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Stress and anxiety among dental practitioners during the COVID-19 pandemic: A cross-sectional survey

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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. Dental professionals are at great risk of contracting coronavirus disease 2019 (COVID-19).

Objectives. The objectives of this study were to determine the levels of stress and anxiety among dental professionals, and to determine which dental procedures cause the greatest amount of stress and anxiety during the COVID-19 pandemic.

Material and methods. This cross-sectional survey was conducted by requesting voluntary participation of dental healthcare workers through the authors' own e-form, which consisted of our self-developed questionnaire, the Perceived Stress Scale (PSS) and the Generalized Anxiety Disorder-7 scale (GAD-7). The simple and multiple linear regression analyses were used to assess the effect of dental procedures and other factors associated with stress and anxiety among the participants. A p-value ≤ 0.05 was considered statistically significant.

Results. This survey included 85 participants (32 males, 53 females) with a mean age of 31.6 ±6.0 years. Significant associations were found between severe stress for scaling ($p < 0.001$; $p < 0.001$), complex fillings ($p < 0.001$; $p < 0.001$), root canal treatment (RCT) ($p = 0.001$; $p = 0.007$), crown and bridge work ($p < 0.001$; $p < 0.001$), denture work ($p = 0.034$; $p = 0.001$), third molar extractions ($p < 0.001$; $p < 0.001$), surgical procedures ($p < 0.001$; $p = 0.001$), and implant placement ($p = 0.001$; $p = 0.022$) and the PSS and GAD-7 scores, respectively.

Conclusions. Dental healthcare workers exhibit severe stress and anxiety associated with elective dental procedures. Dental emergencies should take precedence and elective dental treatment should be carried out with utmost caution, ensuring all protective measures. Psychological support for dental healthcare professionals should be made accessible.

Keywords: anxiety, stress, psychological, dentistry, COVID-19

Cite as
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Introduction

Coronavirus disease 2019 (COVID-19) is thought to have originated in Wuhan, China, and has spread across the globe. It has infected over 53 million people and killed more than 1.3 million.[1] The contagion spreads through both aerosol droplets and contact transmission.[2] Patients exhibiting symptoms are the main source of transmission; however, asymptomatic patients and patients in the incubation period of the infection may also transmit the virus.[2] Reports on the widespread transmission of COVID-19 to healthcare professionals have made it essential to develop strict safety protocols to protect frontline workers.[3,4]

The risk of cross-infection between dental practitioners and patients is extremely high, as dental interventions cause the generation of aerosols. Additionally, dentists and dental auxiliaries work in close proximity to patients.[5] As recommended, dentists have implemented exceptional hand hygiene, the use of personal protective equipment (PPE), such as masks, gloves, gowns, goggles, and face shields, and a thorough disinfection of all surfaces in negative pressure rooms.[6] Initially, the scheduling of elective procedures was not recommended and only dental emergencies were performed during the pandemic; however, as the duration of the pandemic could not be predicted, elective dental services have also been resumed.[7]

The pandemic has caused severe distress to all people and patients worldwide. At times like these, there can be a substantial impact of stress and anxiety on our daily lives. Cohen et al. developed the Perceived Stress Scale (PSS) to objectively determine stress in individuals due to life events and how they perceive these events in terms of stress.[8] Additionally, Spitzer et al. introduced the Generalized Anxiety Disorder-7 scale (GAD-7), providing clinicians with a brief index to determine anxiety in patients.[9] The GAD-7 scale is credited with a sensitivity of 89% and a specificity of 82% when using the threshold score of 10. Therefore, this is a highly accurate measure to determine the severity of anxiety symptoms.[9]

The risk of infection with COVID-19 for healthcare providers has raised stress and anxiety among dental professionals.[10,11] The literature lacks data on the COVID-19 infection rates among dentists; only a few surveys have been conducted, finding less than 1% of dentists affected by the disease.[12,13] These surveys highlight the dentists' perception of COVID-19 and the precautionary measures taken by them to prevent disease transmission.

Objectives

The objectives of this study were to assess stress and anxiety among general dental practitioners, specialist dental practitioners and dental surgery assistants while treating dental patients during the COVID-19 pandemic, and to determine which dental procedures cause the greatest amount of stress and anxiety.

Methods

This cross-sectional survey was conducted at the Aga Khan University Hospital in Karachi, Pakistan, between July 20th and August 5th, 2020, after obtaining an ethical approval (2020-4997-11263) from the institutional ethics review committee. The sample size was calculated using the one sample mean sample size calculator,[14] assuming a sample variance as 25, a margin of error of 5 points, an equivalence limit of 2, with a confidence level (*CI*) of 95%, and a power of 80%. It was calculated that a minimum of 24 subjects (*n*) were required in each group with a total sample size of 72 (*N*).

General dentists, dental specialists and dental assistants were contacted via social media and requested to participate voluntarily in the present study through our e-form drafted in the English language. General dental practitioners were defined as those who have obtained a bachelor's degree in dental surgery (BDS, 16 years of education). Specialist dental practitioners were those with at least 2 years of postgraduate specialization in any of the dental specialties (orthodontics, oral and maxillofacial surgery, operative dentistry, prosthodontics, periodontics, or pedodontics). Dental surgery assistants were regularly practicing auxiliaries, working in any private or public dental clinic or hospital. Those general dental practitioners, specialist dental practitioners and dental surgery assistants who were not in clinical practice, participants who did not respond despite 5 reminders, and those who provided incomplete responses were excluded.

The general dental practitioners, specialist dental practitioners and dental surgery assistants who met the eligibility criteria were sent the survey form via a Google Docs link. If they failed to return the filled forms, they were sent gentle reminders 5 times over a period of 15 days. Demographic information and the level of stress associated with dental procedures were recorded using a self-developed questionnaire. The level of stress was assessed using PSS.[8] Anxiety was assessed by means of GAD-7.[9]

Statistical analyses

Data was analyzed using the Stata® software, v. 12 (StataCorp, College Station, USA). Frequency and percentages were reported for categorical variables, such as reasons for stress and anxiety among dental professionals, and the amount of stress they experienced with different dental procedures. For continuous variables, the median (*Me*) and interquartile range (*IQR*) values were reported. The Shapiro–Wilk test was applied for determining the normality of the data, which showed a non-normal distribution; therefore, we used non-parametric tests. The Mann–Whitney *U* test was used for comparisons between genders. The comparison of the stress and anxiety *Me* scores among the 3 groups was performed using the Kruskal–Wallis test. Unadjusted and adjusted

β coefficients with their 95% *CI*s were reported by using the linear regression analysis to determine the dental procedures associated with stress among the participants as well as to adjust the results for confounding factors. A p-value <0.05 was considered statistically significant.

Results

Eighty-five participants (32 males, 53 females) completed our survey and were included in this study. They were of a mean age of 31.6 ±6.0 years. The distribution of dental professionals who participated in the survey was as follows: dental assistants – 28% (18 males, 6 females); general dentists – 29% (4 males, 21 females); maxillofacial surgeons – 8% (2 males, 5 females); operative dentists – 9% (2 males, 6 females); orthodontists – 20% (5 males, 12 females); and prosthodontists – 5% (1 male, 3 females). Figure 1 presents reasons for stress and anxiety among dental healthcare workers. Significant differences were found between genders in the experience (p = 0.011), GAD-7 (p < 0.001) and PSS (p < 0.001) scores (Fig. 2). Further comparisons were made after the stratification of data with respect to gender. The comparison of the PSS scores among the 3 male healthcare worker groups showed significant differences (p = 0.021). Also, the comparison of the PSS and GAD-7 scores among the 3 female healthcare worker groups showed significant differences (p = 0.012 and p = 0.037, respectively) (Table 1).

The simple linear regression analysis showed significant associations between the independent variables of age (p = 0.033), female gender (p = 0.001), stress during the last 2 months (p < 0.001), job security (p < 0.001), dental procedures (p < 0.001), aerosol-generating procedures (p < 0.001), and non-aerosol-generating procedures (p < 0.001) and the PSS scores, which reflects significant amounts of stress among dental practitioners during the COVID-19 pandemic. Significant associations were also found between severe stress connected with various dental procedures and the PSS scores, as shown in Table 2.

The simple linear regression analysis found significant associations between age (p = 0.012), female gender (p < 0.001), stress during the last 2 months (p < 0.001), job security (p = 0.001), dental procedures (p < 0.001),

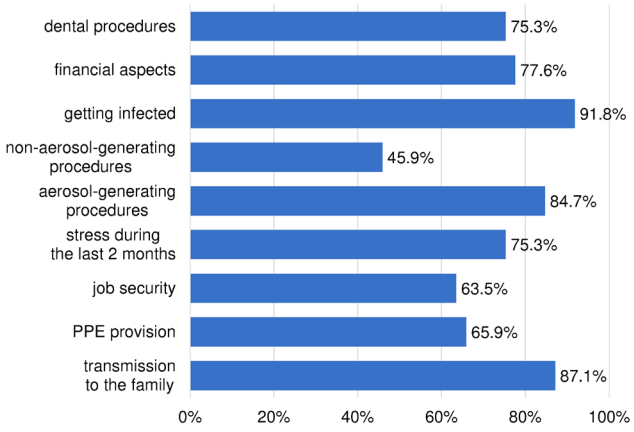

Fig. 1. Reasons for stress and anxiety among dental healthcare workers
N = 85; PPE – personal protective equipment.

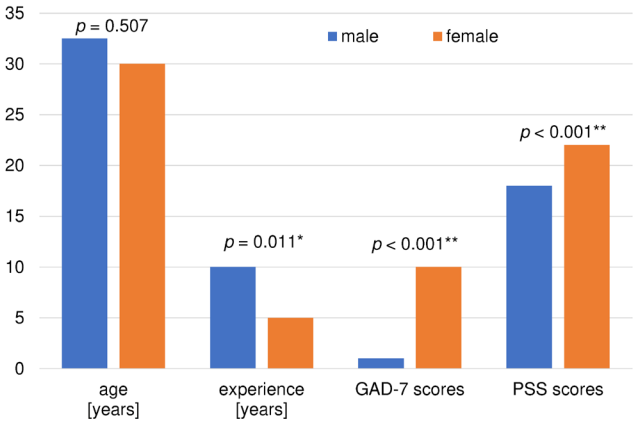

Fig. 2. Comparisons between genders
N = 85; GAD-7 – Generalized Anxiety Disorder-7 scale; PSS – Perceived Stress Scale; * $p \leq 0.05$; ** $p < 0.001$ (Mann–Whitney *U* test).
Data presented as median (*Me*).

aerosol-generating procedures (p < 0.001), and non-aerosol-generating procedures (p < 0.001) and the GAD-7 scores, indicating severe anxiety among dental practitioners. Significant associations were also found between severe stress connected with dental procedures such as scaling (p < 0.001), complex fillings (p < 0.001), root canal treatment (RCT) (p = 0.007), crown and bridge work (p < 0.001), denture work (p = 0.001), third molar extractions (p < 0.001), surgical procedures (p = 0.001), and implant placement (p = 0.022) and the GAD-7 scores (Table 3).

Table 1. Comparison of the stress and anxiety scores between the groups

Parameter	Males				Females			
	general dentists *n* = 4	specialist dentists *n* = 10	dental assistants *n* = 18	*p*-value	general dentists *n* = 21	specialist dentists *n* = 26	dental assistants *n* = 6	*p*-value
Stress scores	22.0 (20.5, 22.8)	18.0 (15.0, 21.5)	15.5 (1.8, 20.0)	0.021*	24.0 (22.0, 26.0)	22.0 (19.0, 22.3)	20.0 (16.3, 25.3)	0.012*
Anxiety scores	8.0 (5.5, 12.8)	1.5 (0.0, 7.5)	0.0 (0.0, 4.5)	0.056	10.0 (8.0, 18.5)	7.0 (5.0, 12.5)	15.5 (9.0, 18.0)	0.037*

N = 85; $p \leq 0.05$ (Kruskall–Wallis test).
Data presented as median (*Me*) (interquartile range (*IQR*)).

