russia
EZ-Fill Xpress	information not available		Essential Dental Systems, South Hackensack, USA
MM-Seal	base: epoxy resin, ethylene glycol salicylate, calcium phosphate, bismuth subcarbonate, zirconium oxide	catalyst: polyaminobenzoate, triethanolamine, calcium phosphate, bismuth subcarbonate, zirconium oxide, calcium oxide	Micro-Mega, Besançon, France
Obturys	paste A: 4,4'-isopropylidenediphenol, oligomeric reaction products with l-chloro-2,3- epoxypropane, zirconium dioxide, silicon dioxide	paste B: oxirane, 2-methyl-, polymer with oxirane, bis(2-aminopropyl) ether, zirconium dioxide, silicon dioxide	Itena, Paris, France
Obtuseal	base: TCD-diamine, a radiopaque excipient	catalyst: calcium hydroxide, DGEBA (diglycidyl ether of bisphenol A) and radiopaque excipient	A.T.O., Zizine, France
Perma Evolution	paste A: 4-[2-(4-hydroxyphenyl) propan-2-yl]phenol-epichlorohydrineresin, alkylglycidyl ether, barium sulfate, tricalcium phosphate, diphenylolpropan-diglycidyl ether	Paste B: polyalkoxyalkylamine-copolymer, 5-amino-1,3,3- trimethylcyclohexanmethylamin, aqua, barium sulfate, tricalcium phosphate, nanodispersed silicon dioxide, polyhexamethylene biguanides-hydrochloride	Becht, Germany
Radic Sealer	base: poly epoxy resin, zirconium oxide	catalyst: TEA (triethanolamine), zirconium oxide, calcium oxide	KM, Seoul, Korea
Sealer 26	powder: calcium hydroxide, bismuth oxide, hexamethylenetetramine, titanium dioxide	resin: bisphenol epoxy resin	Dentsply, Rio de Janeiro, Brazil
Sealer Plus	base: bisphenol A-coepichlorohydrin, bisphenol F epoxy resin, zirconium oxide, silicone and siloxanes, iron oxide, calcium hydroxide	catalyzer: hexamethylenotetramine, zirconium oxide, silicone and siloxanes, calcium hydroxide, calcium tungstate	MK Life, Porto Alegre, Brazil
Sicura seal	base: epoxy oligomer resin, ethylene glycol salicylate, calcium phosphate, bismuth carbonate, zirconium oxide	catalyst: polyaminobenzoate, triethanolamine, calcium phosphate, bismuth carbonate, zirconium oxide, calcium oxide	Dentalica, Milan, Italy
SimpliSeal	base: epoxy oligomer resin, ethylene glycol mono salicylate, calcium phosphate, bismuth subcarbonate, zirconium oxide	catalyst: poly(1.4-butanediol)bis (4-aminobenzoate), triethanolamine, calcium phosphate, bismuth subcaronate, zirconium oxide, calcium oxide	DiscusDental, Culver City, USA
2Seal	paste A: bisphenol A epoxy resin, bisphenol F epoxy resin, calcium tungstate, zirconium oxide, silica and iron oxide pigments	paste B: dibenzyldiamine, aminoadamantane, tricyclodecane-diamine, calcium tungstate, zirconium oxide, silica and silicone oil	VDW, Munich, Germany

* information obtained from the manufacturers.

On the other hand, Sicura seal and SimpliSeal contain ethylene glycol salicylate, also known as 2-hydroxyethyl salicylate, which is formed from the condensation of the carboxyl group of salicylic acid with one of the hydroxyl groups of ethylene glycol.[45,46] Salicylates are very often used in the formulation of topical anti-inflammatory products for the treatment of mild to moderate pain.[45,46] Additionally, derivatives of salicylate resins are used to obtain resins/polymers[47] and it has been shown that the flow ability of some sealers is influenced by the type of salicylate resin and its particle size.[46]

Finally, regarding the ERBS compositions listed in Table 1, it must be taken into consideration that specific processes and/or ingredients for formulating sealers are proprietary of the manufacturer. Moreover, many manufacturers do not provide any information about the composition ratio of these sealers.[46] These issues inherently limit an ample discussion on the above-mentioned structure-properties relationship.

Physicochemical properties

The physicochemical properties of ERBSs are described in the sections that follow, and a condensed table of information regarding these properties is presented in Table 2, including their flow, film thickness, solubility, setting time, dimensional change, and radiopacity.

Flow

According to the American National Standards Institute and American Dental Association (ANSI/ADA) No. 57 and The International Organization for Standardization (ISO) 6876, RCCs should have a minimum flow rate of 17 mm.[48,49] Available evidence shows that the sealers AH Plus,[11,12,20,21,50–58] ThermaSeal Plus,[50] Acroseal,[11] Adseal,[11,20,56,59] EasySeal,[53] EZ-Fill Xpress,[52] MM-Seal,[58] Pherma Evolution,[12] Radic Sealer,[20] Sealer Plus,[21,51] and SimpliSeal[52] meet the established requirements. On the other hand, 1 study evaluated Dia-Proseal and AH Plus (Table 2),[59] which fell short of achieving the required values; this difference may be due to the methodology used since the authors mention that more precise evaluation techniques (rheometer) should be used.[59]

The activation of sealer cements with sonic and ultrasonic protocols has shown an increase in flow values of AH Plus and Adseal, which attained the highest values after ultrasonic activation while still complying with ANSI/ADA No. 57 and ISO 6876 standardizations. The heat generated during this process reduced the viscosity of the sealers, increasing their flow and improving their rheological and mechanical properties, especially their cohesive strength.[63] On the other hand, the manufacturer of EZ Fill Xpress recommends that it be warmed using a heated spatula to improve its fluidity.[64] However, high flow may result in apical extrusion, possibly leading to periapical tissue injury due to RCC cytotoxicity[50] and subsequent postoperative pain.[65]

Film thickness

ANSI/ADA No. 57 and ISO 6876 suggest that this thickness should not exceed 50 μm.[48,49] Resin-based sealers have shown greater adhesion to dentin in thicker layers. On the contrary, in thin layers, there is greater penetration of the RCC into the dentinal tubules. In this regard, the resin matrix of the cement penetrates the dentinal tubules, while the filling particles do not, due to their larger size, thus leaving a layer enriched with particles but without resin in the canal wall, resulting in a lower adhesion strength.[13,14] These findings suggest that the "ideal" thin film for this type of RCC needs to be reconsidered.[14]

The sealers AH Plus,[11,52,53] Easy Seal,[53] EZ-Fill Xpress,[52] and SimpliSeal[52] meet standardizations. On the other hand, 1 study reported values of 85 ±8 μm for the film thickness of AH Plus.[55] Acrosel and Adseal obtained values higher than 50 μm (Table 2). Although the different studies comply with the standardized methodology, the available information does not specify the causes of the variations in the results.

Water solubility

Solubility indicates the mass loss of the material when immersed in water. RCCs must have a low solubility.[60] The solubility, according to ANSI/ADA No. 57 and ISO 6876, must be less than 3%.[48,49] Conventional methodologies for assessing solubility have some limitations, so microcomputed tomography (micro-CT) imaging methods are currently being used to complement the tests performed by ANSI/ADA No. 57 and ISO 6876.[57]

The difference in material weight before and after immersion in water may not represent the solubility of all RCCs, as some of these materials may absorb water, even though they exhibit solubility.[57] A soluble RCC can degrade and leach chemicals over time, creating voids within the material or at its interface with surrounding tissues/materials.[54] These voids could serve as pathways for microorganisms to transverse the root canal into the periapical tissues, while the leaching of chemicals can irritate periapical tissues.[53,54]

ERBSs have low solubility,[11,55] which may be due to the strong cross-linking of these RCCs.[55,58] This characteristic is desirable if the stability of the material in the intraradicular space is taken into account but may not be the best property when the material is extruded. The fate of the RCC will depend on its solubility in tissue fluids and its susceptibility to phagocytosis.[66,67] According to a solubility evaluation of AH Plus and Obturys, values of 0.0% and 0.2% at 24 h, respectively, were obtained.[60] The solubility studies of AH Plus,[21,51,53–60] Topseal,[61] Acroseal,[11,61]

Adseal,[11,56,59] AH-26,[61] Dia-Proseal,[59] EasySeal,[53] MM-Seal,[58] Obturys,[60] Sealer 26,[51] Sealer Plus,[21] and 2Seal[61] meet the standardizations (Table 2).

Setting time

This time should not exceed more than 10% of that indicated by the manufacturer[49]; however, a sufficiently long time is required to allow the placement and adjustment of the sealing material, which provides a clinical advantage.[68] On the other hand, a slow setting time may cause tissue irritation and affect solubility, leading to seal failure,[54] and is therefore considered a critical clinical issue.[57] The setting time of AH Plus can be affected by the portion of the tube from which the paste is dispensed, i.e., the initial, intermediate, or final segment.[15,55] Thus, it is more fluid at the beginning than at the end, since it is not uniform and its consistency changes along the tube; there is incomplete miscibility between the components, which certainly alters the monomer–catalyst ratios.[15] The setting times obtained by different authors are detailed in Table 2. Their high values are probably due to the occurrence of slow polymerization between the amines in the epoxy resin, where the conversion of monomers into polymers occurs gradually.[55,58]

One study evaluated how sonic and ultrasonic activation influences the setting times. AH Plus increased its time from 7.71 ±0.02 to 8.63 ±0.24 and 16.52 ±0.12 h,

Table 2. Summary of the physicochemical properties of epoxy resin-based sealers (ERBSs)

ERBSs	Flow [mm]	Film thickness [μm]	Solubility [%]	Setting time [min]	Dimensional change [%]	Radiopacity [mm Al]
AH Plus	39.16 ±3.85[11] 21.87 ±1.40[20] 21.2 ±0.27[50] 32.25[54] 19.81 ±1.58[21] 23[55] 36.80 ±0.57[36] 34.48 ±0.07[56] 21.3 ±1.1[57] ≈14[59] 36.42 ±0.40[58] 21.94 ±0.74[51] 23[52] 18 ± 1.0[53]	43.65 ± 0.49[11] 85 ± 8[55] 21–30[52] 8 ± 1[53]	0.30 ± 0.02[11] 0.001[54] −0.25 ±0.10[55] 0.212 ±0.046[21] 0.73 ±0.76[56] 0.2 ±0.4[57] ≈ 0.00001[59] 0.41 ±0.21[58] 7 days: 0.20 ±0.08[51] 30 days: 0.21 ±0.07[51] 24 h: 0.0 ±0.0[60] 4 weeks: 0.1 ±0.1[60] 0.1 ±0.1[53]	711.33 ±95.03[11] 1,345 ±16[55] 617–869[54] 437 ±7–849 ±15[21] 463.0 ±1.45[56] 385.0 ±4.5[57] 463.60 ±13.22[58] 497 ±19[51] ≈1,440[52] 1,440[53]	0.50 ±0.36[56] −0.4 ±0.2[57] ≈1.9[59] 2.2 ±2.1[53]	14.50 ±1.69[11] 8.05[54] 15.74 ±0.25[55] 18.4[62] 7.58 ±0.14[21] 7.65 ±0.54[56] 9.2 ±0.5[57] ≈14[59] 7.52 ± 1.59[58] 9.50 ± 0.30[51]
Topseal	–	–	24 h: 0.07[61] 28 days: 0.082[61]	–	–	–
ThermaSeal Plus	21.3 ±0.47[50]	–	–	–	–	–
Acroseal	39.66 ±2.51[11]	65.50 ±6.36[11]	24 h: 0.36[61] 28 days: 0.746[61]	1,230.00 ±42.42[11]	–	5.86 ±0.73[11]
Adseal	37.66 ±2.08[11] 21.87 ±1.40[11] 55.16 ±0.01[56] ≈ 22.5[59]	65.00 ±7.07[11]	0.24 ±0.00[11] −1.68 ±1.96[56] ≈−0.00009[59]	70.00 ±9.00[11] 241.33 ±9.71[56]	8.84 ±4.05[56] ≈1.9[59]	5.84 ±0.66[11] 4.34 ±0.67[56] ≈7[59]
AH-26	–	–	24 h: 0.28[61] 28 days: 1.75[61]	–	–	–
DiaProSeal	≈16.5[59]	–	≈−0.00009[59]	–	≈1.9[59]	≈7.5[59]
EasySeal	17.3 ±0.8[53]	6 ±2[53]	2.7 ±0.3[53]	246[53]	3.4 ±1.4[53]	–
EZ-Fill Xpress	20[52]	31–40[52]	–	≈120–180[52]	–	–
MM-Seal	52.75 ±0.60[58]	–	0.94 ±0.17[58]	47.60 ±4.39[58]	–	3.32 ±0.90[58]
Perma Evolution	35.78 ±0.46[12]	–	–	–	–	–
Radic Sealer	20.80 ±0.84[11]	–	–	–	–	–
Obturys	–	–	24 h: 0.2 ±0.0[60] 4 weeks: 0.6 ±0.2[60]	–	–	–
Sealer 26	–	–	7 days: 0.45 ±0.20[51] 30 days: 0.95 ±0.21[51]	–	–	–
Sealer Plus	19.19 ±0.52[21] 18.95 ±0.74[51]	–	0.266 ±0.027[21]	138 ±10–210 ±18[21] 196 ±14[51]	–	5.42 ±0.20[21] 4.00 ±0.90[51]
SimpliSeal	23[52]	1–10[52]		≈110[52]	–	–
2Seal	–	–	24 h: 0.037[61] 28 days: 0.04[61]	–	–	–

Cements without available information were excluded from the table.

respectively, as these procedures can raise the temperature inside the root canals by up to 2°C. The ultrasonic devices may generate radicals in the organic portion (catalysts) due to increases in temperatures and pressures, generating a slow polymerization reaction.[56] On the contrary, Adseal showed the opposite behavior, decreasing the setting time from 4.02 ±0.16 to 2.60 ±0.19 h with sonic and to 2.36 ±0.12 h with ultrasonic activation, which may be related to the different percentages and types of polymerizing agents present in the compositions of these sealers.[11,56]

Dimensional change after setting

ANSI/ADA No. 57 standardizations recommend that this value should range from −1% (linear shrinkage) to +0.1% (expansion).[48] ERBSs are considered "shrinkage-free" during the setting reaction[11]; however, their expansion is still possible because they are capable of absorbing water.[55] AH Plus,[53,56,59] Adseal,[56,59] Dia-Proseal,[59] and Easy Seal[53] did not meet the standard (Table 2). These studies showed increases in dimensional changes, which could be explained by water absorption. However, Adseal showed higher values, owing to its property of high hygroscopicity, which distinguishes it from other cement and could contribute to improving the sealing capacity.[59] Another possible explanation for the latter result is the relatively high values of the standard deviation in this study, suggesting measurement inconsistencies. Additionally, the different methodologies used in different studies are prone to errors, as air bubbles may be present in the freshly mixed sealer materials, thus changing their density.[53]

The existence of voids is of clinical relevance because shrinkage of sealers of as low as 1% can result in voids and spaces that are sufficiently large enough for the penetration of bacteria and their harmful products.[69,70] In a study that evaluated the single cone technique in root canals via micro-CT and nano-CT, AH Plus demonstrated a significantly higher void fraction in terms of internal, external, and combined voids compared to Total BC and Sure Seal, which are calcium silicate-based sealers (CSBSs).[69]

Radiopacity

ANSI/ADA No. 57 and ISO 6876 standardizations require a radiopacity greater than 3 mm/Al.[48,49] The sealers AH Plus,[21,51,54–59,62] Acroseal,[11] Adseal,[11,56,59] Dia-Proseal,[59] MM-Seal,[58] and Sealer Plus[21,51] meet the standardizations (Table 2). AH Plus and Sealer Plus have the same radiopacifying agents, namely calcium tungstate, zirconium oxide, and iron oxide,[55,58] while Adseal has bismuth subcarbonate and zirconium oxide, and Acroseal contains only bismuth subcarbonate.[11] It has been reported that there is a deposit of radiopacifying agents at the lower end of the tube, while the upper portion may present a lower content,[11,55] which could be due to the above-mentioned incomplete miscibility between the organic and inorganic components contributing to segregation between both phases.

On the other hand, the radiopacity test shows variations in the behavior of the sealers in relation to the activation protocols of AH Plus and Adseal. As regards sonic activation, the variation in radiopacity may be related to greater or lesser exposure to the inorganic compounds present, which can occur randomly and are due to the hydrodynamic movement caused by the sound waves. Application of the ultrasonic protocol increased the radiopacity of AH Plus and reduced that of Adseal, which may be due to the induced changes in the crystal structures of the radiopacifying agents. The cavitation phenomenon, which induces the implosion of air bubbles and causes a local increase in temperature and pressure conditions, in combination with microflows generated by cavitation oscillations, would cause dispersion effects and agglomerate fragmentation in the inorganic components present in the sealers.[56]

Effects of heat application

Obturation techniques with high temperatures and/or long durations are associated with earlier polymerization, resulting in changes in the chemical structure of epoxy monomers, amine hardeners, and calcium tungstate fillers. These changes are temperature- and time-dependent, and the latter would have a greater impact.[63]

For AH Plus, it has been reported that heat treatment had an adverse effect on physical properties, such as setting time, which was reduced to 12.9 ±0.7 min when the temperature was raised from 37°C to 140°C for 10 min.[71] This reduction may be associated with a change in the setting reaction.[72] The flow rate was raised to 25.6 ±0.7 mm when the temperature was raised from 25°C to 140°C.[71]

In one study, temperatures of 37°C or 100°C for 1 min were used on AH Plus, resulting in a reduction in setting time and an increase in film thickness.[73] This ERBS showed a decrease in its N–H groups when heated at 100°C for 1 min, whereby the reduction of polyamines (dibenzyl diamine, aminoadamantane, and tricyclodecane) affected the polymerization process, with changes in the physical and mechanical properties of the material.[73] However, the overheating of AH Plus was performed using temperatures above those applied in clinical conditions.[72]

Adhesion to dentine

The chemical adhesion of epoxy resins to the tooth structure is produced by covalent bonds between the open epoxy groups and the exposed amino groups in the collagen network of the dentin. This is one of the reasons

for the good dislodgment resistance of ERBSs.[74–76] Mechanical bonding is provided by the penetration of the cement into the dentin tubules (tags), and its characteristics depend on the physical properties of the RCCs.[1]

Unlike methacrylate resins, epoxy resins have a lower tag frequency. This may be due to the hydrophilic characteristics of the methacrylate resins as well as their slow chemical reaction, which promotes the reduction of shrinkage stress and allows the sealer to flow more freely, reaching deeper into the dentinal tubules and thus forming a greater number of tags. However, the micromechanical retention of sealers through the penetration of the tags into the tubules is not the most important factor affecting adhesion.[77] The higher bond strength of AH Plus, in contrast to its low tag formation, could be explained by the higher prevalence of cohesive failures for this RCC[16] in contrast to methacrylate resins that presented mixed or adhesive failures with dentin.[77]

Factors that can influence bonding strength

Dentin wettability, the use of antimicrobial irrigants and chelating agents

Adhesion can be affected by the condition and degree of wettability of the dentin,[78] due to the hydrophobic nature of cements.[79] Residual moisture could adversely affect the conversion of the epoxy resin monomer, leading to incomplete polymerization of the resin and decreased bond strength to dentin.[78,79] The use of sodium hypochlorite (NaOCl) may affect the adhesion of ERBSs if it is used as a final irrigant.[80,81] Traces of this strong oxidizing agent or its oxidative by-products, such as hypochlorous acid and hypochlorite ions, would also compromise the bond strength of the sealer to root dentin and its sealing capacity.[80] Another logical reason for this is that oxygen bubbles, which form after the use of NaOCl, impede the penetration of the sealer into the fine openings of the dentin tubules.[80]

Evidence shows that the final irrigation with EDTA 17%, SmearClear, and QMiX promoted proper smear layer removal, which ensured the adequate bond strength of AH Plus.[82]

Laser

Laser application is another type of treatment of the dentin surface that can influence the bond strength of the RCC.[83] A study on the effect of chemical treatments and the use of lasers on the bond strength revealed that citric acid had a higher average bond strength compared to the Er:YAG laser for RealSeal, AH Plus, and EndoREZ sealers, but not Acroseal.[84] On the contrary, EDTA activation with Nd:YAG (1,064 nm) and diode (980 nm) lasers resulted in better bond strength of the ERBSs at the level of all root canal thirds compared with EDTA alone and EDTA with ultrasonic agitation. The application of these wavelengths, together with EDTA activation, could increase the permeability of the root dentin.[85]

Filling techniques

The highest values of bond strength have been observed using the lateral condensation technique (LCT) and Tagger's hybrid technique (THT).[86] Similar results were obtained in another study wherein the strengths of the bonds to human dentin using AH Plus/gutta-percha (GP), Sealer 26/GP, Epiphany SE/Resilon, and Epiphany SE/GP root canal filling materials, when LCT or THT were used, were evaluated by means of push-out tests. The highest push-out forces were obtained when the canals were obturated using LCT with AH Plus and GP, followed by Sealer 26 and GP.[87] On the other hand, the lowest bond strengths were found with the continuous wave condensation technique, which could be explained by the presence of a thin cement layer, although the micro-CT images showed better results regarding the filling quality.[86]

Considering the need for heat to obtain a positive result in thermoplasticized GP techniques, a systematic review compared these techniques to cold lateral condensation, using micro-CT to evaluate the quality of root canal filling.[88] Although it was evidenced that neither technique could completely obturate the root canal, thermoplasticized techniques did have significantly fewer voids in most studies, which is clinically desirable. It is relevant to point out that six out of the nine included studies used ERBSs.[88]

Retreatment

Once the sealer penetrates the dentin tubules, its removal during retreatment is physically impossible[89]; therefore, no filling material can be completely removed.[90,91] Several studies have evaluated the retreatability of CSBSs compared to AH Plus, showing that the former achieved better results with less RCC residues and shorter retreatment times.[90,91] On the other hand, obturation with BC Sealer and a single GP master cone may result in blockage of the apical foramen and a loss of permeability in some cases, which is not the case for AH Plus obturation. The inability to regain working length and/or permeability may compromise retreatment by preventing adequate cleaning and shaping of the apical canal space, which may harbor bacteria. There is also evidence of retreatability for AH Plus and EndoSequence BC sealer, as they showed similar characteristics during retreatment procedures.[89]

The use of GP solvents like xylene and Endosolv E has been evaluated demonstrating a negative effect on the bond strength of AH Plus to the root canal. These solvents can change the chemical composition of the dentin surface because they are oil-based, making it difficult to

remove them completely from the root canal. This waxy film may interfere with the development of resin–dentin bonds.[92]

Biological properties

Biocompatibility (cytotoxicity)

RCCs have demonstrated severe inflammation, but over time, most sealers lose their irritant components and become relatively inert.[22,93] In cases wherein RCCs are extruded, they may be solubilized in periradicular tissue fluids, phagocytized, or become encapsulated by fibrous connective tissue.[66] In a study, only 15% of cases with AH Plus extrusion have shown complete clearance of the material over periods of even 10 years.[66]

The cytotoxicity of an ERBS seems to be directly related to its component epoxy resin and to the type of polymerization promoted by the amines, with the waste products of this reaction being toxic to cells.[4] It has been suggested that ERBSs containing bisphenol A diglycidyl ether can produce cytotoxicity upon release since it is a mutagenic component of these materials.[10,93] These cements could release small amounts of formaldehyde, which could explain their short-term toxicity.[4,22,93] AH Plus also has a greater release of calcitonin gene-related peptide compared to EndoSequence, which indicates a greater potential for causing pain and neurogenic inflammation.[89]

In the case of SimpliSeal, its calcium oxide and calcium phosphate components could contribute to its improved biocompatibility. On the other hand, although Sealer Plus has a similar composition to AH Plus, the addition of $Ca(OH)_2$ in its composition improved its histological results, leading to mild inflammation at 7 days.[22]

As for Sicura Seal, bisphenol A diglycidyl ether is not included in its composition; however, exudates or polymerization and/or degradation products may cause increased cytotoxicity.[93] The cytotoxicity of AH-26 occurs mainly in the first hours after polymerization since this sealer contains hexamethylenetetramine, which decomposes into ammonia and formaldehyde, which have shown significant cytotoxic effects.[10]

Antimicrobial effects

RCCs seem to have some degree of antimicrobial activity due to their composition. This effect is time-dependent, and it is unknown whether it can prevent reinfection of the root canal system in the long term.[94] In this regard, the development of RCCs that have long-term antibacterial properties has been suggested to prevent potential reinfection.[94–96] In recent years, there have been attempts to modify RCCs with antimicrobial nanoparticles, antibiotics, and antiseptics to endow them with such properties, but with minimal or no impact on their physicochemical properties. However, studies used different methodologies to evaluate these effects which precludes the possibility of direct comparisons.[94]

The incorporation of a small percentage of quaternary ammonium polyethylenimine (QPEI) nanoparticles into AH Plus[95,96] and an experimental ERBS[97] have exhibited a strong antibacterial effect on species such as E. faecalis found in dentinal tubules.[95–97] In addition, it has been proven that adequate physical properties are maintained in the experimental cement with added QPEI.[97] The use of quaternary ammonium-based compounds and functionalized nanoparticles seems promising as an approach for conferring bacterial inhibition. Nevertheless, the safety of nanoparticles for human body systems and tissues must first be confirmed before proceeding with their clinical use.[94]

Bioactivity/Biomineralization

A bioactive material has the ability to create a hydroxyapatite (HA) layer when it is in contact with calcium- and phosphate-rich tissue fluid.[98] The pH level, along with the release of calcium ions, are closely involved in this process.[21] Sealers with calcium oxide or $Ca(OH)_2$ included in their composition have the ability to dissociate into calcium and hydroxyl ions, which could lead to an increase in the local pH and the formation of mineralized tissues.[21] The release of hydroxyl ions, or even the release of calcium ions, depends on the material's area of contact with tissue fluids and its chemical characteristics (hydrophilic or hydrophobic), the presence of calcium-containing substances, the setting time, and the solubility.[21,99]