Table 2. Simple linear regression analysis of the Perceived Stress Scale (PSS) scores

Variable/Level of stress		β coefficient	*p*-value	95% *CI*	R^2
Age		−0.232	0.033*	−0.446, −0.020	0.054
Female gender		4.478	0.001*	1.952, 7.005	0.130
Stress during the last 2 months		6.975	<0.001**	4.341, 9.610	0.250
Job security		5.663	<0.001**	3.233, 8.093	0.206
Financial aspects		0.247	0.876	−2.903, 3.397	0.0003
Dental procedures		6.469	<0.001**	3.774, 9.165	0.215
Aerosol-generating procedures		7.783	<0.001**	4.557, 11.010	0.217
Non-aerosol-generating procedures		5.585	<0.001**	3.250, 7.920	0.214
Getting infected		10.705	<0.001**	6.542, 14.869	0.240
PPE provision		5.804	<0.001**	3.342, 8.265	0.210
Transmission to the family		8.360	<0.001**	4.902, 11.812	0.218
Scaling	mild	1.625	0.630	−0.055, 8.305	0.228
	moderate	10.375	0.001*	4.156, 16.594	
	severe	9.688	<0.001**	4.964, 14.411	
Simple fillings	mild	5.359	0.002*	2.056, 8.663	0.261
	moderate	8.980	<0.001**	5.163, 12.796	
	severe	7.556	0.023*	1.062, 14.048	
Complex fillings	mild	1.100	0.584	−2.882, 5.082	0.270
	moderate	7.715	<0.001**	3.936, 11.495	
	severe	8.700	<0.001**	4.591, 12.809	
RCT	mild	−0.952	0.704	−5.918, 4.013	0.193
	moderate	5.515	0.012*	1.249, 9.782	
	severe	6.686	0.001*	2.916, 10.457	
Crown/Bridge	mild	3.343	0.177	−1.539, 8.226	0.234
	moderate	5.222	0.013*	0.432, 10.013	
	severe	10.451	<0.001**	5.925, 14.978	
Dentures	mild	7.611	<0.001**	3.774, 11.448	0.218
	moderate	7.986	0.001*	3.322, 12.650	
	severe	6.011	0.034*	0.463, 11.560	
Orthodontics	mild	5.512	0.007*	1.518, 9.506	0.130
	moderate	5.317	0.019*	0.882, 9.753	
	severe	8.429	0.158	−3.352, 20.209	
Simple extractions	mild	7.723	<0.001**	4.264, 11.180	0.262
	moderate	3.048	0.022*	0.737, 9.339	
	severe	3.923	0.043*	0.196, 11.650	
Third molar extractions	mild	3.773	0.010*	1.430, 10.120	0.300
	moderate	4.900	0.047*	0.063, 9.735	
	severe	9.178	<0.001**	3.803, 12.332	
Surgical procedures	mild	4.135	0.120	−1.108, 9.418	0.203
	moderate	3.383	0.038*	0.320, 10.846	
	severe	8.708	<0.001**	4.794, 12.621	
Implant placement	mild	9.867	<0.001**	5.169, 14.565	0.219
	moderate	8.667	0.001*	3.448, 13.885	
	severe	7.400	0.001*	3.151, 11.649	
Pedodontics	mild	1.747	0.391	−2.128, 5.776	0.099
	moderate	3.506	0.075	−0.366, 7.378	
	severe	7.818	0.035*	0.565, 15.071	

N = 85; *CI* – confidence interval; RCT – root canal treatment; * $p < 0.05$; ** $p < 0.001$.

Table 3. Simple linear regression analysis of the Generalized Anxiety Disorder-7 scale (GAD-7) scores

Variable/Level of stress		*β* coefficient	*p*-value	95% *CI*	R^2
Age		–0.292	0.012*	–0.518, –0.066	0.074
Female gender		6.547	<0.001**	4.021, 9.072	0.243
Stress during the last 2 months		7.068	<0.001**	4.196, 9.939	0.224
Job security		4.704	0.001*	1.969, 7.438	0.124
Financial aspects		1.679	0.322	–0.675, 5.034	0.012
Dental procedures		6.056	<0.001**	3.076, 9.035	0.165
Aerosol-generating procedures		8.886	<0.001**	5.495, 12.276	0.247
Non-aerosol-generating procedures		5.944	<0.001**	3.439, 8.449	0.212
Getting infected		8.082	0.001*	3.282, 12.883	0.119
PPE provision		4.640	0.001*	1.853, 7.427	0.117
Transmission to the family		8.654	<0.001**	4.195, 12.392	0.203
Scaling	mild	2.250	0.527	–4.793, 9.293	0.252
	moderate	12.100	<0.001**	5.544, 18.656	
	severe	10.563	<0.001**	5.583, 15.542	
Simple fillings	mild	6.449	<0.001**	2.953, 9.945	0.279
	moderate	9.310	<0.001**	5.271, 13.349	
	severe	3.370	0.332	–3.502, 10.242	
Complex fillings	mild	2.818	0.209	–1.614, 7.250	0.212
	moderate	6.462	0.003*	2.255, 10.668	
	severe	8.900	<0.001**	4.327, 13.473	
RCT	mild	–1.690	0.326	–6.970, 3.589	0.205
	moderate	7.074	0.003*	2.534, 11.612	
	severe	3.358	0.007*	1.369, 9.387	
Crown/Bridge	mild	2.919	0.266	–2.272, 8.111	0.245
	moderate	4.139	0.110	–0.954, 9.232	
	severe	10.681	<0.001**	5.868, 15.493	
Dentures	mild	4.767	0.026*	0.588, 8.943	0.192
	moderate	7.417	0.003*	2.338, 12.495	
	severe	10.567	0.001*	2.016, 7.650	
Orthodontics	mild	3.643	0.084	–0.495, 7.781	0.186
	moderate	5.476	0.020*	0.880, 10.072	
	severe	3.143	0.610	–9.063, 15.349	
Simple extractions	mild	5.333	0.009*	1.370, 9.297	0.154
	moderate	3.500	0.163	–1.443, 8.443	
	severe	0.750	0.821	–5.816, 7.316	
Third molar extractions	mild	5.525	0.029*	0.574, 10.476	0.208
	moderate	6.150	0.029*	0.641, 11.659	
	severe	7.317	<0.001**	3.471, 11.162	
Surgical procedures	mild	1.012	0.725	–4.684, 6.708	0.189
	moderate	4.869	0.093	–0.827, 10.565	
	severe	7.625	0.001*	3.391, 11.859	
Implant placement	mild	3.633	0.173	–1.632, 8.899	0.145
	moderate	9.333	0.002*	3.485, 15.182	
	severe	5.600	0.022*	0.837, 10.363	
Pedodontics	mild	2.857	0.183	–1.373, 7.088	0.134
	moderate	6.063	0.004*	1.997, 10.128	
	severe	5.000	0.195	–2.616, 12.616	

$N = 85$; * $p < 0.05$; ** $p < 0.001$.

The multiple linear regression analysis showed significant associations between the fear of transmitting the virus to family members (p = 0.002), PPE provision (p = 0.003), job security (p = 0.007), stress during the last 2 months (p = 0.011), and age (p = 0.034) and the PSS scores, with 48% of variance in the PSS scores being explained by these factors (Table 4).

The multiple linear regression analysis showed significant associations between the fear of transmitting the virus to family members (p = 0.048), aerosol-generating procedures (p = 0.016), age (p = 0.002), and stress during the last 2 months (p = 0.006) and the GAD-7 scores, with about 40.5% of variance in the GAD scores being explained by these factors (Table 4).

Discussion

This survey indicates a significant amount of stress and anxiety among dental practitioners associated with treating patients during the COVID-19 pandemic. Dental professionals are at high risk of contracting COVID-19 due to their exposure to saliva, blood and aerosol droplets that are produced during dental procedures.[15]

The outbreak of COVID-19 caused disruption in dental services and many practices were shut down temporarily. Guidelines such as those by the American Dental Association (ADA) and the Centers for Disease Control and Prevention (CDC) were rapidly developed to help standardize patient care and minimize the spread of the infection.[16,17] These changes prompted investigation into the knowledge and attitude of dentists with regard to providing dental treatment during the pandemic. Khader et al. investigated the awareness and perception of as well as attitude toward COVID-19 among dentists.[18] Although the authors found that dentists possessed adequate knowledge about the pathogen, they lacked the understanding of the protective measures which needed to be implemented to prevent disease transmission. A study by Ahmed et al. indicated that 87% of dentists were afraid of acquiring the infection while providing treatment despite being aware of the necessary precautions.[19] Similarly, this study shows that although dentists, specialists and dental assistants are well-informed, they fear that they may contract the virus and infect their family members. Greater PSS and GAD-7 scores were reported for the female gender as compared to males. As many female dentists often have domestic duties and are mothers, their concerns related to the risk of transmission of the virus to immediate family members is understandably greater than in the case of male dentists. Significant associations between the stress and anxiety outcomes related to the outbreak of the pandemic and conducting dental procedures with the PSS and GAD-7 scores indicate psychological effects on dental healthcare workers. For example, 43.5% of the participants either did not perform or assist in the scaling of a patient's dentition during this pandemic. Furthermore, the fear of contracting the disease through the aerosolized droplets produced during dental treatment was reported by 84.7% of the participants. This is in concordance with a study by Gambarini et al.[20]

Reverse transcription polymerase chain reaction (RT-PCR) tests have been widely conducted for the detection of the COVID-19 infection.[21] However, these tests have shown rates of false negative results that range between 2% and 29%, which is equal to 71–98% sensitvity.[22] The neglect of COVID-19 protocols in several dental centers around the country has raised fears in dental professionals. These observations may have contributed to the high PSS and GAD-7 scores noted particularly for general dentists in our study. Many dental centers nationally and internationally have adopted preventive measures, such as a pre-procedural mouth rinse with either 0.2% povidone-iodine or 0.5–1% hydrogen peroxide, and yet dentists are hesitant when undertaking routine dental procedures.[23,24] Lower PSS and GAD-7 scores were observed in dental assistants of both genders. This may be due to the lack of education, awareness and knowledge among these individuals.

Table 4. Multiple linear regression analysis

Scores	Variable	β coefficient	p-value	95% *CI*
PSS scores	Transmission to the family	4.779	0.002*	1.799, 7.759
	PPE provision	3.215	0.003*	1.091, 5.338
	Job security	3.104	0.007*	0.865, 5.341
	Stress during the last 2 months	3.359	0.011*	0.794, 5.922
	Age	–0.174	0.034*	–0.335, –0.014
	Adjusted R^2		0.483	
GAD-7 scores	Transmission to the family	3.861	0.048*	0.029, 7.693
	Aerosol-generating procedures	4.949	0.016*	0.937, 8.961
	Age	–0.295	0.002*	–0.479, –0.110
	Stress during the last 2 months	4.134	0.006*	1.213, 7.055
	Adjusted R^2		0.405	

N = 85; * $p < 0.05$; ** $p < 0.001$.

A great possibility of cross-contamination exists with elective dental procedures.[16] Our results show significant associations between scaling, fillings, extractions – both simple and complex, denture work, crown and bridge work, implant placement, and other surgical procedures and the PSS and GAD-7 scores. These procedures pose a greater risk of infection transmission, as dental healthcare workers are exposed to the oral environment for prolonged periods of time and there is a constant production of fine aerosol-containing dental debris and saliva.[25] This justifies any apprehension a dental healthcare professional may have toward treatment that can be deferred.

Emergency dental care continues to be provided to patients despite the ongoing pandemic. Protocols have been put into place for the alleviation of pain due to dental disease. The National Health Service (NHS) recommended that all non-urgent dental care be suspended, which included orthodontic treatment.[26] As seen in the results of this study, severe stress or anxiety were not significantly associated with orthodontic treatment, most probably due to the nature of orthodontic appointments. Associations between the GAD-7 scores and simple fillings, simple extractions and pediatric procedures were statistically non-significant, unlike in the case of the PSS scores. In contrast, both the PSS and GAD-7 scores showed significant associations with severe stress when performing all other dental procedures. It is possible that this difference in the PSS and GAD-7 scores is due to the perception that simple procedures require a shorter time of exposure to a patient. Nonetheless, the possibility of contracting the virus remains. Furthermore, the pediatric population has shown to be vulnerable and poses a transmission risk. This should remind the dental community to take all the necessary precautions during the treatment of these patients.[27]

To the best of our knowledge and based on the literature review, there have been no studies assessing stress and anxiety among dental professionals with regard to different dental procedures during the COVID-19 pandemic. The results of this survey provide novel information regarding the inclination of dental healthcare workers to provide routine care during the pandemic. As many dental procedures are not emergencies, the reservations of healthcare workers about providing elective dental care were highlighted. A possible limitation of this online survey could be a sampling error leading to bias in the results. In addition, the number of subjects in the subgroups was small and a greater number of females participated in this study. Nonetheless, based on the present results, we recommend that psychological support and treatment should be made accessible to dental healthcare workers during the COVID-19 pandemic to maintain their mental health. We also suggest studies be conducted that would compare stress and anxiety between other medical professionals and dental healthcare workers as well as methods to reduce the risk of transmission of the virus to dental healthcare workers and patients so that both groups could be safe in these unprecedented times.