Based on these biological events, and with the goal of promoting biochemical conditions that accelerate tissue recovery,[100] nanostructured fillers of synthesized bioactive glass (BAG), HA, fluoride substituted hydroxyapatite (FHA),[7] and magnesium hydroxide,[101] among others, have been incorporated into AH Plus. ERBSs such as Acroseal,[11] Sealer Plus,[21] Sealer 26,[11] Dia-Proseal,[59] and Obtuseal[102] have $Ca(OH)_2$ within their composition. However, due to some of the physicochemical properties that each of them possesses, they are not able to release sufficient hydroxyl ions or calcium to promote mineralization. Thus, 1 study analyzed the results of Sealer Plus, in which it was determined that its extremely short setting time in conjunction with its low solubility precludes the release of hydroxyl ions[21]; meanwhile, Acroseal showed the longest setting time, but its calcium release was lower compared to Sealapex due to the presence of its insoluble epoxy base, so it did not demonstrate bioactivity either.[99]

BAG and HA nanostructured fillers represent a promising approach, as they improve the in vitro capacity of ERBSs for apatite formation, while FHA particles do not improve apatite layer formation.[7] As for magnesium hydroxide, it has been found to adequately stimulate bone

mineralization, and it has been mentioned that it would be an ideal additive to achieve bioactivity in cements such as AH Plus, as it causes greater osteoblastic differentiation compared to calcium ions.[101]

ERBSs vs. CSBSs

Recently, CSBSs have been introduced in the market as a new class of RCCs.[103] Their biological properties, such as high alkalinity sealing capacity, antibacterial properties, as well as bioactive induction of periapical healing and hard tissue formation,[23] as well as their fine particle structure and ability to set in wet environments,[103] have been highlighted as their main advantages over conventional sealers.[24] Considering these properties, a recent study suggested that GuttaFlow® Bioseal could even represent a promising material for root-end filling as it showed progressive healing, better tissue organization, and a reduction in the inflammatory response.[104]

We are facing a paradigm shift in obturation approaches, in which the objective is no longer only to provide a hermetic seal against bacteria and the reinfection of the root canal but, rather, to establish a more biological concept of obturation, in which CSBSs could become the most important sealers in coming years.[23] However, the number of formulations available on the market, the lack of relevant information on CSBSs in the literature, their high solubility compared to ERBSs,[6] as well as the unavailability of long-term clinical studies[105] prevents the recommendation and positioning of these RCCs as the gold standard in the field of root canal obturation.

Finally, if we consider that bioactivity and biomineralization are the desired properties in an RCC, perhaps the time has come for sound analysis, e.g., a position statement on this issue and a modification of the requirement list of an ideal sealer as originally proposed by Grossman.[5] In fact, some authors have already listed the capacity to be bioactive as an ideal criterion.[9]

Highlights of clinical interest

Shake sealer cements before use.

Discard the initial portion of the dispensing tube, as it may alter the flow, the setting time and radiopacity.

The ultrasonic activation of ERBSs can help to seal anatomical complexities. Take care of sealer extrusion.

ERBS have low solubility, so they are more stable, thus showing fewer spaces and voids, which could affect long-term clinical results.

ERBS can be used in controlled-heat obturation techniques with minimal changes in their chemical structure.

These sealers can be used with LCT and THT, obtaining higher bond strength values and, with the continuous wave condensation technique, show better results in terms of filling quality.

According to present evidence, when using the single cone technique, ERBS may not be a good option, owing to their higher void fraction, as opposed to CSBSs.

The use of ERBS is highly compatible with irrigation protocols that use chelating agents as the final irrigant, prior to root canal drying.

The use of oily solvents should be avoided during retreatment.

Extrusion should be avoided, as it may cause some degree of short-term cytotoxicity.

Conclusions

Despite the large amount of commercially available options for endodontic obturation, the “ideal” material has not yet been identified. This has led to the development of several obturation materials and experimental sealers incorporating nanoparticles and conferring them favorable physicochemical properties, such as increased antibacterial efficacy and bioactivity, which may lead to a concept transformation from a purely preventative cement into a biologically active one.

In general, the ERBSs have good flow properties, film thickness, solubility, dimensional stability, sealing capacity, and radiopacity. They are also able to adhere to dentin while exhibiting low toxicity and some antibacterial effects. However, their main disadvantage is their lack of bioactivity and biomineralization capability. AH Plus sealer, which has been extensively studied, is still considered the gold standard and has become the most important representative of a considerable number of sealer formulations based on epoxy resins, some of which, at present, even lack scientific evidence. The latter emphasizes the need for relevant research on the physicochemical and biological properties of some ERBSs, with the aim of supporting their clinical use with sufficient evidence via prospective and long-term studies. Finally, clinicians and researchers should consider formulation components of the different ERBSs to understand the characteristics and properties of these types of RCCs.

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

Comparative evaluation of resin-based sealers and bioceramic sealers for postoperative pain after endodontic treatment: A systematic review

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Abstract

The systematic review aimed to compare and evaluate the effect of resin-based sealers and bioceramic sealers on postoperative pain after endodontic treatment. Two reviewers independently conducted electronic search in PubMed, the Web of Science, ScienceDirect, the Wiley Online Library, SpringerLink, Google Scholar, and the Cochrane Library, employing a complete dual-review process to ensure the inclusion of all relevant studies in the review. The search was carried out until November 2021. After selecting eligible studies, the risk of bias assessment was carried out using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). A total of 1,931 studies were identified from the electronic search, and finally 10 studies were included after full-text assessment. In all our included studies, the visual analog scale (VAS) was used for recording pain scores. Most of the studies recorded pain intensity starting from 6 h to 7 days. The results showed that there was no significant difference between resin-based sealers and bioceramic sealers in terms of incidence or intensity of postoperative pain at any point in time.

Keywords: postoperative pain, root canal filling materials, root canal obturation, root canal sealers, endodontic pain

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Introduction

Despite significant improvements in endodontics, the pain experienced after treatment is inadvertent, but often a significant emotional concern for both patients and endodontists.

Patients after endodontic treatment experience pain ranging from 1.9% to 82.9%. Different endodontic treatment procedures are known to be associated with postoperative pain, such as calculation of working length with the apex locator connected to every other file, frequency of visits, instrumentation technique used, and also depends on the type of root canal filling materials used.[1]

Bacteria present on the outer surface of the tooth roots are thought to maintain periapical radiolucency and apical periodontitis.[2] Since the biofilm within the apical part of the canal can be difficult to detect and capture, some authors advised foraminal enlargement (FE).[3–5] This additional procedural step is shown to promote periapical healing in animal models.[6,7] However, there is disagreement about the needed extent of enlargement. An ideally prepared root canal should have a progressively tapering conical shape, which preserves the apical foramen and the original canal curvature without transportation. It has been shown that root canal preparation with engine-driven NiTi endodontic instruments results in significantly less canal transportation and fewer preparation errors without significantly compromising the tooth structure. The thickness of the remaining dentine following intra-radicular procedures may be the most important iatrogenic factor that correlates to the incoming fracture resistance of the root. Currently, available NiTi file systems have the best shaping ability, cleaning ability, and three-dimensional efficiency while at the same time preserving dentine structure and reducing the impact on tooth strength. Despite the advanced flexibility of NiTi alloy compared with stainless steel, fracture of NiTi endodontic instruments remains a problem in clinical practice. Providing NiTi files are used judiciously, the fracture incidence appears to be comparable.[8–10]

Adequate root canal filling further plays an important role in endodontic treatment because it prevents bacterial infection through reduced coronal leakage, closes the apex to fluid leakage in the periapical tissues, and reduces the microbial load in the root canal, thus arresting the disease progression.[11–13]

The sealers within the canal system disrupt periodontal tissue through the apical foramina, lateral canals, or leaching and interfere with the healing ability of the periodontal tissues. Thus, local inflammation caused by these materials eventually leads to postoperative pain. The severity of these inflammatory reactions depends on a variety of factors, including the composition of the sealers.[14,15]

It has been disclosed in various studies, that bioceramic materials improve the effectuality of endodontic treatment. Bioceramic sealers usually contain particles of zirconia, alumina, bioactive glass, calcium silicates, hydroxyapatite, and soluble calcium phosphates. This structure inside the sealer makes it resistant to leaks and makes it compatible with the biological environment. Bioceramic materials release biologically active substances that stimulate intratubular biomineralization in pre-osteoblasts and also promote odontoblastic differentiation, thereby enhancing the effectiveness of endodontic treatment.[16–18]

Resin-based sealers have improved physical properties, but on the other hand, their cytotoxic effects should be of concern, which requires the need to establish a better root-filling material. To overcome this, bioceramic sealers have recently been established with less cytotoxic compounds compared to resin-based sealers. It has also been suggested that there is better root integrity after root canal filling using bioceramic sealers. The solubility of these sealers remains a critical aspect of their properties.[19–22]

The three-dimensional canal system is usually obturated with gutta-percha and endodontic sealers. These materials are designed for use within the three-dimensional canal system, but sometimes, they interact closely with the periapical tissues, leading to inflammation and irritation of sensory nerve cells.

Endodontic sealer extrusion is a very common condition, but in very small amounts, it is usually well tolerated by periapical tissues. However, if the filling material is accidentally forced out to nearby neurovascular structures, nerve damage and subsequently altered sensation may occur. It is important to discuss that all root canal filling sealers are generally neurotoxic to some degree. Also, sealer extrusion is linked to future complications, such as nerve damage that may trigger symptoms of pain and cause flare-ups.[23–25]

To avoid problems with sealer extrusion, it is imperative to select sealers with better physicochemical properties and lower toxicities. AH Plus is a bisphenol epoxy resin that has been reported to cause an increase in postoperative pain after unintended sealer extrusion. However, patients showed less severe pain sensitivity with calcium silicate-based sealers compared to AH Plus sealers.[26]

However, this topic should be an area of interest to be discussed in additional literature and post-endodontic pain assessments after the release of calcium silicate-based material out of the apical foramen have yet to be identified.

There is a growing trend among clinicians who use calcium silicate-based sealers over resin-based sealers, but there is no literature evidence to prove its effectiveness in reducing pain after non-surgical root canal treatments. Therefore, the aim was to systematically review the scientific evidence regarding the influence of epoxy-resin and calcium silicate sealers on the incidence of postoperative pain after root canal treatment.

Methodology

Study design

The protocol for this study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and the PICO strategy.[27]

Research question and outcome

The focused question (PICO) was developed as follows: Does obturation with recently launched calcium silicate-based sealers (intervention) positively affect the postoperative pain (outcome) more than the epoxy resin-based sealers (comparison) in patients undergoing non-surgical root canal treatment (P)?

The primary outcome of this systematic review was to compare and evaluate the intensity of postoperative pain after obturation using calcium silicate-based sealers or epoxy resin-based sealers.

Selection criteria

Inclusion criteria

The following types of studies were considered:

1. Healthy patients (>15 years old) undergoing non-surgical root canal treatment, without restrictions concerning sex, the type of endodontic diagnosis or the type of tooth treated.
2. Randomized controlled trial (RCT) studies, controlled clinical trials (CCTs), and prospective and retrospective cohort studies.
3. Studies that used any resin-based sealers.
4. Studies that used any calcium silicate-based sealers.
5. Studies that included patients requiring root canal retreatment.
6. Studies that used the visual analog scale (VAS) scale.
7. Studies that were in English.
8. Studies that had documented follow-up time.

Exclusion criteria

The following types of studies were not taken into consideration:

1. Studies that were not RCTs, such as in-vitro studies, case reports, case series, and reviews.
2. Animal studies.
3. Studies with patients taking non-steroidal anti-inflammatory drugs (NSAIDs) that might interfere with the assessment of pain after endodontic treatment.
4. Patients with periapical lesions.
5. Studies with incomplete data regarding methods or those which used any method other than VAS for measuring postoperative pain outcomes.

Search strategy in the databases

PubMed, the Web of Science, ScienceDirect, the Wiley Online Library, SpringerLink, Google Scholar, and the Cochrane Library were used for the electronic search. The research was carried out until November 2021 with search alerts as a self-updating tool. Moreover, any relevant articles obtained from the cross-referencing of the screened articles were also included.

The following MeSH terms and synonyms were used for the initial search: ("pain, postoperative" OR "postoperative pain" OR "post obturation pain") AND ("root canal obturation" OR "endodontic obturation" OR "root canal sealer" OR "root canal sealant" OR "root canal filling materials"). A manual search of the endodontic journals in the journal section of our college library was also carried out.

Study selection

Duplicate studies were manually removed by the two reviewers and considered only once. Then, the studies were individually screened for their eligibility by the two reviewers, who analyzed the titles and abstracts of the studies that were retrieved. In case of any disagreement, a third reviewer was consulted. Then, the full texts of the selected studies were read, and the studies that met the inclusion criteria were retrieved by the same reviewers.

Data extraction from the eligible studies

After selecting the eligible articles, two independent reviewers extracted the following data: (a) author, year of publication and country; (b) study design; (c) sample size; (d) age (mean in years); (e) diagnosis of the disease condition; (f) type of teeth; (g) number of visits; (h) instrumentation; (i) obturation technique; (j) obturation material; (k) postoperative pain assessment time; and (l) postoperative pain assessment scale. The variation in the opinion between the authors over data extraction was resolved through discussion. In many selected studies, multiple treatment groups were present; in such cases, the data conforming to PICO was selected. In case of any obscure or missing data, the respective corresponding authors were contacted through mail (up to two times over 4 weeks). For the standardization of this review, studies that used VAS scores from 0–100 mm were converted to 0–10 cm.