Conclusions

Dental practitioners suffer from significant stress and anxiety related to acquiring the infection during the COVID-19 pandemic. There is an escalated fear of getting infected while providing treatment and of transmitting the infection to family members. Dentists should carefully evaluate the dental needs of all patients before undertaking elective dental procedures, whereby all dental emergencies should be handled immediately while adhering to safety guidelines. Psychological support should be provided to dental healthcare professionals to maintain adequate mental health.

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Clinical condition of the oral cavity in overweight and obese patients

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Abstract

Background. The increasing prevalence of both obesity and periodontal disease in adults has raised interest among researchers in a correlation between these conditions. Obesity is caused by a poorly balanced diet, rich in sugars, that leads to the accumulation of excessive amounts of plaque, which results in the development of gingivitis, periodontitis and caries. It is known that there is a correlation between these 2 disease entities, but the mechanisms of the interaction have not been explored to date. Thus, attempts to address this research question seem justified.

Objectives. The aim of the study was to compare selected parameters of dental and periodontal health as well as the oral hygiene status between overweight/obese adults and a control group. Additionally, eating habits and other factors affecting obesity in adults were examined in comparison with the control group on the basis of a self-developed questionnaire.

Material and methods. The study included 120 adult patients (men and women), aged 19–55 years, divided into a study group of 60 overweight/obese individuals and a control group of 60 individuals with a normal weight based on the body mass index (BMI). The study involved anthropometric measurements (BMI, waist circumference – WC and hip circumference – HC) and dental examination, including dental caries examination (the decayed, missing and filled teeth index – DMF), oral hygiene assessment (the approximal plaque index – API) and periodontal tissue examination (pocket depth – PD, clinical attachment level – CAL, bleeding on probing – BOP, and the community periodontal index – CPI). Sociomedical examination was performed taking into account dietary and hygienic habits.

Results. The group with BMI $\geq$ 25 kg/m^2 was found to have worse parameters of periodontal health and unsatisfactory oral hygiene status as compared to the control group. This group also presented lower regularity of eating meals and a higher rate of sweets consumption.

Conclusions. Lower regularity of eating meals and higher sweets consumption, combined with poor hygiene habits, are reflected in increased rates of gum inflammation and plaque accumulation as well as worsened periodontal tissue status. A positive correlation between periodontal disease and BMI points to the need to arrange for periodontal disease prevention and treatment among overweight and obese patients.

Keywords: diet, overweight, periodontal disease, oral hygiene

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Introduction

Periodontal disease is a chronic inflammatory condition with increasing prevalence in Poland, which makes it not only a health problem, but also a social issue. It affects about half of the adult population of the United States over the age of 30,[1] and is one of the leading causes of tooth loss.[2,3] The growing prevalence of overweight and obesity in adults worldwide has contributed to raised interest among researchers in using obesity-related indices to assess the risks of many chronic health conditions, including periodontal disease. Gingivitis observed in overweight and obese patients may be a result of metabolic disorders, inflammatory factors or improper oral hygiene habits. The latter are associated with the frequent consumption of sweetened, pulpy and highly processed food products, snacks, and sweetened carbonated beverages, which is a risk factor for becoming overweight, particularly in children and adolescents. The consumption of free sugars is a risk factor for both dental caries and obesity. Given that the excessive intake of sugars and social deprivation are risk factors for dental caries and obesity, it has been hypothesized that these 2 outcomes may be more likely to co-exist within the same individuals or populations. Aside from free sugars and socio-economic deprivation, obesity in children and young people is affected by many complex behavioral and societal factors, including the overall calorie intake, the level of physical activity, genetic factors, and the media. Dental caries is also affected by exposure to fluoride, the overall dietary composition, oral bacteria, the salivary composition and flow rates, and the tooth enamel structure. Obesity caused by a poorly balanced diet, rich in sugars, can lead to the accumulation of excessive amounts of dental plaque, causing the growth of *Streptocccus mutans* (*S. mutans*) bacteria and *Lactobacillus spp.* bacteria, which can result in the development of gingival inflammation, periodontitis and caries. It is believed that obese patients are more likely to lose their teeth over-early due to untreated caries and periodontitis, which results in the premature extraction of teeth. Moreover, overweight and obesity can affect salivary secretion and the properties of saliva, including changes in its microbiological composition. The relationship between obesity and the occurrence of chronic, moderate inflammation of the salivary glands has received attention. The inflammatory mediators secreted by the adipose tissue of obese people, such as resistin, pro-inflammatory cytokines, interleukins IL-1, IL-6, IL-8, and IL-10, and tumor necrosis factor alpha (TNF-α), may influence the development of periodontitis.[4] Tumor necrosis factor alpha is a major mediator of periodontal tissue destruction by bacterial endotoxins. The concentration of TNF-α in periodontal tissue is higher in people with periodontitis as compared to those without periodontitis, and decreases when inflammation is successfully treated. It has also been shown that the concentration of TNF-α in gingival fluid is directly related to the body mass index (BMI). Thus, obesity may exacerbate the course of periodontitis. It is now known that there is a correlation between these 2 disease entities; however, the mechanisms of the interaction between them have not been fully explored to date. Therefore, further research addressing this question is justified.

In light of the relationship between obesity and periodontal disease, often discussed in the literature, the objective of this paper was to compare selected parameters of dental and periodontal health as well as the oral hygiene status between overweight and obese adults and a control group.

Material and methods

The study included 120 adult patients (men and women), aged 19–55 years, who reported to the Department of Periodontology and Oral Diseases at the Faculty of Dentistry of the Medical University of Warsaw and a private dental practice in Warsaw, Poland, between June 2013 and May 2015. The methodology adopted for taking patient history and physical examination was approved by the Bioethics Committee of the Medical University of Warsaw (KB/194/2013).

The inclusion criteria for overweight/obese patients were as follows: BMI ≥ 25 kg/m^2; and for women – waist circumference (WC) >88 cm and the waist-to-hip ratio (WHR) >0.8, or for men – WC > 102 cm and WHR > 1.0.

The exclusion criteria were more than a single missing tooth or a chronic disease.

All patients were generally healthy; they underwent anthropometric assessment, including the BMI, WC and hip circumference (HC) measurements as well as the clinical examination of the teeth and periodontal tissues, and oral hygiene status assessment. The results were recorded in individual patient dental examination charts.

The study group was made up of 60 overweight/obese individuals, including 38 women and 22 men, with a mean age of 39 years. All had BMI ≥ 25 kg/m^2: 41.7% had BMI in the range of 25–30 kg/m^2 and 58.3% had BMI > 30 kg/m^2. The control group was made up of 60 individuals, including 34 women and 26 men, aged 19–43 years, with a mean age of 34 years, and BMI in the range of 18–24.9 kg/m^2.

Following dental examination, dental health was assessed using the decayed, missing and filled teeth count (DMF), while the oral hygiene status was evaluated according to the approximal plaque index (API), without intraoral dyeing.

The clinical condition of the periodontium was examined based on the measurements of pocket depth (PD) and bleeding on probing (BOP). Moreover, periodontal probing was used to measure PD and clinical attachment level (CAL) at 4 sites of the tooth, which gives a total of 112 evaluated sites.

The community periodontal index for treatment needs (CPITN) procedure according to Ainamo et al.[5] was applied to assess prevention and the treatment needs (TN) of the participants. All 6 sextants were evaluated: 17–14; 13–23; 24–27; 34–37; 33–43; and 44–47.

Sociomedical examination was also performed, taking into account diet, and dietary and hygiene habits.

Statistical analysis

The χ^2 test was used for the primary comparative analysis of the 2 groups. If the expected count in at least 1 field of the four-field table was <5, the two-tailed Fisher's exact test was then used. The adopted level of statistical significance was $p < 0.05$ for all tests.

Results

Detailed data on the general characteristics of the study population, divided according to gender, average age, education, smoking, and BMI distribution, are presented in Table 1.

Table 2 presents the comparison of the oral hygiene and periodontal tissue status between the groups with BMI ≥ 25 kg/m^2 and BMI < 25 kg/m^2. Statistically significant differences were found for the following variables: API ($p = 0.031$); BOP ($p < 0.001$); PD ($p = 0.015$); and CPITN ($p < 0.001$). The summary is presented below:

– API: in the BMI ≥ 25 kg/m^2 group, 48.3% of patients had API in the range of 40–69% and 38.3% had API ≥ 70%; in the BMI < 25 kg/m^2 group, 23.3% had API ≥ 70% and 8.3% had a normal API (<25%);
– BOP: in the study group with BMI ≥ 25 kg/m^2, the mean BOP was 55%, while in the control group, the mean BOP was 27.5%;
– PD: in the patient group with BMI ≥ 25 kg/m^2, the mean PD was 3.0 mm, compared to 2.7 mm in the group with BMI < 25 kg/m^2;

Table 1. General characteristics of the population

Characteristics	Group BMI ≥ 25 kg/m^2 *n* = 60	Group BMI < 25 kg/m^2 *n* = 60
Gender *n* (%)		
female	38 (63.3)	34 (56.7)
male	22 (36.7)	26 (43.3)
Age [years]	28–55	19–43
BMI [kg/m^2] *n* (%)		
<18.5	0 (0.0)	4 (6.6)
18.5–24.9	0 (0.0)	56 (93.3)
25.0–30.0	25 (41.7)	0 (0.0)
>30.0	35 (58.3)	0 (0.0)
Education *n* (%)		
primary	6 (10.0)	6 (10.0)
vocational	3 (5.0)	7 (11.7)
secondary	28 (46.7)	29 (48.3)
higher	23 (38.3)	18 (30.0)
Smoking *n* (%)		
non-smoker	36 (60.0)	26 (43.3)
smoking for 2–4 years	3 (5.0)	4 (6.7)
smoking for >4 years	13 (21.7)	18 (30.0)
smoking for >20 years	8 (13.3)	12 (20.0)

BMI – body mass index.

Table 2. Oral hygiene and periodontal tissue status in the study group and the control adult population

Parameter	Group BMI ≥ 25 kg/m^2 *n* = 60	Group BMI < 25 kg/m^2 *n* = 60	*p*-value
DMF *M* (min–max)	13 (11–16)	12 (11–15)	0.132
API [%] *n* (%)			
<25	0 (0.0)	5 (8.3)	0.031*
25–39	8 (13.3)	14 (23.3)	
40–69	29 (48.3)	27 (45.0)	
≥70	23 (38.3)	14 (23.3)	
BOP [%] *M* (min–max)	55.0 (42.0–64.5)	27.5 (13.0–45.0)	<0.001*
PD [mm] *M* (min–max)	3.0 (2.5–3.5)	2.7 (2.0–3.0)	0.015*
CAL [mm] *M* (min–max)	2.7 (2.0–3.2)	2.0 (1.0–3.0)	0.075
1–2 mm *n* (%)	23 (38.3)	33 (55.0)	
3–4 mm *n* (%)	35 (58.3)	26 (43.3)	
>4 mm *n* (%)	2 (3.3)	1 (1.7)	
CPI TN			
0 0	2 (3.3)	7 (11.7)	<0.001*
1 1	0 (0.0)	11 (18.3)	<0.001*
2 2	14 (23.3)	29 (48.3)	<0.001*
3 2	28 (46.7)	13 (21.7)	<0.001*
4 3	16 (26.7)	0 (0.0)	<0.001*

DMT – decayed, missing and filled teeth index; API – approximal plaque index; BOP – bleeding on probing; PD – pocket depth; CAL – clinical attachment level; CPI – community periodontal index; TN – treatment needs; *M* – mean; min – minimum; max – maximum; * statistically significant.

– CPI: in the study group, the highest percentage of patients (46.6%) was CPI-3, while in the control group, CPI-2 prevailed at 48.4%.

According to TN based on CPI, 96.7% of patients with BMI ≥ 25 kg/m^2, compared to 70% in the control group, required professional cleaning of the tooth surface from plaque and tartar as well as oral hygiene instruction.

Table 3 presents a statistically significant difference ($p = 0.037$) in the severity of periodontal disease according to the classification of the American Academy of Periodontology (AAP).

Table 3. Periodontal tissue status in the study and control groups – American Academy of Periodontology (AAP) classification

Periodontal tissue status	Group BMI ≥ 25 kg/m^2 *n* = 60	Group BMI < 25 kg/m^2 *n* = 60	*p*-value
Severity of periodontal disease			
healthy	0 (0.0)	8 (13.3)	0.037*
gingivitis	8 (13.3)	4 (6.7)	
slight chronic periodontitis	8 (13.3)	10 (16.7)	
moderate chronic periodontitis	22 (36.7)	17 (28.3)	
severe chronic periodontitis	22 (36.7)	21 (35.0)	
Extent of periodontal disease			
healthy	11 (18.3)	13 (21.7)	0.625
localized	20 (33.3)	21 (35.0)	
generalized	29 (48.3)	26 (43.3)	

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

Table 4. Comparative analysis of the study group and the control adult population regarding dietary habits, based on a survey

Dietary habits	Group BMI ≥ 25 kg/m^2 *n* = 60	Group BMI < 25 kg/m^2 *n* = 60	*p*-value
Knowledge about nutrition *n* (%)			
bad	4 (6.7)	3 (5.0)	0.705
sufficient	15 (25.0)	18 (30.0)	
good	35 (58.3)	30 (50.0)	
very good	6 (10.0)	9 (15.0)	
Meal regularity *n* (%)	24 (40.0)	39 (65)	0.006*
Number of meals *M* (min–max)	3 (3–4)	3 (3–5)	0.712
Diabetic diet *n* (%)	4 (6.7)	0 (0.0)	0.118
Meat and fat consumption frequency *n* (%)			
none	0 (0.0)	0 (0.0)	<0.001*
< once a week	0 (0.0)	0 (0.0)	
once a week	5 (8.3)	22 (36.7)	
> once a week	55 (91.7)	38 (63.3)	
every day	0 (0.0)	0 (0.0)	
Dairy consumption frequency *n* (%)			
none	0 (0.0)	0 (0.0)	0.032*
< once a week	5 (8.3)	11 (18.3)	
once a week	14 (2.3)	22 (36.7)	
> once a week	41 (68.3)	27 (45.0)	
every day	0 (0.0)	0 (0.0)	
Fish consumption frequency *n* (%)			
none	4 (6.7)	4 (6.7)	0.088**
< once a week	13 (21.7)	5 (8.3)	
once a week	27 (45.0)	24 (40.0)	
> once a week	16 (26.7)	27 (45.0)	
every day	0 (0.0)	0 (0.0)	
Fruit and vegetables consumption frequency *n* (%)			
none	0 (0.0)	0 (0.0)	0.104
< once a week	6 (10.0)	4 (6.7)	
once a week	10 (16.7)	20 (33.3)	
> once a week	44 (73.3)	36 (60.0)	
every day	0 (0.0)	0 (0.0)	
Sweets consumption frequency *n* (%)			
none	1 (1.7)	5 (8.3)	0.002*
< once a week	5 (8.3)	19 (31.7)	
once a week	21 (35.0)	17 (28.3)	
> once a week	33 (55.0)	19 (31.7)	
every day	0 (0.0)	0 (0.0)	
Fast food consumption frequency *n* (%)			
none	9 (15.0)	5 (8.3)	0.467
< once a week	16 (26.7)	12 (20.0)	
once a week	24 (40.0)	29 (48.3)	
> once a week	11 (18.3)	14 (23.3)	
every day	0 (0.0)	0 (0.0)	
Amount of liquids received daily [L] *n* (%)			
<0.5	10 (16.7)	9 (15.0)	0.927
0.5–1.5	26 (43.3)	25 (41.7)	
>1.5	24 (40.0)	26 (43.3)	

* statistically significant; ** trend-level significance.

In the patient group with BMI ≥ 25 kg/m^2, a higher percentage of patients was found to have severe or moderate chronic periodontitis at 36.7% each. In the group with BMI < 25 kg/m^2, the distribution was more even, with severe chronic periodontitis in 35% of patients and more patients showing evidence of less severe chronic periodontitis. Healthy patients accounted for 13.3% of subjects in the control group, compared to 0% in the patient group with BMI ≥ 25 kg/m^2 (Table 3).

The patients also differed in terms of periodontal disease progression, according to the new classification from 2017. In the patient group with BMI ≥ 25 kg/m^2, 48.3% of patients were classified as stage II of periodontitis, compared to 43.3% in the group with BMI < 25 kg/m^2 (Table 3).

In the analysis of the survey responses, a significant difference was observed concerning the regularity of food consumption (p = 0.006); 40% of respondents in the group with BMI ≥ 25 kg/m^2 had meals regularly, while this percentage was 65% in the control group (Table 4).

Analyzing the frequency of eating individual foods, a statistically significant difference was found between the groups in the frequency of eating meat and fat (p < 0.001), dairy products (p = 0.032) and sweets (p = 0.002) as well as a trend-level significance in the frequency of eating fish (p = 0.088) (Table 4).

The results showed that 91.7% of patients in the study group with BMI ≥ 25 kg/m^2 consumed meat and fat more often than once a week vs 63.3% in the control group with BMI < 25 kg/m^2. Similarly, dairy products were consumed more frequently than once a week in the BMI ≥ 25 kg/m^2 group at 68.3% vs 45% in the control group. In the group with BMI ≥ 25 kg/m^2, the consumption of sweets occurred more often than once a week in 55% of patients, while in the group with BMI < 25 kg/m^2, the distribution was more balanced, with 31.7% reporting the consumption of sweets less frequently than once a week and 8.3% reporting no consumption at all. In addition, 45% of people in the group with BMI < 25 kg/m^2 consumed fish more often than once a week, whereas in the BMI ≥ 25 kg/m^2 group, 45% of people reported consuming fish once a week and 21.7% even less often (Table 4).

Statistically significant differences were also found in the responses to questions about the frequency of follow-up visits to the dentist (p = 0.018) and hygienic habits, including the movement performed while brushing the teeth (p = 0.022), the type of brush used (p = 0.025), the use of dental floss (p < 0.001), the use of mouthwash (p = 0.005), and the occurrence of bleeding gums when brushing the teeth (p = 0.003) (Table 5).

Table 5. Comparative analysis of the study group and the control adult population regarding oral hygiene habits, based on a survey

Oral hygiene habits	Group BMI ≥ 25 kg/m^2 n = 60	Group BMI < 25 kg/m^2 n = 60	p-value
Frequency of follow-up visits			
< once every 12 months	29 (48.3)	18 (30.0)	0.018*
once every 12 months	19 (31.7)	16 (26.7)	
> once every 6 months	12 (20.0)	26 (43.3)	
Frequency of daily tooth brushing			
once a day	15 (25.0)	9 (15.0)	
twice a day	26 (43.3)	32 (53.3)	0.548
3 times a day	15 (25.0)	15 (25.0)	
>3 times a day	4 (6.7)	4 (6.7)	
Bleeding gums	31 (51.7)	15 (25.0)	0.003*
Using an electric toothbrush	11 (18.3)	22 (36.7)	0.025*
Movement during tooth brushing			
circular	19 (31.7)	14 (23.3)	
transverse	18 (30.0)	10 (16.7)	0.022*
sweeping	10 (16.7)	25 (41.7)	
combined	13 (21.7)	1 (18.3)	
Toothpaste with fluoride	58 (96.7)	60 (100.0)	0.496
Use of dental floss	11 (18.3)	33 (55.0)	<0.001*
Use of mouthwash	15 (25.0)	30 (50.0)	0.005*
Frequency of gum chewing after meals			
never	18 (30.0)	11 (18.3)	
rarely	25 (41.7)	25 (41.7)	0.124
often	15 (25.0)	24 (40.0)	
always	2 (3.3)	0 (0.0)	
Tooth loss	14 (23.3)	8 (13.3)	0.160
Diagnosed periodontitis	9 (15.0)	5 (8.3)	0.255
Awareness of periodontal disease	18 (30.0)	12 (20.0)	0.206

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

In the BMI ≥ 25 kg/m^2 group, 48.3% of patients had follow-up visits less frequently than once every 12 months, while in the control group, 43.3% visited the dentist more often than once every 6 months (Table 5).

In the group with BMI ≥ 25 kg/m^2, 31.7% of patients brushed their teeth in a circular motion and 30% used a transverse motion, while in the group with BMI < 25 kg/m^2, patients brushing their teeth with a sweeping motion dominated at 41.7%. In the group with BMI ≥ 25 kg/m^2, the percentage of patients using an electric toothbrush and dental floss was 18.3% each, while in the group with BMI < 25 kg/m^2, the percentages of patients using an electric toothbrush and dental floss were 36.7% and 55%, respectively. Similarly, in the group with BMI ≥ 25 kg/m^2, only 25% of patients used mouthwash, while in the group with BMI < 25 kg/m^2, the percentage was 50% (Table 5).

Discussion

The increasing prevalence of overweight/obesity as well as periodontal disease in adults has met with growing interest among researchers due to the possibility of using obesity-related indices to assess the risk of developing periodontal disease.[6]

The first studies on the relationship between obesity and periodontal disease in people were undertaken in Japan, where 241 patients aged between 20 and 59 years were examined.[7] It was demonstrated that a high BMI value was positively associated with periodontal disease prevalence. The analysis, including adjustments for age, gender, hygiene habits, and tobacco smoking, proved that periodontal disease was 8.6 times more common in subjects with BMI ≥ 30 kg/m^2 as compared to the control group with BMI < 20 kg/m^2.[7] A later study by Saito et al. with 643 patients aged 19–79 years demonstrated a statistically significant positive correlation between elevated BMI and periodontal disease prevalence ($p < 0.002$), which was confirmed by finding the relationship between high BMI and WHR and high PD values ($p < 0.001$). Interestingly, high WHR was linked to the risk of periodontal disease, particularly in the higher categories of BMI.[8]

Over the last 10 years, a significant body of literature and meta-analyses has been devoted to the association between overweight/obesity and periodontal disease, revealing a significant positive correlation.[6–14] Some authors found a directly proportional relationship between BMI and the severity of periodontal disease.[6,7] Dalla Vecchia et al. investigated the association of obesity with periodontitis, demonstrating a significant correlation between the occurrence of these 2 conditions, particularly in adult non-smoking women.[15] Khader et al. studied the relationship between periodontal disease and obesity among the adult inhabitants of Jordan, concluding that high BMI as well as high WC were significantly associated with an increased risk of periodontal inflammation.[16]

The findings from the present study confirm earlier reports on a positive correlation between the overall obesity (based on BMI) and the occurrence of periodontal disease. Increased PD values were noted in the study group with BMI ≥ 25 kg/m^2. It was also demonstrated that patients with BMI ≥ 25 kg/m^2 tended to have increased plaque accumulation and symptoms of periodontitis based on BOP. Kongstad et al. investigated the relationship between obesity based on BMI and the loss of gum attachment by means of the CAL and BOP measurements, but only inconsiderable correlations were found between these parameters.[17]

The authors therefore suggest that the distribution of body fat may be a better prognostic factor for the development of periodontal disease than general body fat. Even though overweight and obesity in adults are commonly defined with reference to BMI, this index fails to describe body fat distribution. Hence, additional studies should focus on this relationship. In the literature, there have been reports on the considerably more frequent occurrence of periodontal disease in association with symptoms of abdominal adiposity, diagnosed by measuring WC, HC and WHR.[15–17] However, this is not the only important aspect of the development of periodontal disease. Obese individuals have been found to have increased levels of plaque accumulation as compared to those with a normal weight, which may suggest a two-way interaction of risk factors in the occurrence and progression of periodontal disease.