Risk of bias assessment

Two reviewers independently assessed the quality of selected studies using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). This tool assessed 5 important domains (bias from the randomization process, bias due to deviation from the intended

intervention, bias due to the missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results), and all these domains were rated as a high, unclear/some concerns or low risk of bias. The study was judged to be at an overall high risk of bias if at least one domain had this result. A rating of some concerns was decided if multiple domains substantially lowered confidence in the result or some concerns were raised in at least one domain. Studies found not to be at high risk of bias for any domain or judged to be at an overall low risk of bias for all the domains were identified as low-risk.[28]

Results

Search details

The electronic search was conducted, and a total of 1,931 studies were identified. After removing the duplicates, 1,320 studies were screened for their title and abstracts. Twenty studies were selected for the full-text assessment process, and finally, 10 studies were eligible to be included in this analysis.[1,11,12,14,16–19,26,29] The detailed depiction of search details is given in Fig. 1.

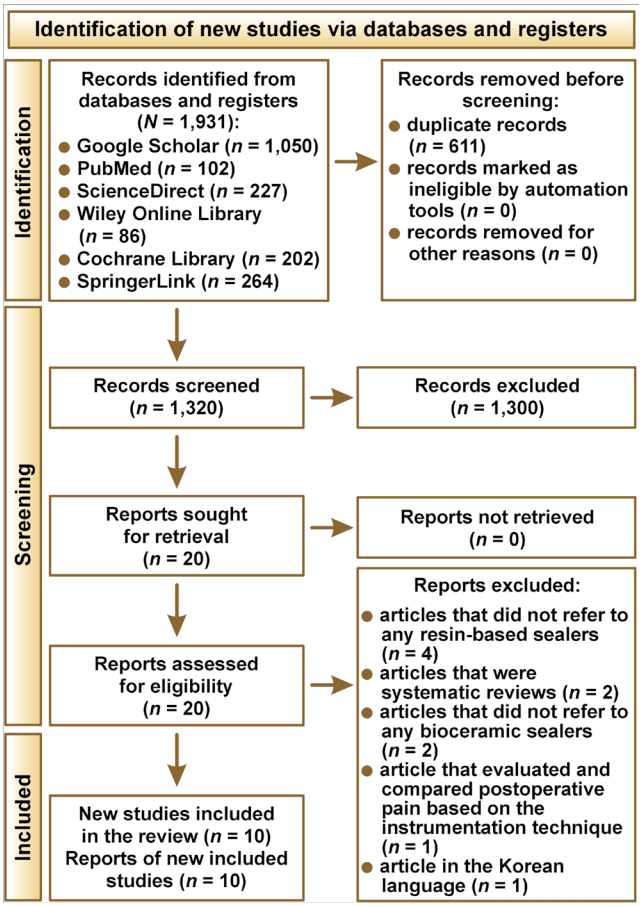

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the study screening procedure and selection

Study design and characteristics

A well-detailed presentation of the data extracted from the included studies is given in Table 1.

All the studies were published between 2018 and 2021. Nine studies were parallel design RCTs, and one study was a split-mouth controlled trial.[16] All the studies were done with ethical approval, but only 2 studies were reported according to the guidelines of CONSORT (Consolidated Standards of Reporting Trials).[8,11] The total number of patients analyzed in the studies included 842 patients. A female predominance was noticed.

The mean age was reported to range from 27.16 to 49.04 years. Among the 10 studies, 4 studies included teeth with necrosed pulp,[11,14,19,29] 2 studies included teeth that were asymptomatic with irreversible pulpitis,[17,27] 1 study included teeth that required retreatment,[13] 2 studies included both vital and non-vital teeth,[1,18] and 1 study included vital and non-vital teeth, and teeth that needed retreatment.[12]

The resin-based sealer AH Plus was used as a control group in all included studies for comparison with calcium silicate-based bioceramic sealers. Regarding the instrumentation, 3 studies used Reciproc VDW,[1,17,19] 2 studies used WaveOne Gold,[11,26] 1 study used ProTaper Next,[18] 1 study used ProTaper Gold,[14] 1 study used both ProTaper Next and WaveOne Gold,[29] 1 study used ProTaper Universal retreatment files with ProTaper Gold,[16] and 1 study mentioned only nickel-titanium rotary files.[12]

The obturation techniques used varied between the studies – 2 studies used the single-cone technique,[17,19] 2 studies used the warm vertical compaction technique,[16,26] 2 studies used the lateral compaction technique,[14,29] 1 study used the continuous-wave compaction technique (AH Plus sealer) and the single-cone technique (Endoseal MTA),[18] 1 study used the single-cone and vertical compaction technique,[11] 1 study filled root canals using the HEROfill Soft-Core obturator system,[1] and 1 study used the system B technique for root canal obturation.[12]

All the 10 studies used VAS (0–10 cm) for the assessment of postoperative pain after endodontic treatment. The pain scores were measured, ranging from 6 h to 1 week. Studies that used scales other than VAS were excluded.

Three studies assessed the incidence of pain within 6 h and 12 hours after the endodontic procedure,[1,17,26] whereas all 10 eligible studies assessed pain 24 h after the endodontic treatment. Eight studies assessed the pain incidence 7 days after the procedure.[11,12,14,16–19,29] The highest VAS scores were recorded at 6 h and 12 h after the procedure, followed by 24 h. The pain scores were greatly reduced by 48 h, and there were no significant differences in pain intensity between the groups 72 h after the procedure.

Table 1. Study characteristics

Author, year of publication, country	Study design	Sample size	Age (mean in years)	Tooth condition diagnosis	Type of teeth	Number of visits	Instrumentation	Obturation technique	Obturation material	POP assessment time	POP assessment scale
Shim et al., 2021, Korea[18]	RCT	AH Plus: 32 (12M, 20F), Endoseal: 35 (24M,11F)	49.04 ±16.62	pulp necrosis and vital teeth	anterior premolar, molars	1	ProTaper Next	AH Plus: continuous-wave technique, Endoeal: single-cone technique	AH Plus, Endoseal	7 days (24 h, 48 h, 72 h, 96 h,120 h, 144 h, 168 h)	VAS
De Souza Ferreira et al., 2020, Brazil[11]	RCT	AH Plus: 20 (4M, 16F), Endofill: 20 (8M, 12F), MTA Fillapex: 20 (7M, 13F)	41	asymptomatic necrosis and apical periodontitis	anteriors and premolars	2	WaveOne Gold	single-cone and vertical obturation technique	AH Plus, Endofill, Fillapex	24 h, 48 h and 7 days	VAS
Aslan and Dönmez Özkan, 2021, Turkey[17]	RCT	AH Plus: 26 (10M, 16F), BC Sealer: 30 (12M, 18F), Endoseal MTA: 28 (6M, 22F)	AH Plus: 37.15 ±11.93, BC Sealer: 32.46 ±13.20, Endoseal MTA: 39.57 ±13.09	asymptomatic irreversible pulpitis	mandibular first and second molars	1	Reciproc silver VDW	single-cone technique	AH Plus, BC Sealer, Endoseal MTA	6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h	VAS
Fonesca et al., 2019, Brazil[19]	RCT	AH Plus: 32 (14M, 18F), BC Sealer: 32 (12M, 20F)	AH Plus: 37.09 ±13.10, BC Sealer: 38.8 ±14.18	teeth with pulp necrosis	maxillary anterior teeth	1	Reciproc VDW	single-cone technique	AH Plus , premixed Sealer Plus BC	24 h, 48 h, 72 h, and 7 days	VAS
Graunaite et al., 2018, Lithuania[16]	split-mouth RCT	AH plus: 61 (36F, 25M), Totalfill BC: 61 (36F,25M)	49.5	asymptomatic apical periodontitis in endodontically treated teeth	permanent molars	1	ProTaper Universal retreatment files, ProTaper Gold system	warm vertical condensation technique	TotalFill BC Sealer	24 h, 48 h, 72 h, and 7 days	VAS
Khandelwal et al., 2022, India[14]	RCT	AH Plus: 19 (15M, 4F), Bioroot RCS:19 (11M, 8F), Tubliseal: 19 (12M, 7F)	AH Plus: 41.68, Bioroot RCS: 43.63, Tubliseal: 41.57	necrotic pulp with chronic apical perodontitis	maxillary anterior teeth	2	ProTaper Gold	lateral compaction technique	AH Plus, Bioroot RCS, Tubliseal	24 h, 48 h, 72 h, and 7 days	VAS
Jacoub et al., 2018, Egypt[29]	RCT	60 patients	no data	asymptomatic non-vital tooth without periapical lesions	mandibular first and second molars	1	ProTaper Next, WaveOne Gold	lateral compaction technique	AH Plus with ProTaper Next – Group 1, AH Plus with WaveOne Gold – Group 2, TotalFill with ProTaper Next – Group 3, TotalFill with WaveOne Gold – Group 4	12 h, 24 h, 48 h	VAS
Atas et al., 2019, Turkey[1]	RCT	AH Plus: 78 (vital teeth: 39 (16M, 23F), devital teeth: 39 (15M, 24F)), iRoot SP: 78 (ISP-V: 39 (17M, 22F), ISP-D: 39 (19M, 20F))	AH Plus V: 30.69 ±10.39, AH Plus D: 36.33 ±11.08, ISP-V: 35.00 ±12.55, ISP-D: 40.69 ±11.87	both vital and non-vital teeth	mandibular premolar and molar	1	one-shape system and a VDW silver motor	HEROfill Soft-Core obturator	AH Plus V, AH Plus D, iRoot SP Vital, iRoot SP Devital	6 h, 12 h, 24 h, 72 h	VAS
Drumond et al., 2021, Brazil[26]	RCT	AH Plus: 13, BC Sealer: 13, Bio-C Sealer: 13	AH Plus: 34.4 ±7.6, BC Sealer: 32.2 ±10.3, Bio-C Sealer: 33.3 ±10.2	asymptomatic irreversible pulpitis	molar teeth with 3 root canals	1	WaveOne Gold single-file reciprocating system	vertical compaction (Schilder's technique)	AH Plus, BC Sealer, Bio-C Sealer	6 h, 12 h, 24 h, 48 h, and 7 days	VAS
Tan et al., 2021, Singapore[12]	RCT	AH plus: 80 (38M, 42F), TotalFill BC: 80 (38M, 42F)	AH plus: 27.6, TotalFill BC: 26.6	vital, non-vital and previously root-filled teeth	anteriors, premolars, molars	2	nickel-titanium rotary files	AH plus: non-standardized GP with system B, TotalFill BC: matched TotalFill GP and system B	AH Plus, TotalFill BC	1, 3, 7 days	VAS

POP – postoperative pain; RCT – randomized controlled trial; M – male; F – female; VAS – visual analog scale.

Risk of bias assessment

The risk of bias assessment of the 10 studies presented a low risk of bias in 7 studies,[1,12,14,16,19,26,29] whereas 3 studies were judged to raise some concerns.[11,17,18] The main shortcomings were related to bias due to deviations from the intended intervention. Two studies did not provide sufficient information about the blinding process.[17,18] One study raised some concerns over the randomization process.[18] The information on the selection of the reported results was insufficient in 1 study.[11] The risk of bias in the 10 studies is summarized in Table 2.