A study by Górska et al. focusing on patients aged 35–44 years from large Polish cities showed that adults in Poland had some of the worst periodontal health in Europe, and among those studied, as much as 16% required comprehensive periodontological treatment (CPI-4).[18] Furthermore, 23% of the studied population needed to improve their oral hygiene and undergo supragingival scaling (CPI-2), while more than 40% required oral hygiene training and subgingival scaling (CPI-3).[18] A study by Konopka et al. aimed to explore the relationship between BMI and periodontal tissue parameters in a randomly chosen group of 200 inhabitants of Wrocław aged 35–44 years.[19] The results revealed statistically significant dependencies between BMI and API and BOP. The study confirmed that particularly obese women failed to properly clean interdental spaces, and therefore required more extensive prophylactic action.[19]

The present study showed that only 3.3% of patients in the BMI ≥ 25 kg/m^2 study group had healthy periodontium, while 46.7% of overweight and obese patients needed oral hygiene instruction and subgingival scaling (CPI-3), and 26.7% required comprehensive periodontological treatment (CPI-4). In the healthy control group, calculus was found in 48.3% of individuals; they needed to improve their oral hygiene habits and to undergo treatment.

In conclusion, the data from this study may be of significance in terms of public health and can be used in the development of prevention programs aimed at controlling overweight/obesity and periodontal disease in Poland. As BMI is not the most accurate measure of obesity, the criteria for measuring obesity should also take into account WC. Irrespective of the above findings, patients should be advised by their general practitioners, medical specialists and dentists to modify their health behaviors, both general and oral, in order to improve their quality of life and reduce the possible negative consequences resulting from the interplay of oral and systemic diseases.

Our study showed a statistically significant difference in the number of meals consumed during the day between the study and control groups. This difference was evaluated in relation to the CAL value, which showed that patients eating more often and consuming 4–5 meals a day had lower BMI and lower CAL, which indicates a less severe degree of periodontal tissue changes. Studies show that people eating 1–2 meals a day tend to gain weight, have higher blood cholesterol levels and more impaired carbohydrate tolerance than people who eat 5 meals a day or more.[20]

Our own research showed that the group with BMI ≥ 25 kg/m^2 had higher consumption of sweets as compared to the control group, statistically significant differences were found in the frequency of eating meat and fat and dairy products, and a trend in the frequency of eating fish was noted. In relation to the clinical parameters of periodontitis, these patients were characterized by worse oral hygiene and more advanced inflammatory changes in periodontal tissues.

A study by Yudkin confirmed that diet affects oral health.[21] First of all, an excessive carbohydrate intake, combined with improper oral hygiene, can lead to the development of caries and periodontal disease. The researcher hypothesized that these disease entities are early warning signals of the development of diabetes, obesity and coronary heart disease.[21]

By analyzing the frequency of check-ups at the dentist and hygiene habits, such as the movement performed while brushing the teeth, the type of toothbrush used, the use of dental floss and mouthwash, and the occurrence of bleeding gums when brushing the teeth, our study showed greater care for oral hygiene in the group of patients with a normal weight, including the more frequent use of an electric toothbrush and cleaning the teeth with a sweeping motion.

Patients with normal BMI used dental floss and mouthwash more often, and they also had more regular dental check-ups every 6 months. It was shown that the less patients cared about oral hygiene, the higher the values of API and BOP were observed in patients with BMI ≥ 25 kg/m^2. These results coincide with a study of 292 patients by Prpić et al., who showed that obese people aged 31–75 had worse oral health, used dental floss/interdental brushes less often and had more missing teeth as compared to the group of patients with a normal weight.[22]

A study by Hujoel et al. showed that the lack of daily usage of dental floss is strongly positively associated with obesity in patients suffering from periodontal disease.[23] These authors pointed out, however, that the habit of daily flossing of interdental spaces could also be nothing more than a sign of a generally accepted healthy lifestyle in people with a normal weight, which emphasizes how complicated and multifactorial the epidemiology of oral diseases can be.[23]

Patients should be educated about what foods are part of a healthy diet, and we should make them aware of the impact of the diet not only on their overall health, but also on their oral health. Patients suffering from periodontal disease should include in their diet foods containing anti-inflammatory nutrients, such as fatty fish, rich in omega-3 fatty acids, and vitamin D as well as fruit and vegetables.

Conclusions

The analysis of these findings led the authors to certain conclusions. The group of obese and overweight adults presented lower regularity of eating meals and higher sweets consumption, combined with poor hygiene habits, which was reflected in increased rates of inflammation of the gums, increased plaque accumulation as well as worsened periodontal tissue status. Moreover, the positive correlation found between the occurrence of periodontal disease and the overall obesity (BMI) points to the need to arrange for periodontal disease prevention and treatment among overweight and obese patients.

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Evaluation of the tone and viscoelastic properties of the masseter muscle in the supine position, and its relation to age and gender

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Abstract

Background. The masseter muscle can be evaluated in various ways to examine its condition in healthy individuals or to identify pathological changes in the muscle.

Objectives. This study aimed to examine the tone and viscoelastic parameters of the masseter muscle, which is the focal muscle of various pathologies, to reveal its relationship with age and gender, and to determine the reference values of this muscle in healthy individuals.

Material and methods. Individuals aged 18–50 years were evaluated. They were divided into 3 groups in terms of age. A total of 389 individuals participated in the study (18–28 years: 131 males, 104 females; 29–39 years: 29 males, 56 females; and 40–50 years: 30 males, 39 females). The tone and viscoelastic properties of the masseter muscle were evaluated bilaterally in the supine position.

Results. The mean age of all individuals was 28.64 ±9.68 years. The masseter muscle tone was found to be higher in men than in women. The elasticity of the muscle was higher in women ($p < 0.05$). It was determined that the masseter muscle tone and stiffness increased, whilst its elasticity decreased with aging ($p < 0.05$). A weak positive correlation was found between the right and left masseter muscle tone and age ($r = 0.307$ and $r = 0.325$, respectively; $p = 0.001$). There was a moderate positive correlation between the right and left masseter muscle stiffness and age ($r = 0.507$ and $r = 0.511$, respectively; $p = 0.001$). A strong positive correlation was observed between the right and left masseter muscle elasticity and age ($r = 0.614$ and $r = 0.645$, respectively; $p = 0.001$).

Conclusions. The data obtained in this study may assist clinicians in evaluating the treatment of the pathological conditions related to the masseter muscle as well as in the planning of treatment and pre- and post-operation evaluations.

Keywords: viscosity, aging, gender identity, muscle tone, masseter muscle

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Introduction

The masseter is one of the muscles of mastication, primarily responsible for the elevation and some protraction of the mandible. The masseter muscle thickness is extensively studied, as it is related to the craniofacial mechanisms. The activity of this muscle is also associated with chewing, swallowing, temporomandibular joint disorders (TMD), craniomandibular dysfunctions, bruxism, and orofacial pain.[1–3] In a study by Ariji and Ariji, the formation of intramuscular echogenic bands (structures that reflect sound waves in ultrasound) was observed and the bands in the masseter muscle were thickened in patients with TMD.[4] The masseter muscle can be evaluated in various ways to examine the condition of the muscle in healthy individuals or to identify pathological changes in the muscle. In recent studies, the masseter muscle was evaluated by means of electromyography (EMG),[5,6] ultrasonography (USG)[7] and palpation.[8] The muscle activity can be determined by placing EMG electrodes over the skin or EMG needles into the muscle. This method is invasive and can be painful.[7] Modalities such as elastography, shear-wave elastography (SWE) or free oscillation techniques are valid and reliable in the evaluation of the mechanical properties of muscles and tendons. However, these modalities may have limited availability in clinics because of high purchasing and maintenance costs, and the requirement of technical expertise.[9] Thus, there is a need for easy-to-use, cost-effective, objective, reliable, and valid methods to evaluate the mechanical properties of the musculoskeletal system.[10] Palpation is a prominent and easy method for the evaluation of cases when digital measurements are not available.[11] Masseter muscle palpation is a subjective and qualitative evaluation. On the other hand, the objective measurement of the viscoelastic properties of the muscle with Myoton® PRO (Myoton, Tallinn, Estonia) has high test-retest reliability.[12,13] It has been observed that the myotonometric measurements obtained with EMG and USG show a high level of correlation with the measurements obtained with the Myoton PRO device.[14]

It has been stated in studies that the masseter muscle thickness, the masticatory function and the craniofacial mechanisms are related. Aging affects facial morphology, the muscle thickness, occlusal morphology, and bite force. It has also been reported that muscle anatomy is related to the physiognomy and anthropometric variables of individuals. There are some suggestions that the muscle thickness is related to facial morphology. Some authors emphasized that the thickness of the head and neck muscles, muscle pain, and facial morphology could be associated with bite force and occlusal factors. In addition, there seems to be a relationship between the masseter muscle thickness and various features of dental arches, such as the alveolar process thickness and the maxillary dental arch width.[3,4,7] The activity of the muscle is associated with the chewing behavior and swallowing, and impaired activity may be associated with TMD. The masseter is the largest jaw-raising muscle and also provides the greatest contribution to jaw closure, and its size is closely related to bite force. It is known that variations in the size of this muscle may be a critical factor regarding individual differences in oral functions.[3,7] We believe that the data obtained in this study may assist clinicians in evaluating the treatment of the pathological conditions related to the masseter muscle as well as in the planning of treatment and pre- and post-operation evaluations. There are several studies on chewing muscles that have evaluated the muscles with the use of the Myoton PRO device, but studies that focus on the masseter muscle are rare. This study aimed to examine the tone and viscoelastic parameters of the masseter muscle, which is the focal muscle of various pathologies, to reveal its relationship with age and gender, and to determine the reference values of this muscle in healthy individuals.

Material and methods

Participants and the study design

In our study, 420 individuals aged 18–50 years were randomly selected from the students and staff of the Hasan Kalyoncu University in Gaziantep, Turkey, and evaluated.

All subjects were initially screened using the Fonseca anamnestic index (FAI), which has been validated in the Turkish population and assesses factors such as chewing, parafunctional habits, movement limitations, joint noise, and dizziness.[15] A total of 389 individuals who were considered to have no dysfunction in the temporomandibular joint (i.e., had scores between 0 and 15), no primary and secondary headache, no toothache because of dental disease, and no denture problems, including pain or ill-fitting dentures, were included in the study. Individuals who had history of trauma to the face or the temporomandibular joint, history of whiplash, rheumatic disease, joint hypermobility, previous orthodontic or prosthodontic treatment, sleep-related conditions (e.g., obstructive sleep apnea syndrome), cognitive incapacity, medical disorders, or severe malocclusion or other malformations that may affect occlusion were excluded. They were divided into 3 groups in terms of age. Individuals aged 18–28 years (131 males, 104 females), 29–39 years (29 males, 56 females) and 40–50 years (30 males, 39 females) were evaluated. The study was conducted between June 2018 and June 2019.

The physical characteristics and demographic information concerning the individuals were recorded before the test. The tone and viscoelastic properties of the masseter muscle were evaluated bilaterally in the supine

position with the Myoton PRO device (Fig. 1). The mean value was calculated after taking 3 consecutive measurements at the measurement site for each parameter. The measurement site was assumed as the highest point of the muscle belly and was marked with a water-based pen to provide an anatomical reference point. The mandible was placed centrally with no contact between the upper and lower teeth.[16]

Ethical approval

Ethical approval was obtained from the ethics committee of the Hasan Kalyoncu University (decision No. 2019/61). The subjects were informed about the purpose and content of the study. Written consent was obtained from all individuals.

Measurement tools

Myoton® PRO device

The Myoton PRO device is a non-invasive, portable, hand-held myotonometer used to evaluate the viscoelastic properties of soft tissues.[17] This device is known as cost-effective, reliable, valid, and easy-to-use in evaluating the mechanical properties of the musculoskeletal system.[18,19] The muscle tone and viscoelastic parameters (stiffness and elasticity) were assessed by taking myotonometric measurements bilaterally from the skin overlying the masseter by means of Myoton PRO. The examiner marked the masseter with a small ink dot.

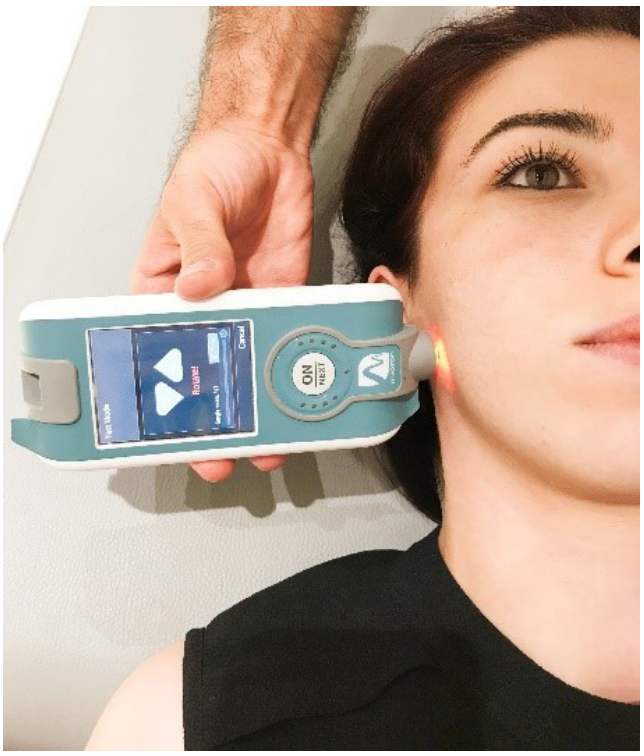

Fig. 1. Evaluation of the mechanical properties of the masseter muscle

This device has shown good-to-excellent reliability in healthy individuals,[20] the elderly,[12] cancer[21] and stroke patients,[22] athletes,[23] and patients with neurodegenerative disease.[24] The device measures the mechanical oscillations of the assessed soft tissues, induced by a mechanical impulse that is of a short duration (15 ms) and involves constant mechanical force (up to 0.6 N). Measuring the mechanical oscillations occurring due to the mechanical impulse yields the following data: oscillation frequency [Hz]; logarithmic decrement (elasticity); and stiffness [N/m].[25] Resting muscle tone is the elastic and/or viscoelastic stiffness in the absence of contractile activity. Elasticity is the property whereby a body, when deformed by the applied load, recovers its previous configuration when the load is removed. The applied force is proportional to the strain within the elastic limit. Stiffness is a biomechanical feature of a muscle that characterizes its resistance to contraction or an external force that disrupts its initial state.[26]

Fonseca anamnestic index

Fonseca et al. developed the Fonseca anamnestic index (FAI), which is a 10-item instrument that allows the assessment of jaw function limitation, pain frequency, psychological distress, and the parafunctional behaviors related to TMD.[27] The cross-cultural adaptation of the English version of FAI was completed in 2020 by Kaynak et al.[15] The specificity was 83.7% and the sensitivity – 93.57%. They found that FAI had a high level of accuracy (*AUC* (area under curve) = 0.928; 95% *CI* (confidence interval) = 0.890–20.964), a high sensitivity value (131 individuals with TMD diagnosed by means of FAI, compared to 140 individuals with TMD diagnosed by the dentist), and a high specificity value (54 individuals with no TMD diagnosed by means of FAI, compared to 65 individuals with no TMD diagnosedby the dentist and the physical therapist). The results demonstrated that the Turkish version of FAI (FAI-T) had good-to-excellent test-retest reliability and a high level of internal consistency, and provided considerable evidence that FAI-T could be used as a screening tool for the identification of TMD.[15] Stasiak et al. stated that FAI was very sensitive (97.21%) in identifying patients who actually had TMD, but not very specific (26%) in identifying non-TMD patients, thus being indicated for use in the initial screening of patients only.[28]

Data analyses

The power analysis was performed with the use of the G*Power software, v. 3.1.9.2 (www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3), based on the expectation of a large effect size (f = 0.40) for comparisons among 3 age groups in terms of numerical variables for each gender (α = 0.05; $1\text{-}\beta$ = 0.80).

The minimum required total sample size was estimated as 66 for 3 groups and 22 for each age group. The IBM SPSS Statistics for Windows software, v. 24.0 (IBM Corp., Armonk, USA), was used to analyze the data. The normal distribution of the data was determined with the Shapiro–Wilk test. The Mann–Whitney *U* test was used to make comparisons between 2 groups. Since the number of groups was more than 2, the Kruskal–Wallis test was used to compare non-normally distributed variables. If, according to the Kruskal–Wallis test, the *p*-value was found to be significant, multiple comparison tests were used to determine the source of the difference. Also, Spearman's rank correlation test was used to determine the relationships between numerical variables. A *p*-value of less than 0.05 was considered statistically significant.

Results

The mean age of all individuals was 28.64 ±9.68 years. The demographic characteristics of the participants are given in Table 1.

It was found that there were differences between genders in terms of viscoelastic measurements and tone of the right and left masseter muscles. The tone of the right and left masseter muscles was higher in men than in women ($p = 0.185$ and $p = 0.035$, respectively). The measurements on both sides were similar in both genders in terms of stiffness ($p > 0.05$). The elasticity of the muscle, in terms of logarithmic decrement, on the right and left sides was higher in females ($p < 0.05$) (Table 2).

Mechanical properties of the masseter muscle in all individuals

According to the results of Dunn's multiple comparison test, the right and left masseter muscle tone and stiffness were significantly lower in the 18–28 years age group (group 1) as compared to the other 2 groups ($p < 0.05$) except for the right masseter muscle tone, where the difference was insignificant ($p = 0.051$), and there was no significant difference between the age groups of 29–39 years (group 2) and 40–50 years (group 3) ($p > 0.05$). The right and left masseter muscle elasticity was significantly higher in group 1 than in the other 2 groups ($p < 0.05$), for the right masseter muscle, it was similar between groups 2 and 3 ($p > 0.05$), whereas for the left masseter muscle, it was significantly higher in group 2 than in group 3 ($p < 0.05$). In light of these results, it can be said that as age increases, the masseter muscle tone and stiffness increase, and the elasticity of the muscle (logarithmic decrement – if the value increases, elasticity decreases) decreases (Table 3 and Table 4).

Mechanical properties of the masseter muscle in male individuals

Based on Dunn's multiple comparison test results for males, it was observed that the group 1 values for the right and left masseter muscle tone were significantly lower than in group 2 and group 3 ($p < 0.05$). For the right masseter muscle, the tone values were significantly higher in group 2 than in group 3 ($p < 0.05$), whereas

Table 1. Demographic characteristics of the participants

Characteristic	All individuals ($N = 389$)	Males ($n = 190$)	Females ($n = 199$)	*Z*	*p*-value
Age [years]	28.64 ±9.68	27.29 ±9.57	29.92 ±9.63	−3.064	0.002*
Height [m]	1.69 ±0.86	1.75 ±0.07	1.64 ±0.06	−13.614	0.001*
Weight [kg]	71.91 ±14.42	76.11 ±13.98	67.90 ±13.72	−5.399	0.001*
BMI [kg/m^2]	25.14 ±4.58	24.87 ±4.06	25.40 ±5.02	−0.827	0.408

BMI – body mass index; * statistically significant.
Data presented as mean ± standard deviation (*M ±SD*).

Table 2. Tone, stiffness and elasticity of the right and left sides of the masseter muscle in all individuals, and distribution in terms of gender

Variable	All individuals ($N = 389$)	Males ($n = 190$)	Females ($n = 199$)	*Z*	*p*-value
MMTR [Hz]	14.87 ±2.12	15.10 ±2.40	14.65 ±1.78	−1.325	0.185
MMSR [N/m]	283.78 ±70.79	280.25 ±79.68	287.16 ±61.11	−2.772	0.060
MMDR [log]	1.78 ±0.33	1.73 ±0.33	1.82 ±0.31	−3.277	0.001*
MMTL [Hz]	14.62 ±1.83	14.82 ±1.87	14.44 ±1.77	−2.107	0.035*
MMSL [N/m]	280.16 ±57.14	277.33 ±59.86	282.86 ±54.43	−1.527	0.127
MMDL [log]	1.76 ±0.34	1.69 ±0.33	1.82 ±0.34	−4.135	0.001*

MMTR – right masseter muscle tone; MMSR – right masseter muscle stiffness; MMDR – right masseter muscle elasticity; MMTL – left masseter muscle tone; MMSL – left masseter muscle stiffness; MMDL – left masseter muscle elasticity; * statistically significant.
Data presented as *M ±SD*.

Table 3. Comparison of age groups in terms of tone, stiffness and elasticity of the right and left sides of the masseter muscle in all individuals and according to gender

Gender	Variable	18–28 years (n = 235)	29–39 years (n = 85)	40–50 years (n = 69)	χ^2	p-value
All individuals	MMTR [Hz]	14.52 ±1.96	15.21 ±2.13	15.65 ±2.38	22.25	0.001*
	MMSR [N/m]	267.82 ±66.93	308.40 ±61.67	307.80 ±79.08	66.52	0.001*
	MMDR [log]	1.64 ±0.28	1.90 ±0.21	2.08 ±0.33	115.80	0.001*
	MMTL [Hz]	14.29 ±1.67	15.05 ±1.88	15.22 ±2.04	22.44	0.001*
	MMSL [N/m]	264.83 ±57.91	298.32 ±48.98	310.01 ±44.69	72.11	0.001*
	MMDL [log]	1.61 ±0.27	1.86 ±0.27	2.13 ±0.29	128.81	0.001*
Males	MMTR [Hz]	14.75 ±2.01	16.05 ±2.51	15.72 ±2.79	10.815	0.004*
	MMSR [N/m]	265.24 ±70.50	322.10 ±81.72	305.33 ±96.08	32.674	0.001*
	MMDR [log]	1.62 ±0.28	1.86 ±0.21	2.07 ±0.38	48.541	0.001*
	MMTL [Hz]	14.48 ±1.70	15.86 ±1.99	15.29 ±2.08	15.544	0.001*
	MMSL [N/m]	262.99 ±56.39	303.69 ±54.25	314.47 ±56.65	33.513	0.001*
	MMDL [log]	1.58 ±0.26	1.74 ±0.25	2.12 ±0.32	52.994	0.001*
Females	MMTR [Hz]	14.23 ±1.54	14.77 ±1.77	15.60 ±2.04	18.997	0.001*
	MMSR [N/m]	271.09 ±62.33	301.30 ±47.53	309.69 ±64.33	31.892	0.001*
	MMDR [log]	1.66 ±0.27	1.92 ±0.21	2.09 ±0.29	58.975	0.001*
	MMTL [Hz]	14.05 ±1.60	14.63 ±1.69	15.18 ±2.04	15.011	0.001*
	MMSL [N/m]	267.13 ±59.97	295.54 ±46.28	306.59 ±33.13	36.891	0.001*
	MMDL [log]	1.65 ±0.29	1.92 ± 0.25	2.13 ±0.27	68.451	0.001*

* statistically significant (Kruskal–Wallis test).
Data presented as *M* ±*SD*.

there was no significant difference between groups 2 and 3 for the left masseter muscle in terms of tone ($p > 0.05$). The right and left masseter muscle stiffness values in group 1 were significantly lower than in the other 2 groups ($p < 0.05$), and there was no significant difference between group 2 and group 3 ($p > 0.05$). The right and left masseter muscle elasticity in group 1 was significantly higher than in the other 2 groups ($p < 0.05$). Also, the right and left masseter muscle elasticity was significantly lower in group 3 than in group 2 ($p < 0.05$) (Table 3 and Table 4).

Mechanical properties of the masseter muscle in female individuals

Based on Dunn's multiple comparison test results for females, the right and left masseter muscle tone was significantly lower in group 1 than in the other 2 groups ($p < 0.05$), and both values were significantly lower in group 2 than in group 3 ($p < 0.05$). The right and left masseter stiffness values in group 1 were significantly lower than in the other 2 groups ($p < 0.05$), and there was no significant difference between group 2 and group 3 ($p > 0.05$). The right and left masseter muscle elasticity in group 1 was significantly higher than in the other 2 groups ($p < 0.05$), and the values in group 2 did not differ significantly from those in group 3 ($p > 0.05$) (Table 3 and Table 4).

Table 4. Dunn's multiple comparison test results for all individuals and both genders according to age group

Gender	Variable	18–28 years vs 29–39 years p-value	18–28 years vs 40–50 years p-value	29–39 years vs 40–50 years p-value
All individuals	MMTR [Hz]	0.003*	0.051	0.414
	MMSR [N/m]	0.001*	0.001*	0.565
	MMDR [log]	0.001*	0.001*	0.189
	MMTL [Hz]	0.001*	0.026*	0.265
	MMSL [N/m]	0.001*	0.001*	0.438
	MMDL [log]	0.005*	0.001*	0.001*
Males	MMTR [Hz]	0.042*	0.001*	0.024*
	MMSR [N/m]	0.001*	0.001*	0.129
	MMDR [log]	0.001*	0.001*	0.027*
	MMTL [Hz]	0.023*	0.001*	0.129
	MMSL [N/m]	0.001*	0.001*	0.079
	MMDL [log]	0.001*	0.001*	0.005*
Females	MMTR [Hz]	0.001*	0.001*	0.001*
	MMSR [N/m]	0.003*	0.001*	0.196
	MMDR [log]	0.001*	0.001*	0.473
	MMTL [Hz]	0.001*	0.001*	0.013*
	MMSL [N/m]	0.001*	0.001*	0.485
	MMDL [log]	0.001*	0.001*	0.066

* statistically significant.