Discussion

This systematic review aimed to assess the occurrence of postoperative pain after root canal treatment performed with two different root canal sealers namely resin-based sealers and calcium silicate-based bioceramic sealers. The occurrence of postoperative pain after endodontic treatment is not attributed to a specific factor and is associated with several other factors, including age, gender, pulpal, and periradicular status, type of teeth treated, pre-operative pain conditions, and the procedure carried out during root canal treatment such as the instrumentation technique used, irrigation protocol, and obturation techniques followed.[29]

There have been various compositions of root canal sealers developed over the years. The formula of the root canal sealers determines the chemical reactions and properties of the materials. The activation of a local inflammatory response in the periapical tissues is due to the release of chemical mediators, mainly reactive oxygen species (ROS). In vivo studies have shown that oxidative stress is specifically produced by ROS and it has been shown to be linked with inflammatory pain. Whereas, in vitro studies proved that the production of ROS is raised by four to seven times in dental pulpal cells that had been treated with root canal sealers.[30,31]

The systematic review also included studies that reported sealer extrusion. Whereas, the results of the eligible studies showed no significant association between sealer extrusion and the occurrence of postoperative pain, irrespective of the type of sealer used.[1,14,19] Nevertheless, it is justified by the reason that the sealer extrusion was only 1–2 mm in all the cases included in the studies, and none of the cases presented extrusions close to anatomical structures. Therefore, if the vital anatomical structures are not involved, sealer extrusions in small amounts do not give rise to any postoperative complications.[1,14,19,32]

The calcium silicate-based materials are more biocompatible than the resin-based sealer AH Plus. This is justified by the fact that the cytotoxicity of AH Plus is associated with the release of the component amine and epoxy resin. Further studies showed that there is a release of formaldehyde (3.9 ppm) in small amounts that is attributed to the cytotoxicity of the sealer immediately after mixing. Filter diffusion test and MTT assays revealed little cytotoxic effects even after 24 h of mixing. However, the studies that were conducted clinically provide a contrary result compared to the previously observed in vitro analyses.[33–35]

Previous studies showed that bioceramic sealers showed increased flowability than the resin-based sealers and a higher extrusion rate (59.4%) than the AH Plus sealers (28.1%). Conversely, a recent study presented that obturation with AH Plus contributed to significantly more extrusion beyond the apical foramen (62.1%) than bioceramic sealers (47.4%). The studies presented low rates of flare-ups and moderate postoperative pain in the first 48 h. However, further clinical studies are required regarding the same.[12,19,36]

In some of the included studies, it was reported that the presence of pre-operative pain positively influenced the occurrence and incidence of postoperative pain. Seven of the eligible studies included had asymptomatic patients in their study to rule out pre-operative pain, which is an important predisposing factor to the occurrence of postoperative pain. All the included studies in

Table 2. Risk of bias assessment of the included studies

Study	Randomization process	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall bias
Shim et al.[18]	?	?	+	+	+	?
De Souza Ferreira et al.[11]	+	+	+	+	?	?
Aslan and Dönmez Özkan[17]	+	?	+	+	+	?
Fonesca et al.[19]	+	+	+	+	+	+
Graunaite et al. (spli-mouth design)[16]	+	+	+	+	+	+
Khandelwal et al.[14]	+	+	+	+	+	+
Jacoub et al.[29]	+	+	+	+	+	+
Atas et al.[1]	+	+	+	+	+	+
Drumond et al.[26]	+	+	+	+	+	+
Tan et al.[12]	+	+	+	+	+	+

(+) low risk; (?) unclear risk (some concerns); (–) high risk.

this systematic review showed no statistically significant differences in the incidence of postoperative pain among the studied root canal sealers at various time points. Also, there is no possible correlation between gender or age and postoperative pain at any time point. The most severe pain post endodontic treatment occurred up to a period of 24 h, and this short duration of pain after endodontic treatment is related to the production of ROS due to leakage of unpolymerized components in the root canal sealer during their setting process in the first 24 h. The setting time of AH Plus and bioceramic sealers was found to be about seven hours and four hours, respectively.[37–39]

Some of the studies reported the usage of rescue medications when the discomfort was too great for the patient. The results of the eligible studies showed a small proportion of patients requiring anti-inflammatory drugs during the first 24 h of their postoperative period, regardless of the sealer group to which they were allotted.

Pain is produced by both physiological and psychological components. The perception of pain is subjective, and pieces of the literature suggest the use of a rating scale as it is a reliable and effective method for recording pain intensity by the patient. In all our included studies, VAS was used for recording pain scores. For the standardization of analysis, VAS was converted to 0–10 cm. Most of the studies recorded pain intensity starting from 6 h to 7 days.[40,41]

The study also presented some limitations that should be addressed. The analysis of pain intensity is only by subjective perception and as it is a distinctive experience for every patient, the results may not represent the entire population group. Further studies are required to assess postoperative pain and complications after sealer extrusions and its influence on oral health-related quality of life (OHRQoL). On the other hand, this is the first systematic review that assesses postoperative pain caused by root canal obturation using resin-based and calcium silicate-based sealers by including a larger number of articles and participants in the quantitative analysis and also assessing the postoperative pain associated with the extrusion of the studied sealers, thereby improving the body of evidence.

Conclusions

Within the limitations of this study, there was no significant difference in the incidence of postoperative pain after root canal treatment using bioceramic sealers compared to resin-based root canal sealers. Also, the results of the eligible studies showed no significant association between sealer extrusion and the occurrence of postoperative pain, irrespective of the type of sealer used. Further studies are required to justify the results obtained in this study, to increase the accuracy, and to determine the causes of postoperative pain after endodontic treatment in several pulpal and periodontal conditions.

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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Actinomycotic osteomyelitis of the maxilla in a female patient: A rare case report with the review of the literature

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Abstract

Actinomycotic osteomyelitis is a rare chronic suppurative, granulomatous, fibrosing saprophytic infection. It is an endogenous infection caused by the *Actinomyces* species, which are part of the normal oral microflora. There is a male predilection for this type of infection, with the male to female ratio of 4:1. Though the etiopathogenesis of the infection is unclear, it is mostly attributed to the disruption of the normal oral microflora and the invasion of the microorganism into deeper tissues through a break in the mucosal barrier due to damage from trauma, extraction or previous injury. The portal of entry can be through the pulpal, periodontal or mucosal route, causing the purulent and necrotic infection of soft tissue, bone, or both. The diagnosis is usually considered when there is a persistent infection without the presence of regional lymphadenopathy and is usually confirmed through the histopathological depiction of the bacterial colonies – 'ray fungus' – as obtaining the positive culture of the causative microorganisms is difficult and is reported to be effective in less than 50%. Patients with such infections are managed with surgical debridement, followed by antibiotic therapy for a longer time period. Recent advances have been emphasized for an early diagnosis and a better prognosis of the therapy.

Therefore, this paper aimed to present a rare case of actinomycotic osteomyelitis of the maxilla in a 45-year-old female patient, and also to review the literature on this rare infection.

Keywords: bacterial infections, osteomyelitis, actinomycosis, maxilla, *Actinomyces*

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Introduction

Actinomycosis is a rare chronic suppurative, granulomatous, fibrosing saprophytic infection caused by the commensal oral and pharyngeal *Actinomycetaceae* family of bacteria. It is a specific chronic inflammation of soft tissue and rarely of bone.[1] The actinomycotic species are non-acid fast, slow-growing, Gram-positive, anaerobic or microaerophilic bacteria resembling fungi. The *Actinomyces* species resemble both bacteria and fungi, but most of the basic characteristics suggest that in fact, they are bacteria. Unlike fungi, they do not have sterols in their cell walls and are susceptible to antibacterial pharmacotherapeutic agents.[2] The principal microorganism involved in this infection is *Actinomyces israelii (A. israelii)*,[3] although other species, like *A. viscosus, A. naeslundii, A. meyeri*, and *A. odontolyticus*, are identified occasionally. *Actinomyces* cause this infection particularly when there is a break in the normal mucosal barrier because of any trauma, extraction, surgery, or a preceding infection.[4] The presence of this break and the devitalized tissue pave the way for the deeper invasion of tissues causing infection.

Actinomycosis is a polymicrobial infection involving the association of other companion bacteria, which are frequently Gram-negative fusiform bacilli, anaerobic streptococci or staphylococci, and facultative anaerobic bacilli that form a mutual/symbiotic anaerobic environment in the body, enabling the growth of the *Actinomyces* species.[5] Thereby, these co-pathogens increase the invasive power of the *Actinomyces* species by releasing enzymes or toxins, or by suppressing the host defensive mechanisms, resulting in the early manifestations of the infection and the failure of the therapy.[5]

Actinomycosis involving bone is rare but possible. Osteomyelitis occurs secondary to the primary infection and the infection spreads through direct invasion into the surrounding adjacent tissues. It burrows through the anatomical planes, unlike the other infections which follow it, creating a lobular 'pseudotumor'.[6] Actinomycotic osteomyelitis of the jaws, especially of the maxilla, is a very rare occurrence because of the abundant blood supply and cancellous architecture of bone as compared to the mandible. There are only very few cases reported in the literature involving the maxilla in a female patient.[3,7–9] Thus, our article is another example of a report of a rare case of actinomycotic osteomyelitis involving the maxilla in a 45-year-old female patient.

Case report

A 45-year-old female patient, a farmer, reported to the Department of Oral Medicine and Radiology with the chief complaint of pain, a bad breath and a growth in the left posterior region of the maxilla (Fig. 1A), along with

Fig. 1. Facial view at day 1 (A), 2 days postoperatively (B) and 1 month postoperatively (C)

headache for the past 2 months. Further, when recording a detailed history, the patient revealed that 2 months before she had a continuous dull pain that aggravated during mastication and subsided at rest. The patient visited a medical practitioner, who administered an intraoral injection on the palate, for which she had no record. After 15 days since the injection administration, the patient started experiencing a continuous sharp pain that aggravated on mastication, followed by the occurrence of a growth in the injected area. After this, the patient visited an ENT specialist, who prescribed her analgesics and vitamin supplements, and advised her to perform blood tests; the results were reported to be within normal limits. The patient was further referred to our Department, as there was not much improvement. The patient also had a history of fever, which occurred one and a half months before. There was no history of change in the size of the patch for the past one and a half months, as reported by the patient.

The patient had no relevant medical, dental and family history. She had also stopped brushing her teeth with a toothbrush 2 months before and had been using her fingers to clean her teeth. The extraoral examination revealed a single submandibular lymph node, palpable on both the right and left side, 1 cm × 1 cm in size, round in shape, mobile, and tender on palpation.

During the intraoral soft tissue examination, an irregular greenish-white patch of size 6 cm × 3 cm on the upper left palatal mucosa was observed, extending from the mesial aspect of tooth 22 to the distal aspect of tooth 27 anteroposteriorly, and from the midline to the palatal marginal gingiva in the 2nd quadrant mediolaterally (Fig. 2A). A bony sequestrum was present on the buccal aspect in relation to the posterior teeth, involving the marginal gingiva and a width of 1 cm of the attached gingiva in relation to teeth 24 and 25 (Fig. 2B). The surrounding area appeared to be inflamed and erythematous. Severe halitosis was present. On palpation, the patchy growth was tender, firm, with a rough surface. When retracting the patchy growth, it could be easily raised, revealing an ulcerative denuded area underneath it. During the examination of the gingiva, generalized gingival inflammation, generalized marginal gingival erythema and bleeding on probing were present.

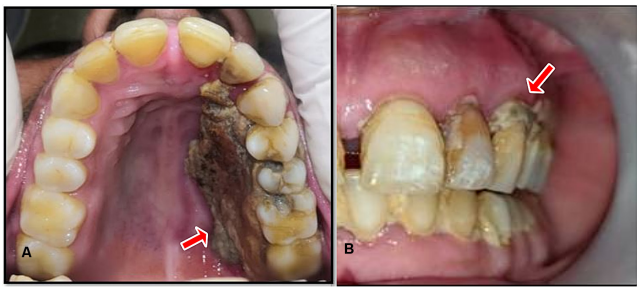

Fig. 2. Intraoral clinical presentation at day 1
A – maxillary occlusal view; B – cropped frontal view.

Other hard tissue findings included deep caries in teeth 25 and 26 with tenderness on percussion, dental caries in teeth 37, 47 and 48, Miller class III mobility of teeth 24, 25 and 27, Miller class I mobility of teeth 23 and 26, the crowding of the mandibular anterior teeth, stains – +++, and calculus – ++.

The intraoral periapical radiographs of the maxillary left posterior region, an orthopantomogram, plain computed tomography (CT) – the paranasal sinus (PNS) view, and the incisional biopsy of the palatal mucosa were advised.

The intraoral periapical radiographs divulged deep dental caries in teeth 25 and 26, and apical periodontitis in teeth 24, 25, 26, and 27. The orthopantomogram revealed deep dental caries in 25 and 26. The plain CT (PNS) exposed the erosion and destruction of the upper left alveolar ridge in the premolar and molar region, extending to the pterygoid plates, and superiorly involving the floor of the left maxillary sinus and the left lateral margin of the hard palate (Fig. 3). It also showed a few air pockets noted in the adjacent soft tissue, a deviation in the nasal septum toward the left side, the left osteomeatal complex block, the left concha bullosa; hypodense mucosal thickening in the maxillary sinuses bilaterally, sphenoidal sinuses, and ethmoidal air cells suggestive of sinusitis.

The incisional biopsy was performed and the patient was prescribed a broad-spectrum antibiotic (ciprofloxacin 500 mg b.i.d) as well as analgesics (paracetamol 325 mg + aceclofenac 100 mg b.i.d.) for 7 days. The histopathological examination under ×400 magnification revealed features suggestive of osteomyelitis with a bacterial and fungal infection, such as necrotic tissue at the periphery with the loss of architecture and the presence of abundant microbial colonization and loose edematous connective tissue in the center, Gram-positive cocci in pairs and chains infiltrating deeper tissues, the non-viable necrotic interconnected trabeculae with the absence of osteocytes and osteoblasts in lacunae, bony trabeculae of irregular ragged borders, necrotic marrow tissue, extravasated red blood cells (RBCs), and chronic inflammatory cell infiltration. After 7 days since the incisional biopsy, an obvious bony sequestrum with the surrounding inflamed mucosa was noted in the same region (Fig. 4).

Fig. 3. Axial sections of plain computed tomography (CT) – the paranasal sinus (PNS) view showing the destruction of bone involving both the lingual and buccal cortical plates (A, B), and a coronal section depicting extension to the floor of the left maxillary sinus (C)

Fig. 4. Intraoral clinical presentation after 7 days since the initial biopsy showing an obvious bony sequestrum with the surrounding inflamed erythematous mucosa

The patient was referred for necessary surgical therapy. Preoperatively, the patient was prescribed the intravenous (i.v.) injection of cefixime 1 g b.i.d., the i.v. injection of metronidazole 100 mL in normal saline (NS) t.i.d. and the i.v. injection of diclofenac 150 mg b.i.d. for 5 days. Sequestrectomy, thorough debridement, curettage, and the extraction of teeth 21–28 (Fig. 5), followed by wound closure with Vicryl® 3-0 sutures (Ethicon, Inc., Somerville, USA) were performed under general anesthesia, and the excised tissue was sent for a histopathological examination again. The patient was prescribed a postoperative broad-spectrum antibiotic (amoxicillin 500 mg t.i.d) for 2 months and analgesics (paracetamol 325 mg + aceclofenac 100 mg b.i.d.) for 10 days.