A weak positive correlation was found between the right and left masseter muscle tone and age (r = 0.307 and r = 0.325, respectively; p = 0.001). There was a moderate positive correlation between the right and left masseter muscle stiffness and age (r = 0.507 and r = 0.511, respectively; p = 0.001). A strong positive correlation was observed between the right and left masseter muscle elasticity and age (r = 0.614 and r = 0.645, respectively; p = 0.001).

Discussion

The major findings of this study, in which we examined the tone and viscoelastic parameters of the masseter muscle in healthy individuals as well as their relationship with age and gender, and aimed to specify the reference values for the muscle, are that the tone of the masseter muscle is higher in males, its elasticity (logarithmic decrement) is higher in females, the stiffness of the muscle is similar in both genders, and the elasticity of the muscle decreases with aging.

It is unavoidable that some changes occur in the muscle structure due to aging. One of the changes is the reduction of the contractile areas of the muscle due to the transformation of contractible fibers into non-contractile areas. However, muscle stiffness tends to increase with aging. Changes in the distribution of muscle fibers are also observed with aging. These changes are characterized by the loss of type II fibers and an increase in type I fibers. As a result, an increase in muscle stiffness occurs, as type I fibers cause more stiffness than type II fibers. These age-related changes have been investigated in several studies.[29,30] Following the previous findings in the literature, we also found that the tone and stiffness of the muscle increase, and its elasticity decreases with aging.

It is known that the total muscle mass in women is 15–20% lower than in men. At the same time, women have weaker muscle tone and strength.[31,32] In terms of jaw muscles, it has been reported that the jaw muscles in men are stronger than in women, and there is a positive correlation between testosterone levels and mouth closing force.[33] In an experimental mouse model study, it was shown that the masseter muscle mass increases by nearly 38% with the supplementation of testosterone.[34] It has been noted in studies that testosterone has a significant effect on the masseter muscle mass.[34] In our study, the tone of the masseter muscle was found to be higher in males than in females, and we think that this result may be due to the effects of sex hormones.

Muscle tendons are weaker and looser in women; this situation causes more joint mobility in women. In other words, elasticity and joint mobility are higher in women.[32] We think that the higher elasticity (logarithmic decrement) of the masseter muscle in the female group in our study can be explained by the differences in the musculoskeletal system of males and females.

Myotonometric measurement results may vary, depending on the position (horizontal or vertical) of the muscles.[24] However, in a study evaluating the stiffness of the masseter muscle in the sitting position, no difference was found between genders.[35] In our study, the measurements were made in the supine position, where there is no activity against gravity. In accordance with the literature, we found that the stiffness of the masseter muscle was similar in both genders.

There are studies in the literature that observed a difference or no difference between the tone and viscoelastic values of the right and left masseter muscle.[36,37] In our study, differences were observed between the values of some parameters of the right and left masseter muscles. We think that these differences could be explained by dominance.

Limitations

The fact that the temporal muscle was not included in the measurements of our study could be viewed as a limitation. Also, all participants came from the same university, and this selection method from the same participant pool was a limitation of our study with regard to sample selection. Although FAI is a simple, quick and easy way to determine myogenic TMD, it is not the gold standard for the clinical evaluation. Bruxism and TMD cases were excluded from the study; they were determined through the FAI questions based upon people's statements. Individuals diagnosed with sleep problems, such as obstructive sleep apnea, were not included in the study. However, since such problems are difficult to diagnose even by a physician due to their complex etiology, their presence was determined based upon people's statements. These are the limitations of our study. In the future, multidisciplinary studies can be designed based on the samples diagnosed by dentists.

Conclusions

The tone and viscoelastic parameters of the masseter muscle can be examined using different evaluation methods to compare pre- and post-treatment changes in the muscle in fields such as plastic surgery, dentistry, physical therapy and rehabilitation, and speech and language therapy. We hope that the results of our study can provide the reference values for studies in these fields.

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Short-term effects of the orthodontic removable traction appliance in the treatment of skeletal Class III malocclusion: A randomized controlled trial

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Abstract

Background. The orthodontic removable traction appliance (ORTA) was introduced as an intraoral removable appliance to treat Class III patients, but the pure treatment effects of ORTA have not been established yet.

Objectives. The aim of the study was to evaluate the skeletal, dental and soft tissue changes following the use of ORTA in treating Class III growing patients, and to compare these changes with those observed in an untreated control group (UCG).

Material and methods. Forty-two patients with Class III malocclusion (mean age: 9.04 ±0.84 years) were randomly allocated to either the intervention group (ORTA) or UCG with a 1:1 allocation ratio. The patients in the ORTA group were treated until a positive overjet was achieved, whereas those in UCG were observed for an average of 6 months. Lateral cephalograms were obtained before (T1) and at the end of the treatment or observation period (T2). Twenty-six variables were used to evaluate treatment changes. The paired and independent *t* tests were used to detect significant differences within and between the groups, respectively.

Results. Forty-two patients who met the inclusion criteria were included primarily. Two patients in UCG dropped out of the study. Therefore, 40 patients were included in the statistical analyses (ORTA: 21; UCG: 19). The orthodontic removable traction appliance was able to correct Class III malocclusion in a mean treatment time of 4.34 ±2.02 months. The maxilla moved forward by a mean of 1.31°, which was significantly greater than in the case of UCG (i.e., a mean difference of 1.02°). The mandible moved significantly backward in the ORTA group (the mean change in SNB: −1.85°) and significantly forward in UCG (the mean change in SNB: 0.97°), leaving the overall sagittal skeletal change significantly greater in the ORTA group as compared to UCG (the mean change in ANB: 3.81°) ($p < 0.001$).

Conclusions. In the short term, ORTA seemed to be an effective intraoral removable appliance in the treatment of growing Class III patients.

Keywords: malocclusion, angle Class III, removable orthodontic appliances

Cite as
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Introduction

Skeletal Class III malocclusion is considered one of the most difficult orthodontic problems to treat.[1] This condition of malocclusion can result from a wide spectrum of skeletal and dental abnormalities.[2] The early treatment of Class III malocclusion in growing patients is a matter exceedingly discussed in the literature.[3]

Several studies have recommended early intervention in the case of developing Class III malocclusion to reduce the need for or the complexity of the 2nd phase of treatment,[4] and to reduce the need for an orthognathic surgery at late adolescence.[5] Many appliances have been advocated for the treatment of this kind of malocclusion by means of growth modification either in primary or mixed dentition, such as the chin cup[6] and the facemask (FM),[7] which are considered effective extraoral appliances. However, the lack of esthetics and the bulky size of these devices reduce patients' cooperation and compromise their clinical success.[8] Therefore, an increased interest in intraoral appliances has been shown in recent years.[9]

The orthodontic removable traction appliance (ORTA) was introduced as an intraoral removable appliance that could be used in conjunction with rapid maxillary expansion (RME) or fixed appliances. It was developed in the 1980s by David Musich as an attempt to overcome the compliance problems encountered in the use of FM.[10] A quick review of the literature reveals that there is only 1 study published as an MSc thesis in 2012 that evaluates this appliance by comparing its effectiveness with FM.[10] Within the limitations of the above-mentioned retrospective study, no statistically significant differences in the skeletal and dental values were found between the 2 examined groups except for SNA, which was greater in the FM group as compared to the ORTA group. Thus, the authors concluded that ORTA could be used as another treatment modality for patients with Class III malocclusion.[10] However, the pure treatment effects of ORTA have not been studied yet, since growth-related changes were not filtered out in the above-mentioned study (i.e., the absence of a control group with no treatment).[10]

Therefore, the objective of the current trial was to evaluate and compare the skeletal, dental and soft tissue changes resulting from the use of ORTA in growing Class III patients with an untreated control group (UCG).

Material and methods

Trial design and any changes after trial commencement

This study was a two-arm, parallel-group, randomized controlled trial. It was approved by the local Research Ethics Committee of the University of Damascus, Syria. It was registered at Clinical.Trials.gov (NCT 03172442). The current study was conducted between May 2017 and February 2019. No changes occurred in the methodology of this study after trial commencement.

Sample size calculation

The sample size was calculated using the G*Power software, v. 3.1.3 (Franz Faul, University of Kiel, Germany), with the following assumptions: a significance level of 0.05; a power of 90%; and a minimal difference in Wits appraisal requiring detection between the 2 treatment groups of 2.5 mm based on the variability of this measurement in a previous study.[1] The power analysis showed that 19 patients in each group were required to conduct the two-sample *t* tests. To compensate for possible dropouts during the trial period, it was decided to enroll 2 additional patients in each group. The patients and their parents were given information sheets and signed informed consent forms.

Participants, eligibility criteria and settings

The study participants were selected from the patients seeking treatment at the Department of Orthodontics of the University of Damascus, Syria, according to the following criteria: skeletal Class III malocclusion caused by maxillary deficiency and/or mandibular prognathism (2 cephalometric conditions had to be met: $-3° \leq ANB \leq 1.5°$ and $-3\ mm \geq$ Wits appraisal $\geq -9\ mm$); an anterior cross-bite or an edge-to-edge relationship; patients with mixed dentition, aged 8–10 years; and good oral hygiene.

The exclusion criteria were as follows: previous orthodontic treatment; patients with syndromes, clefts or craniofacial abnormalities; patients with facial asymmetry; and patients with missing teeth or periodontal diseases.

Randomization and allocation concealment

Seventy patients were examined for eligibility. The number of patients who met the inclusion criteria and agreed to participate in the study was 51. Forty-two of these participants were randomly chosen, and then assigned randomly to the 2 study groups by using a computer-generated list of random numbers with an allocation ratio of 1:1 (21 patients in each group). The assigned group for each patient was concealed using opaque sealed envelopes that were not opened until the patients' sorting was started (Fig. 1).

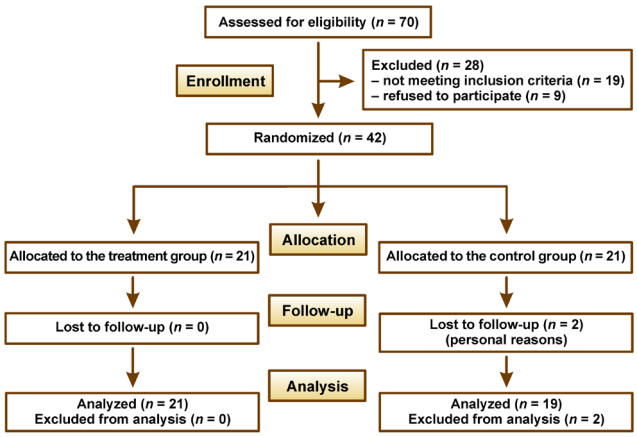

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the patients' recruitment and follow-up in the trial

Blinding

Due to the nature of the trial, blinding of the patients and the clinicians was not applicable. However, all cephalometric radiographs were coded. This ensured that the measurements were carried out by 1 assessor who was totally blinded to the study group (B.A.A.).

Pilot study

Since this was the first time when this device was applied at the University of Damascus Postgraduate Orthodontic Clinic, a pilot study was performed to detect any problems that could arise with the application of ORTA. The pilot study sample consisted of 6 patients (3 boys and 3 girls) meeting the same inclusion criteria as previously mentioned. All of them were treated by means of ORTA according to the design provided in Moore's study.[10] The pilot study revealed that modifications were needed to solve 2 problems. The first one was the lack of the appliance stability during the application of traction. Therefore, it was decided to increase the number of teeth holding the retentive ridges to at least 6 teeth to ensure the stability of the appliance. The other issue was gingival problems, especially at the vestibular side of the lower incisors. Two out of 6 patients had gingival recession on the central incisors and this was attributed to the inferiorly extended edges of the lower clear plate. Therefore, it was decided to trim the edges exactly above the gingival margins of the lower incisors to prevent any gingival injury.