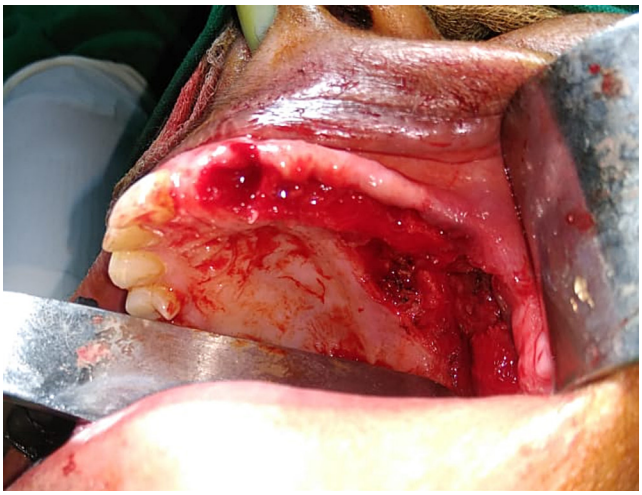

Fig. 5. Intraoperative photograph

The second histopathological examination of the excisional biopsy tissue under ×400 magnification revealed features suggestive of actinomycotic osteomyelitis, like necrotic trabeculae with ragged borders and the absence of osteocytes and osteoblasts in lacunae (Fig. 6A), numerous multinucleated osteoclasts in Howship's lacunae at the periphery of bony trabeculae, central necrotic marrow tissue with extravasated RBCs and chronic inflammatory cell infiltration, bacterial colonies in some areas, where individual colonies appeared round or lobulated, and were made up of a meshwork of peripheral radiating filaments that were hematoxyphilic, along with the eosinophilic peripheral club-shaped ends of the filaments (Fig. 6B). Figures 6C and 6D depict the filaments under ×1,000 magnification and the periodic acid–Schiff (PAS) staining of the actinomycotic colonies under ×100 magnification, respectively.

Satisfactory healing was observed at the 2-day, 1-week and 1-month postoperative follow-ups of the patient (Fig. 1B,1C,7,8) as well as the alleviation of symptoms. The patient was referred for prosthetic rehabilitation after 3 months of the healing period.

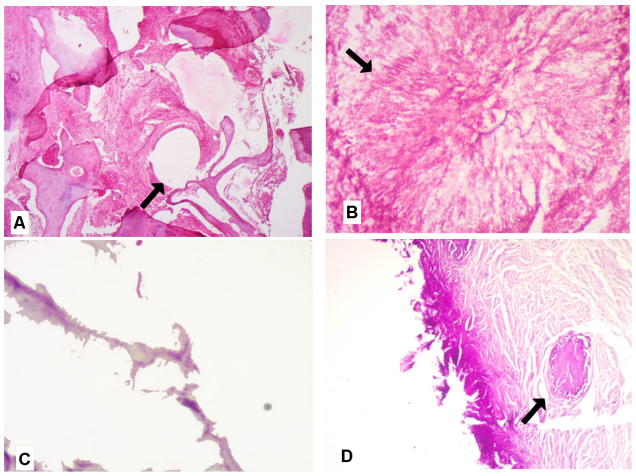

Fig. 6. Histopathological sections depicting necrotic bone with the actinomycotic colonies under ×40 magnification (A), the 'ray fungus' appearance under ×400 magnification (B), filaments under ×1,000 magnification (C), and the periodic acid–Schiff (PAS) staining of the actinomycotic colonies under ×100 magnification

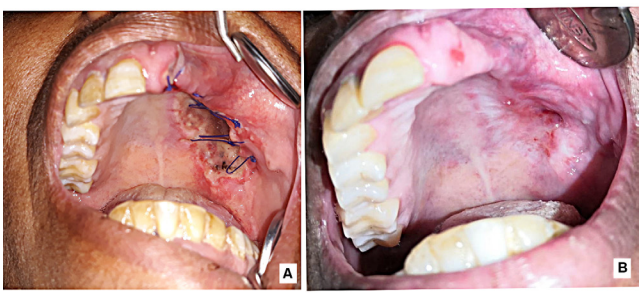

Fig. 7. Intraoral clinical presentation at 2 days postoperatively (A) and 1 month postoperatively (B)

Fig. 8. Orthopantomogram at 1 month postoperatively

Discussion with the review of the literature

Primary actinomycotic osteomyelitis is a rare condition that accounts for only 12% of the cases.[10] In the cervicofacial region, it commonly affects the chin and the angle of the mandible, but rarely the maxilla, as in the present case, as well as the temporomandibular joint (TMJ). The mandible to maxilla prevalence ratio is 4:1.[11,12] The incidence of the *Actinomyces* infection is 53.6% in the mandible, followed by 16.4% in cheeks, 5.7% in the maxilla, and 0.3% in TMJ.[13]

Actinomycotic osteomyelitis is attributed to the invasion of the species, which are normally present in the gingival fluid, dentin cavities and palatine tonsils, on mucosal surfaces, and at post-extraction sites, into deeper mucosal tissues. Although the pathogenesis is unclear, the infection is manifested mainly when there is disruption in the composition of the normal microflora, leading to a chronic primary infection, which results in the pathological changes of bone.[11]

This condition develops only in the presence of certain predisposing circumstances, like immunosuppression, diabetes, the prolonged use of corticosteroids, smoking, alcoholism, and most importantly a break in the epithelium from injury due to trauma or extraction. Also, sinusitis can evolve into such an infection after dental extraction, as reported in the literature.[14] In the present case, the infection could be attributed to trauma to the palatal tissues during the administration of an intraoral injection or the pre-existing sinusitis (chronic inflammation). *Actinomyces* lack the ability to produce the tissue-decomposing enzymes (hyaluronidases), and hence they rely on other co-pathogens, which are the possible source of hyaluronidases, to establish pathogenicity. It could be observed also in the present case, along with the actinomycotic colonies. The most common area of involvement is the head and neck region, accounting for 55% of the cases, although the ophthalmic, neurological, abdominal, respiratory, and urogenital involvement has been reported as well.[6] The most commonly affected age group is between

30 and 60 years, which is in accordance with the present case, and the male to female ratio is 4:1, substantiating the case to be an extremely rare one.[10,15–17]

The infection is clinically manifested as an acute or chronic presentation, with the former being less common. An acute infection is characterized by floating swelling, which is painful, along with a rise in temperature and a tendency to rapidly spread into tissues, resembling an odontogenic infection.[14] A chronic infection is characterized by a progressive, slow increase in volume due to the burrowing of the microorganisms, with or without painful symptoms, and is associated with a slight rise in temperature; it may take weeks, months, or even years for it to develop, and the infection may be accompanied by normal hematological findings and the absence of malaise, as reported in the present case.[10,14,18]

Only a limited number of cases of actinomycotic osteomyelitis have been reported in the literature.[2,19] Despite the patient's history and the physical examination being essential in the diagnosis of any disease, the radiographic examination, the bacterial culture examination, and the histopathological examination of tissues and secretions from the affected site are necessary for the diagnosis of actinomycotic osteomyelitis.[8,11,16]

The radiographic examination can be helpful in determining the extent of invasion into bone, even in the presence of the edema of tissues.[20] Computed tomography can help determine the extent of osteolysis and the formation of fibrous tissue in the infected area, and scintigraphy with gallium can help differentiate the inflammatory changes from neoplasms and assess the effectiveness of treatment. However, no imaging modality can be regarded as a sole method of investigation to confirm the diagnosis of actinomycotic osteomyelitis.[10,11]

The diagnosis depends not only on the clinical findings and the demonstration of microorganisms in the tissue sections or smear, but also upon their culture, which is difficult to obtain in 50% of the cases for numerous reasons.[21] The culturing of the bacteria should be preferably performed when the patient has not been on antimicrobial therapy for at least 7–10 days before the procedure, as otherwise it may interfere with the diagnosis, making it obscure. The histopathological features include a granulomatous appearance with the characteristic round or lobulate colonies of microorganisms within the central abscess formation, which occur as floating in the sea of polymorphonuclear leukocytes, often associated with multinucleated giant cells and macrophages, especially around the periphery. This appearance is the basis of the term 'ray fungus', which is frequently used.[22] All the abovementioned findings are in accordance with the present case. In the current case, the culturing of the microorganisms was not done, and the diagnosis was based on the morbid anatomical, radiographic and histopathological examinations, especially hematoxylin and eosin (H&E) and PAS staining, rather than the identification of the microorganisms by culture. The need for the careful handling of the specimens to obtain a positive anaerobic culture is well emphasized. However, the histopathological examination is also strongly recommended.[23] The *Actinomyces* species stain heavily with the H&E, PAS and Giemsa stains. Also, the Grocott–Gömöri methenamine silver (GMS) staining is helpful for the demonstration of filaments.[24]

Nucleic acid probes and the polymerase chain reaction (PCR) are advisable for the rapid and accurate detection of the microorganisms, as the diagnosis is difficult when it is based only on the clinical and direct identification and/or isolation of the responsible microorganism, which is a laborious process. Molecular testing is considered as the appropriate method for the diagnosis of actinomycotic osteomyelitis of the jaws.[25] It has been recommended for the PCR analysis of *A. israelii* to have a higher sensitivity that the specimen undergoes mild decalcification with ethylenediaminetetraacetic acid (EDTA)[25] rather than with trichloroacetic acid.[26] The same diagnostic approach has also been recommended for the bone biopsies done for the histological examination.[25] On the other hand, although the PCR testing overweighs the conventional identification procedure in terms of identification of slow-growing and non-cultivable microorganisms, the method is expensive and it requires an experienced hand to perform the analysis.

Actinomycotic osteomyelitis often demands vigorous treatment once a sound diagnosis is set. The initial treatment consists of the administration of high doses of penicillin, either orally or intravenously, depending on the severity of the infection, although there may be a necessity of surgical management if there is any tissue necrosis or involvement of bone.[20] All abscesses should be surgically disrupted and penetrated with a hemostat, regardless of their size. Prolonged antibiotic therapy, preferably with penicillin, is recommended after the removal of the foci of infection by draining abscesses, sequestrectomy and/or the excochleation, saucerization and excision of the fibrous/granulation tissue until the exposure of healthy tissue,[12,25] which was done in the present case. Other effective antibiotics include erythromycin, clindamycin, tetracycline, minocycline, cephaloridine, and imipenem.[10,27,28] Penicillin can be administered by i.v. infusion in doses ranging from 3 million to 12 million units daily or as an oral dose of 2–4 g per day for a period of 3–12 months, depending on the host response to the infection. Administering antibiotics for an additional period is recommended, as the lysis of the *Actinomyces* species takes place at a slower rate than in the case of most other bacteria.[28] The prognosis for a satisfactory resolution is excellent and the recurrence is rare,[3,29,30] as demonstrated in the present case. Sometimes maxillofacial reconstruction may be necessary when there is a substantial soft and hard tissue loss, which was not necessary in the present case. The secondary surgical repair or the reconstruction and replacement of the teeth can be attempted once we are confident with the complete resolution and healing of the infection.

Conclusions

Despite a diagnostic dilemma with regard to mucormycosis in presentation, after following a meticulous diagnostic protocol, the current case turned out to be a case of actinomycotic osteomyelitis. The treatment of actinomycotic osteomyelitis, which is a rare and unusual occurrence, is a challenging task. However, it can be overcome with surgical and prolonged antibiotic therapy, and a complete resolution can be achieved, as demonstrated in the present case. The diagnosis of actinomycotic osteomyelitis should be considered in relation to persistent oral infections, as progressive actinomycosis, especially in the maxilla, is likely to lead to serious consequences in the skull base and intracranial involvement. The early diagnosis of actinomycotic osteomyelitis can improve the prognosis and the outcomes of the therapy, thus preventing serious consequences in patients.

Ethics approval and consent to participate

The ethical clearance was obtained from the Research and Ethics Committee, KLE Vishwanath Katti Institute of Dental Sciences, Belagavi, India, with the reference number 20/07/2020/074. Also, the authors declare that the written informed consent was obtained from 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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Research letter

Temporomandibular joint and cervical spine disability assessment in people with hypermobility joint syndrome

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

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Abstract

Background. Temporomandibular disorders (TMDs) and cervical spine problems are a growing public health issue, as they increase the risk of disability in people with hypermobility joint syndrome (HJS).

Objectives. The present study aimed to assess the prevalence of TMD symptoms, and cervical spine and TMJ disability in HJS patients.

Material and methods. A survey was conducted among physical therapy students (mean age: 21 years). The study comprised 2 stages. The 1st one was HJS assessment (the Beighton scale and the Brighton criteria). Based on the assessment, 56 HJS subjects were enrolled for the study. The control group (CG) consisted of 60 HJS-free subjects, according to the aforementioned criteria. The 2nd stage of the study involved conducting a self-administered questionnaire on the prevalence of TMD symptoms. Both the TMD disability questionnaire (TMD-Q) and the neck disability index (NDI) scores were recorded. Pain intensity was assessed using the numeric rating scale (NRS).

Results. The HJS group showed higher NRS scores ($p < 0.001$). Headache, neck and shoulder girdle pain, and temporomandibular joint (TMJ) pain were found to be more severe in almost each patient from the HJS group as compared to CG. Those individuals had a greater degree of disability on the TMD-Q and the NDI scales ($p < 0.001$). The HJS group showed significant positive correlations between the TMD-Q and NDI scores ($p = 0.0035$), and between the TMD-Q and TMJ symptom questionnaire scores ($p = 0.0047$). A significant positive correlation between the NDI and TMJ symptom questionnaire scores was found both in the HJS group ($p < 0.001$) and CG ($p < 0.001$).

Conclusions. The HJS bearers tended to obtain higher TMJ and cervical spine disability scores, at the same time reporting increased headache, neck and shoulder girdle pain, and TMJ pain intensity. Therefore TMJs should be carefully examined for possible signs of dysfunction in HJS subjects prior to dental or prosthetic treatment. According to our data, TMJ and cervical spine disability assessment should be included as a routine practice in the case of HJS patients, who should remain under the long-term care of a multidisciplinary team of doctors and therapists.

Keywords: temporomandibular disorders, cervical spine, disability, joint laxity, hypermobility syndrome

Introduction

Hypermobility joint syndrome (HJS) is classified as a generalized, hereditary connective tissue disorder with a general population prevalence of 2–57%.[1] The contributing factors for HJSs vary in different individuals, and can include impaired protein synthesis and connective tissue matrix production. Disproportion in the type I and III collagen content, as well as cellular imbalance in tissue organization with regard to fibrillin – a major protein coforming elastic fibers – is currently under thorough scientific scrutiny. Most studies aim to unravel a complete list of hereditary contributing factors for HJS development, as the exact genetic factors influencing this condition are not very well known.[2]

The main symptoms of HJS include, but are not limited to, the flaccidity of the joint capsules and ligaments, increased joint mobility, and numerous dysfunctions of body areas congenitally rich in connective tissue.[1]

Hypermobility joint syndrome is believed to be more prevalent in young women, tending to subside as one matures. The healthy aging process seems to be more important than the cessation of connective tissue abnormalities.[3] The disorder significantly reduces the quality of life, as it can be associated with chronic injuries, e.g., joint dislocations and sprains, damage to the ligaments, chronic pain, and persistent fatigue, resulting over time in an impaired sensory function of musculoskeletal system tissues. Repeated trauma may lead to irreversible damage to joint surfaces, which can result in disability.[4]

The diagnostic criteria for HJS embrace the Beighton scale and the Brighton Criteria, both of which are widely used for joint laxity assessment.[5] The Beighton scale includes 5 simple activities that measure joint mobility on a nine-point scale, where excessive joint mobility is defined by a score ≥4. Additionally, special criteria called the Brighton criteria have been developed for the diagnosis of HJS.[6] Hence, the Beighton scale is used for identifying hypermobility and the possibility of symptoms such as joint pain, spine degenerative changes, joint subluxations, physique similar to that observed in Marfan syndrome, skin and/or ocular symptoms, the possibility of herniae, varicose veins, and uterine or anal prolapse. The proper fulfillment of the abovementioned criteria, according to a specific formula, constitutes evidence of HJS.[6] A study by Bravo and Wolff shows that by applying the Brighton criteria, a high detection rate of HJS is achieved.[7]

Hypermobility joint syndrome may be considered a predisposing factor for temporomandibular disorders (TMDs).[8] Some initial reports are available, connecting the prevalence of certain laxity-associated single nucleotide polymorphisms (SNPs) (*COL5A1* rs12722) with intracapsular temporomandibular joint (TMJ) disorders.[9] People with connective tissue disorders tend to overstretch the TMJ capsules and retrodiscal tissue ligaments. Wide-mouth opening and subconscious nocturnal and/or diurnal activities (e.g., bruxism) may lead to TMJ disc displacement and orofacial pain. According to the available data, 70% of HJS patients have been found to have TMJ articular disc displacement without reduction, which does not manifest with clicking/popping, but maximum jaw opening is limited to ≤30 mm.[9,10] As a result, inflammation (e.g., swelling, warming) may occur over time, destroying the articular surfaces, and leading to TMJ structural remodeling and degenerative lesions (osteophytes). In TMJ hypermobility, the activity of the masticatory muscles is reduced, resulting in the disruption of the chewing process, both in adolescents and adults.[11]

Despite reports on HJS and TMDs, there are still no clear, tangible results assessing their co-occurrence and causes, suggesting the need for further research in this area, mostly on the molecular level.[12]

Therefore, the present study aimed to assess the prevalence of TMD symptoms, and cervical spine and TMJ disability in HJS patients. We hypothesized that HJS patients are more prone to develop painful TMDs, which translates into the onset of disability.

Material and methods

This study took place between January 2020 and June 2022 at the Department of Rehabilitation of Musculoskeletal System, Pomeranian Medical University in Szczecin, Poland, and was based on the surveys conducted among physical therapy students (2nd to 4th year, mean age: 21 years). All respondents signed formal, written consent to participate in the study, which was approved by the Bioethics Committee (KB 0012/104/15) and supported by a grant from the Pomeranian Medical University in Szczecin, Poland (MB-329-212/16).

The inclusion criteria were as follows: students of physical therapy who were not disabled, without any known disease, aged 18–25 years. Students with known diseases, inconsistent age, and who did not provided consent to participate in the study were excluded.

Assuming an effect size of 0.5, a power of 0.95 and a significance level of 0.05, the minimal sample size, as calculated using the G*Power software (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower), was determined to be 47.

The 1st stage of the study consisted in a survey to evaluate the presence of HJS with the use of 2 standardized tools – the Beighton and Brighton scales.[13,14] The data was acquired by the same trained and calibrated physical therapist, experienced in working with HJS patients. The Beighton scale is a five-point test assessing the passive extension of the 5th finger of the hand past 90°, the passive adduction of the thumb to the inner surface of the

forearm, the hyperextension of the elbow joint past 10°, the hyperextension of the knee joint past 10°, and the ability to position the hands on the floor while bending forward with the knee joints straight. Each symptom is assigned a '0' or '1' point. The point summary with a minimum score of 4 out of maximum 9 points resulted in the participant being included in the HJS group. The examiner demonstrated certain movement patterns to be repeated in a given time and the examinee performed this movement to the terminal part of their active range, as instructed.[13]

The Brighton scale is complementary to the Beighton test and the scores are integrated. The Brighton criteria were divided into major (Beighton scale: ≥4 points – either present or history – and pain lasting more than 3 months in at least 4 joints) and minor ones (Beighton scale: 1–3 points). The minor criteria comprise the following: pain lasting 3 or more months in 1–3 joints; back pain (lasting 3 or more months); spondylosis; spondylolysis/spondylolisthesis; dislocation/subluxation in more than one joint or more than once in a single joint; soft tissue rheumatism with 3 or more symptoms (epicondylitis, tenosynovitis and bursitis); Marfanoid physique; arachnodactyly; a positive Steinberg sign; carpal tunnel syndrome; skin abnormalities – striae, hyperextensibility, thinning, papillary scars; ocular manifestations – drooping eyelids, myopia, antimongoloid eyelid folds; lower limb varicose veins; hernia; rectal or vaginal/mammary prolapse; and mitral valve prolapse. The recognition of HJS is based on the presence of 2 major criteria or 1 major and 2 minor criteria or 4 minor criteria.[14]

Participants diagnosed with HJS based on the Brighton–Beighton scale were enrolled in the HJS study group (n = 56; 16 males and 40 females).

The control group (CG) consisted of 60 physical therapy students (18 males and 42 females) who were excluded from the study group, thus not meeting HJS thresholds according to the Beighton test and the Brighton criteria.

In the 2nd stage of the study, all participants completed standardized questionnaires about the presence of TMD symptoms and probable bruxism occurrence; the TMJ and cervical disability scores were recorded as well.[15,16] The data collected via the questionnaires was based on self-reports. The 'paper-and-pencil' method was used, and it took approx. 20 min to complete the questionnaires.

Thus, data acquisition was based on the following:

– a self-administered questionnaire containing specific questions about age, gender and the body mass index (BMI), and including subjective health assessment;
– 8 close-ended questions on TMD symptoms (headache, TMJ and preauricular pain, TMJ sounds, an increased activity of masticatory muscles, TMJ locking upon mouth opening, and tooth clenching and/or grinding – self-reported or partner-reported). Pain intensity was assessed using the numeric rating scale (NRS);
– TMD disability questionnaire (TMD-Q) – the subjective evaluation of TMD symptoms and TMJ functional limitations during daily activities. The TMD-Q consisted of 10 statements referring to specialized TMJ functions, such as speaking, dental care, eating, social activities, and non-specialized TMJ functions. Functional limitations were measured on a scale from 0 to 4, where 0 means no limitations, and 4 means maximum limitations. The minimum score was 0, and the maximum score was 40. The higher the score, the greater the degree of disability reported.[15]
– the neck disability index (NDI) – the Polish version of the NDI questionnaire (NDI-Polish version, NDI-PL) was used to evaluate cervical spine issues. It consisted of 10 questions concerning pain intensity, nursing, lifting objects, reading, headache, the ability to focus, working, driving, sleeping, and resting. Each question was graded on a scale of 0–5 points. The composite score was presented on a 0–50-point scale, where 0–4 corresponded to no disability, 5–14 was considered mild disability, 15–24 – moderate disability, 25–34 – severe disability, and 35–50 corresponded to terminal suffering and extreme disability.[16]

Statistical analysis

Data is presented in tables. Quantitative variables are presented as mean and standard deviation ($M \pm SD$), and as median (Me) with the 1st and 3rd quartiles. The normality of the distribution of quantitative variables was assessed using the Shapiro–Wilk test and, alternatively, histograms and quantile–quantile (Q–Q) plots. Pearson's χ^2 test was used for intergroup comparisons of qualitative variables. For quantitative variables with a normal distribution, the t test was used, while for quantitative variables with an abnormal distribution, the Wilcoxon and Kruskal–Wallis tests were used. Kendall's tau-b (τb) test was used for correlation analysis. The analysis was performed using the R language in the RStudio environment (http://www.rstudio.com). The statistical significance level was set at a p-value below 0.05.[17]

Results

A total of 82 women (70.69%) and 34 men (29.31%) participated in the study. A total of 52%, 29%, and 19% were second-, third- and fourth-year students, respectively.

The results regarding group characteristics are presented in Table 1.

There were no significant differences between the groups with regard to age and BMI. However, there was a statistically significant difference between the groups in the Beighton scale scores. Moreover, there was a statistically significant difference in the Brighton scale scores between the study group and CG, indicating HJS occurrence within the study group ($p < 0.001$) (Table 1).

Table 1. Analysis of the age, body mass index (BMI) and the Beighton scale scores in the study group (hypermobility joint syndrome (HJS) subjects) and the control group (CG)

Variable	Group	*M* ±*SD*	min–max	Q1–Q3	95% *CI*	*p*-value
Age [years]	HJS (*n* = 56)	21.2 ±1.15	20–24	20–22	0.307	0.954
	CG (*n* = 60)	21.2 ±1.07	20-24	20–22	0.277	
BMI [kg/m^2]	HJS (*n* = 56)	23.1 ±3.81	12.8–34.5	20.7–24.3	1.020	0.408
	CG (*n* = 60)	23.7 ±3.40	17.3–34.5	21.1–25.3	0.879	
Beighton scale [points]	HJS (*n* = 56)	7 ±1.3	4–9	6–8	0.366	<0.001*
	CG (*n* = 60)	0 ±0.8	0–3	0–1	0.208	

M – mean; *SD* – standard deviation; min – minimum; max – maximum; Q – quartile; *CI* – confidence interval; * statistically significant.

According to the analysis of the subjective health assessment, 50.0% of respondents with HJS assessed their health as good, 44.6% as sufficient, 5.4% as bad, and 0% as very good. In CG, the responses included 50.0% as good, 40.0% as very good, 8.3% as satisfactory, and 0% as bad or very bad.

Prevalence of TMD symptoms

According to the self-assessment questionnaire on TMD symptoms, pain in the adjacent tissues, masticatory motor function disorders, headache, neck and shoulder girdle pain, and TMJ pain were significantly more frequent in the HJS group, and the pain intensity levels were greater. Based on the analysis of the NRS scores, it could be concluded that there was a higher level of headache in the HJS group as compared to CG ($p < 0.001$); in the HJS group, most respondents indicated a NRS level of 3 (35.7%), while in CG, no pain was reported by 68.3% of the respondents. Neck and shoulder girdle pain was also higher in the HJS group, with up to 37.5% of the respondents reporting a NRS level of 5, while in CG, the most common response was no pain (75.0%). Scrutinizing the TMJ pain intensity scores in the HJS group, 30.4% of the respondents reported pain at NRS levels 4 and 5, whereas in CG, 86.7% reported no painful TMDs. Consecutively, in the HJS group, TMJ sounds ($p < 0.001$), TMJ locking upon mouth opening ($p < 0.001$) and tooth clenching and/or grinding ($p < 0.001$) occurred significantly more frequently as compared to controls.

TMJ disability

According to the TMD-Q responses, the HJS group and CG differed significantly with regard to questions 1 (verbal communication; $p < 0.001$), 3 (normal daily activities; $p < 0.001$), 4 (social/recreational activities; $p < 0.001$), 5 (non-specialized jaw function; $p < 0.001$), 6 (sexual function; $p < 0.001$), 8 (response to treatment; $p < 0.001$), 9 (tinnitus/vertigo/ear sounds; $p < 0.001$), and 10 (dizziness; $p < 0.001$). In the HJS group, the respondents were more likely to pinpoint at least one of the issues above, varying in severity, as compared to non-HJS controls (Supplement, available on request from the corresponding author).

Cervical spine disability

Using the cervical spine disability scale (NDI), responses in the HJS and CG groups were significantly different for questions 1 (pain intensity; $p < 0.001$), 3 (object lifting; $p < 0.001$), 4 (reading; $p < 0.001$), 5 (headache; $p < 0.001$), 6 (focus; $p < 0.001$), 7 (work; $p < 0.001$), 9 (sleep; $p < 0.001$), and 10 (rest; $p < 0.001$). There was a statistically significant difference in the degree of cervical spine disability between the groups. In the HJS group, 73.2% had mild disability and 26.8% had moderate disability, while in CG, 83.3% had no disability and 16.7% had mild disability (Supplement, available on request from the corresponding author).

The statistical analysis of the TMD-Q, NDI and NRS scores is presented in Table 2.

People with HJS reported significantly higher pain intensity on NRS ($p < 0.001$). In each case, headache, neck and shoulder girdle pain and TMJ pain were significantly more intense than in CG. Furthermore, HJS individuals expressed a greater degree of disability according to the TMD-Q and NDI scales ($p < 0.001$).

Table 2. Analysis of the temporomandibular disorder (TMD) disability questionnaire (TMD-Q) and neck disability index (NDI) scores, and headache, neck and shoulder girdle pain, and temporomandibular joint (TMJ) pain intensity (numeric rating scale – NRS) in the study and control groups

Variable	Group	*M* ±*SD*	min–max	*Me* (Q1–Q3)	*p*-value
TMD-Q score	HJS (*n* = 56)	10.9 ±3.4	7–21	10 (8–13)	<0.001*
	CG (*n* = 60)	0.7 ±1.1	0–5	0 (0–1)	
NDI score	HJS (*n* = 56)	12.9 ±4.7	6–24	12 (10–15)	<0.001*
	CG (*n* = 60)	2.8 ±2.2	0–9	2 (1–4)	
Headache intensity	HJS (*n* = 56)	3.4 ±1.4	0–6	3 (3–4)	<0.001*
	CG (*n* = 60)	1.1 ±1.7	0–5	0 (0–2)	
Neck and shoulder girdle pain intensity	HJS (*n* = 56)	4.6 ±1.3	0–7	5 (4–5)	<0.001*
	CG (*n* = 60)	0.9 ±1.6	0–5	0 (0–1)	<0.001*
TMJ pain intensity	HJS (*n* = 56)	4.3 ±1.1	2–7	4 (4–5)	<0.001*
	CG (*n* = 60)	0.4 ±1.1	0–4	0 (0–0)	<0.001*

Me – median; * statistically significant.

The mutually intertwining TMD-Q, NDI and the surrounding tissue issues in the HJS group and CG are presented in Fig. 1.

The HJS group showed significant positive correlations between the TMD-Q and NDI scores (p = 0.0035) (Fig. 1A), and between the TMD-Q and TMJ symptoms questionnaire scores (p = 0.0047) (Fig. 1B). An increase in the TMD-Q scores was tied to elevated NDI scores and TMJ symptoms.

A significant positive correlation between the NDI and TMJ symptom questionnaire scores was noted in the HJS groups (p < 0.001) and CG (p < 0.001) (Fig. 1C).

Discussion

According to our study data, the HJS bearers were significantly more prone to headaches, neck pain, and painful TMDs (p < 0.001). In 94.6% of the HJS respondents, headaches were reported, while 100% of them noticed significant cervical spine and TMJ pain, 80.4% reported TMJ sounds, 33.9% reported TMJ locking during jaw movements, and 66.1% noticed tooth clenching and/or grinding. A significant difference (p < 0.001) was observed in all the symptoms mentioned between the two examined groups. The present results confirm those from a study by Abbot et al., who highlighted a higher prevalence of neck pain in HJS-diagnosed study participants.[18] Similarly, other papers reported that the onset of headaches, including migraines, was significantly more prevalent in the HJS group as compared to healthy controls.[19,20] Chiodelli et al. emphasized the need for a more thorough observation of TMD prevalence in HJS bearers, possibly using larger cohorts.[21] Their study concluded that TMJ and preauricular pain were significantly more common in HJS patients.[21] According to Kavuncu et al., up to 79.7% of TMD patients had HJS,[22] with similar results obtained by Pasinato et al. (64.71%).[23] Additionally, the latter group of authors described a higher percentage of myofascial pain without mouth-opening restrictions in HJS participants (81.82%) as compared to non-hypermobile controls (58.33%).[23]

The results of the present study show that an ample prevalence of masticatory movement disorders (tooth clenching and/or grinding) was associated with the HJS group. According to Westling and Mattiasson, sleep-related movement disorders were considered to have greater detrimental effects on hypermobile individuals than on those with no connective tissue disorders.[24] Harkins and Cueva came to another valuable conclusion, namely, that HJS and masticatory parafunctions in women, when present simultaneously, are significantly associated with symptoms of intraorbital TMDs (p < 0.001).[25] Therefore, in patients with HJS, a greater emphasis should be put on tooth clenching and/or grinding. The researchers concluded that bruxism in conjunction with HJS presence might cause irreversible forms of ligament disability in the masticatory motor system and TMJs more rapidly than in non-HJS subjects.[25]

In our study, a significant difference was found between the groups in terms of TMJ pain. Consistently, Pasinato et al. brought up that painful mouth-opening issues were statistically more common in the HJS group than in the non-HJS CG (p = 0.0279).[23] Contrary to these results, no such causal relationship was found by Winocur et al. in a study on adolescent girls.[26]

Our data showed that the HJS patients commonly presented TMJ disability as compared to the non-HJS controls. Hence, a positive correlation between the TMD-Q score (the higher the score, the greater the disability) and the number of TMJ and surrounding tissue symptoms reported in the questionnaire was found (p = 0.0047).

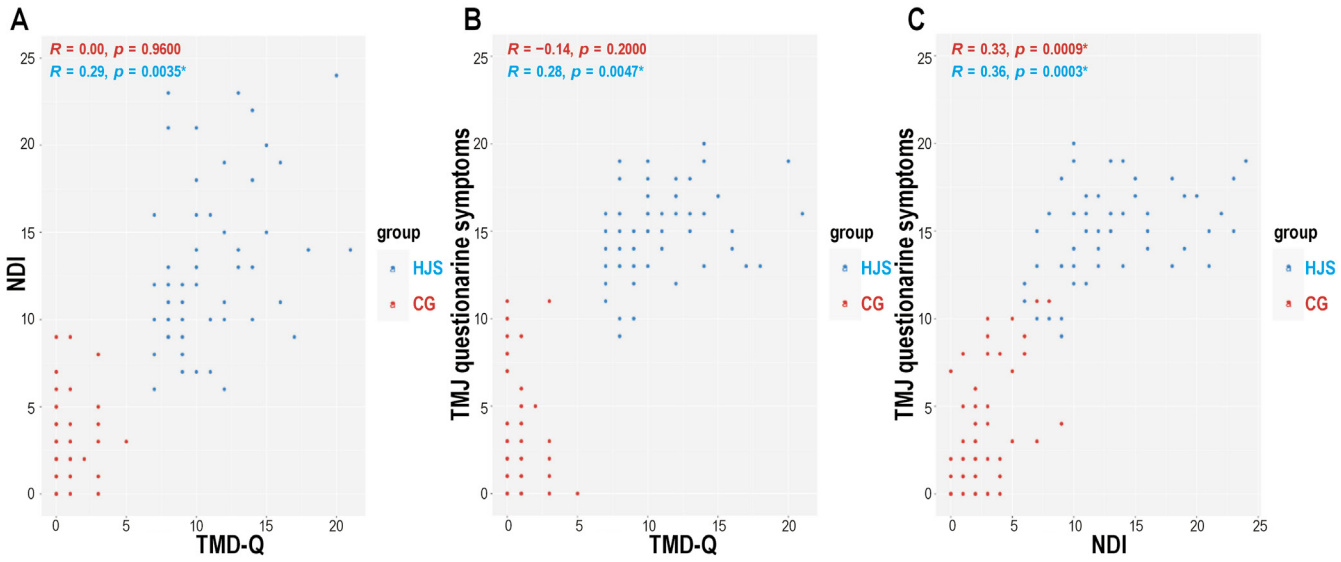

Fig. 1. Correlation between the prevalence of TMJ disability and cervical spine disability (A), TMJ disability and the number of reported TMJ and surrounding tissue symptoms (B), and cervical spine disability and the number of reported TMJ and surrounding tissue symptoms (C)

* statistically significant.

However, we did not find similar studies assessing TMJ disability with the use of TMD-Q in joint laxity cases, which makes our results incomparable with any other scientific data. However, given the validity of TMD-Q for assessing TMJ functions, we could cautiously draw a conclusion that HJS in patients with concomitant TMDs, i.e., pain, sounds, etc., might be considered an additional contributing factor for TMJ disability.

This study confirmed that HJS patients were more prone to the cervical spine disability onset as compared to healthy controls – these conclusions were drawn based on statistical significance. Moreover, we obtained a positive correlation between the NDI and TMJ symptoms questionnaire scores in the HJS group ($p < 0.001$), as well as in controls ($p < 0.001$). Hence, with regard to the previously mentioned considerations, the safest assumption would be that ligament laxity issues could be defined as hereditary, underlying conditions, generalized as a systemically altered quality of the connective tissue. These results suggest an impaired efficiency of the ligaments attached to cervical segments in HJS subjects. Proprioceptive dysfunction, and a greater predisposition to myofascial pain and spine trauma seem to be a contributing factor to the higher incidence and severity of cervical disability in hypermobile patients.[27] Few other studies focused on biomechanical links, despite strong functional relationships between TMJs and the cervical spine. According to Kashif et al., the association of TMDs with cervical spine disability and the NDI score was clearly significant ($p < 0.001$).[28]

Lee et al. showed an increased frequency and intensity of neck pain in the HJS group as compared to those without HJS (frequency: $p = 0.020$; intensity: $p = 0.001$).[29] In contrast, Keser et al. found no association between cervical spine degeneration (magnetic resonance imaging (MRI)), neck pain (the visual analog scale (VAS)) and cervical disability (NDI) in HJS bearers.[30] However, one should notice that their study was conducted on a group of patients aged 20–50 years, which is a significantly different age range in comparison with most groups scrutinized by other authors.

To our best knowledge, we are the first to demonstrate that in HJS patients there is a positive correlation between the presence of TMJ disability (TMD-Q) and cervical spine disability (NDI) ($p = 0.0035$). These results are very promising, hereby encouraging the design and implementation of more studies on this matter in larger cohorts and diverse populations.

The results of this study allowed us to conclude that TMD assessment in HJS patients, with the subsequent implementation of appropriate therapeutic interventions, would contribute to lessening the effects of dysfunction. Standardized procedures to assess the degree of TMJ and cervical spine disability should be considered in the daily clinical work for joint laxity patients. Affected patients require comprehensive, long-term care and follow-up with a skilled, multidisciplinary team of clinicians and therapists.

The obtained data leads to the conclusion that screening for HJS seems to be of highest importance for physical therapy students, as exposure to numerous tensions and overloads is an inherent part of their future profession. The detection of HJS at an early stage should lead to the swift implementation of both preventive and therapeutic methods aimed at reducing the effects of HJS, including observing the principles of ergonomics at work or introducing individual exercises to heal the proprioception function of the joints, which, like drug therapy, should be administered as needed and according to clinical judgment.

Limitations

As our study was based on the patient's self-reports, some participants might not have been fully eligible to understand and answer the questionnaire accurately. Additionally, no molecular tests were performed to confirm HJS, just the 2 solid and widely used questionnaires, i.e., the Beighton scale and the Brighton criteria. Although this is standard practice, it is important to note that the increasing availability of genetic tests assessing connective tissue insufficiency hereditary profiles would yield an earlier, more objective, yet highly personalized standard of care for hypermobile patients.[31,32] Another limitation was the lack of a DC/TMD (Diagnostic Criteria for Temporomandibular Disorders) diagnosis of TMDs and a standardized tool to assess the presence of TMJ dysfunction. In the future, as a follow-up of this study, more data needs to be included from larger patient cohorts in conjunction with molecular tests, a DC/TMD questionnaire and three-dimensional (3D) imaging. These may contribute to a significant increase in TMD recognition and the implementation of relevant treatment modalities in HJS patients.

Conclusions

Hypermobility joint syndrome patients are more likely to experience painful TMDs, headaches and cervical spine pain, which may lead to TMJ and cervical spine disability over time.

Ethics approval and consent to participate

All respondents signed formal, written consent to participate in the study, which was approved by the Bioethics Committee at Pomeranian Medical University in Szczecin, Poland (KB 0012/104/15).

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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