Intervention group: ORTA

The 3 components of the RME-assisted ORTA used in this study were as follows: a lower vacuum plate of 1.5-millimeter thickness (Easy-Vac Gasket; 3A MEDES, Goyang, South Korea) with 2 welded buccal buttons (American Orthodontics, Sheboygan, USA) located at the areas between the lateral incisor and the canine on each side, which were used for attaching intermaxillary elastics (Fig. 2A); a Hyrax-type rapid maxillary expander (Lewa-Dental-Feinmechanik, Remchingen, Germany) with 4 bands placed on the posterior teeth (Fig. 2B); and Class III elastics (Fig. 2C).

The banded rapid maxillary expander was fitted on the maxillary permanent first molars and primary first molars. The expansion screw was activated once per day for the first 7 days to disrupt the circum-maxillary sutures in cases without posterior cross-bites. For patients with posterior cross-bites, the expansion procedure continued until the cross-bites were overcorrected (i.e., the palatal cusps of the upper posterior teeth occluded onto the lingual inclines of the buccal cusps of the lower posterior teeth).

On the lower dental arch, the first step was the application of retentive ridges on several teeth. They were placed on the lateral incisor, deciduous canine and deciduous first molar on each side. This was done by applying a composite resin (Medental International, Vista, USA)

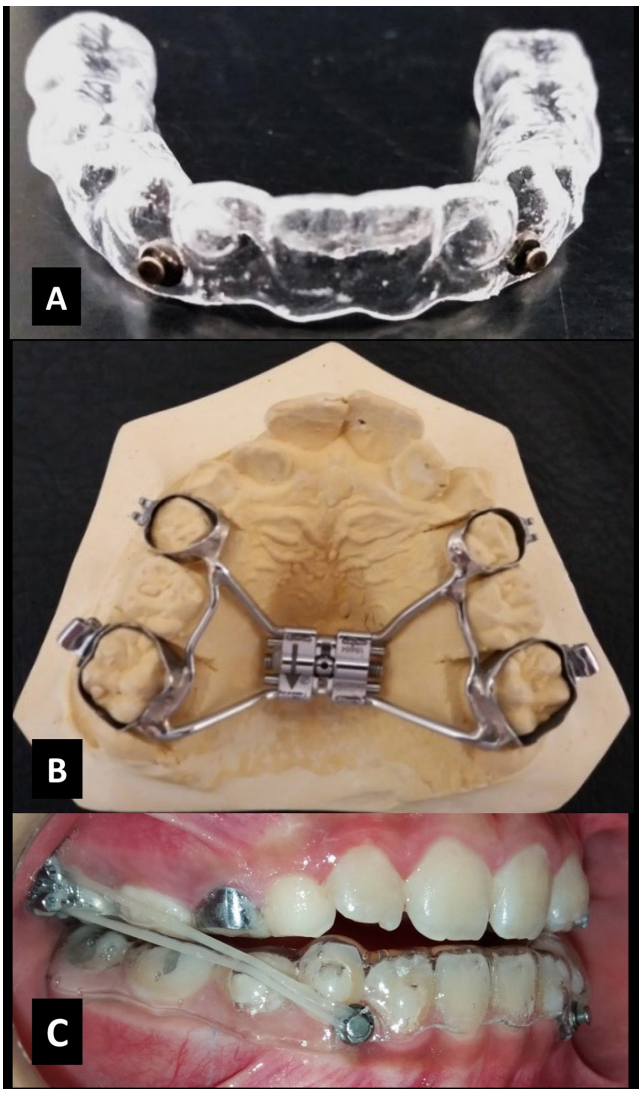

Fig. 2. Orthodontic removable traction appliance (ORTA) used in the current study (A), a Hyrax-type rapid maxillary expander with bands fitted on molars (B) and Class III elastics in their place (C)

to the surfaces of the chosen tooth as a ridge shape. An alginate impression was taken, then thermoplastic plates were constructed using a specific device (Ministar®; Scheu-Dental, Iserlohn, Germany). All clinical procedures were done by the same clinician (B.A.A.).

Elastic traction was started simultaneously with RME. Elastics of a 3/16-inch diameter were attached from the tube of the maxillary permanent first molar to the button in the lower vacuum plate on each side to produce forces ranging from 220 to 240 g, as measured by a force gauge. The patients were instructed to wear ORTA with Class III elastics 24 h per day, except during eating times, and they were asked to change the elastics daily. All patients were treated until at least a 3-millimeter positive overjet was achieved and this was considered the T2 point in the ORTA group. The patients were then instructed to wear the appliance at nighttime only for 2–3 months to maintain the achieved correction. The patients in this group were seen monthly to monitor the achieved results and it was planned to intervene if any significant relapse occurred.

The patients in UCG were left untreated and they were observed for about 6 months. Their records were obtained at the beginning and the end of this period. According to the local Research Ethics Committee guidelines, these patients were treated by postgraduate students immediately after the end of the observation period.

Outcome measurements

Lateral cephalograms of each patient were obtained at the beginning (T1) and the end of the treatment or observation period (T2). All radiographs were taken with maximum intercuspation, relaxed lips and a natural head position. The radiographs were hand-traced and measured by the same researcher (B.A.A.) by using a conventional lightbox and a 0.3-millimeter lead pencil. The reference planes used in this study were the anterior cranial base plane (SN), the Frankfort horizontal plane (FH) and the esthetics line of Ricketts (E-line). In order to evaluate dentoskeletal and soft tissue changes, 11 linear and 15 angular parameters were used in this study (Fig. 3 and Fig. 4).

Method error

Fifteen randomly selected cephalograms were retraced and remeasured 1 month after the first tracing to determine the method error. The paired *t* tests showed no significant differences between the 2 measurements, and the mean errors for angular and linear measurements were less than 0.6° and 0.6 mm, respectively, according to Dahlberg's formula,[11] indicating a negligible error. The intraclass correlation coefficients were greater than 0.90 for all variables, with the majority being greater than 0.95, thus confirming the high reliability of the measurements.

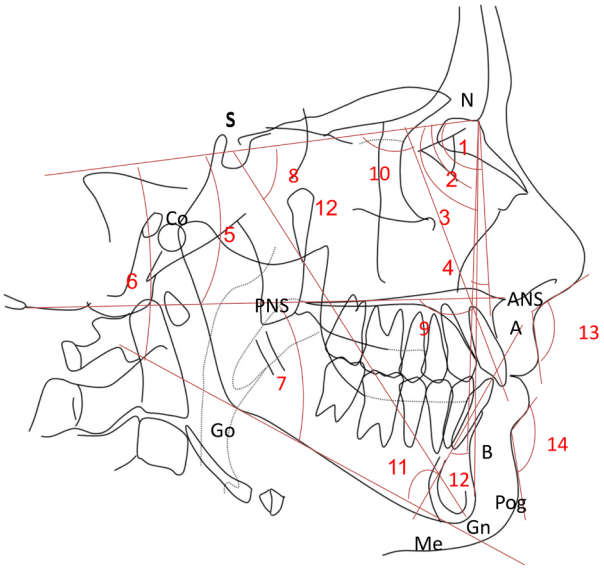

Fig. 3. Angular cephalometric measurements

1: SNA; 2: SNB; 3: SN–Pog; 4: ANB; 5: SN–SPP; 6: SN–GoMe; 7: SPP–GoMe; 8: Y-axis; 9: U1–SPP; 10: U1–SN; 11: L1–GoMe; 12: L1–NB; 13: Nasolab; 14: Mentolab.

S – sella; N – nasion; A – point A; B – point B; Pog – pogonion; SPP – spinal palatal plane; Go – gonion; Me – menton; U1 – upper incisor; L1 – lower incisor; Nasolab – nasolabial angle; Mentolab – mentolabial; Gn – gnathion.

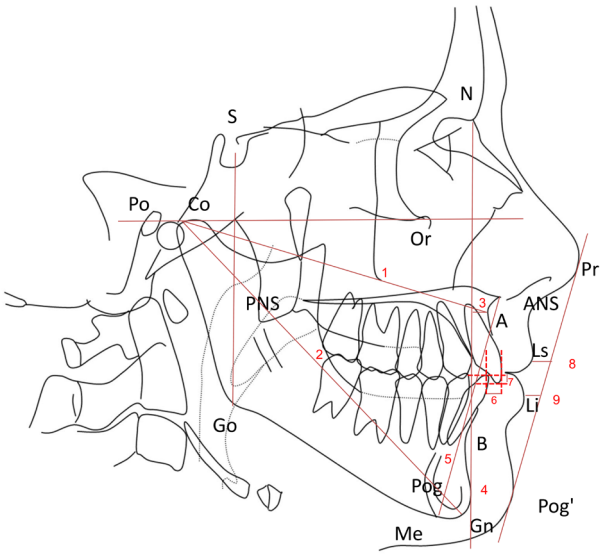

Fig. 4. Linear cephalometric measurements

1: Co–A; 2: Co–Gn; 3: A-to-N perp; 4: Pog-to-N perp; 5: ANS–Me; 6: overjet; 7: overbite, 8: Ls–Esth; 9: Li–Esth.

Co – condylion; perp – perpendicular; Ls – labialis superior; Esth – esthetics line of Ricketts (E-line); Li – labialis inferior; Or – orbitale; Po – porion.

Statistical analyses

All statistical analyses were performed with the IBM SPSS Statistics for Windows software, v. 22 (IBM Corp., Armonk, USA). The Kolmogorov–Smirnov test showed a normal distribution of all variables; therefore, parametric statistics were applied. The intragroup comparisons were analyzed with the paired *t* tests and the intergroup

comparison was evaluated with the *t* test for independent groups. Gender distribution was evaluated using Pearson's χ^2 test. The level of significance was set at 5%.

Results

Forty-two patients who met the inclusion criteria were included primarily (21 patients in each group). Two patients in UCG dropped out of the study for personal reasons. Therefore, 40 patients were included in the statistical analyses. The ORTA group consisted of 21 patients (12 boys, 9 girls; mean age: 8.95 years), whereas UCG consisted of 19 patients (8 boys, 11 girls; mean age: 9.14 years) (Table 1).

There were no statistically significant differences between the 2 groups for the following data: age ($p = 0.458$); gender distribution ($p = 0.342$); and treatment duration (a mean of 18.6 weeks) and the observation period (a mean of 22.1 weeks ($p = 0.094$) (Table 1).

The analysis of cephalometric variables in the ORTA group and UCG at T1 showed no statistically significant differences between the 2 groups (Table 2). In the ORTA group, the cephalometric measurements related to the maxilla (i.e., SNA, Co-A and A-to-N perp) showed significant mean increases of 1.31°, 2.92 mm and 1.41 mm, respectively ($p < 0.001$), whereas no significant increases were detected in UCG ($p > 0.05$) (Table 3). Differences between the 2 groups in SNA, Co-A and A-to-N perp showed a greater average improvement in the ORTA group over the controls of 1.02°, 2.26 mm and 1.39 mm, respectively ($p < 0.01$) (Table 4).

In the ORTA group, the mandible significantly moved backward, i.e., SNB, SN–Pog and Pog-to-N perp showed mean decreases of 1.85°, 1.66° and 2.17 mm, respectively, whereas in UCG, significant mean increases of 0.97°, 0.84° and 1.50 mm were observed, respectively. The analysis showed that differences between the mean changes across the groups for the mandibular position were significant (–2.82°, –2.51° and –3.67 mm for SNB, SN–Pog and Pog-to-N, respectively ($p < 0.001$) (Table 3 and Table 4).

Table 1. Basic sample characteristics

Characteristic	ORTA ($n = 21$)	UCG ($n = 19$)	*p*-value
Age [years] *M* ±*SD*	8.95 ±0.88	9.14 ±0.80	0.458[a]
Treatment duration/ observation period [weeks] *M* ±*SD*	18.62 ±8.65	22.11 ±1.94	0.094[a]
Gender distribution males/females	12/9	8/11	0.342[b]

ORTA – orthodontic removable traction appliance group; UCG – untreated control group; *M* – mean; *SD* – standard deviation; [a] independent *t* test; [b] χ^2 test.

Table 2. Comparison of the initial measurements between the 2 groups

Cephalometric parameter	ORTA ($n = 21$)		UCG ($n = 19$)		*p*-value*
	M	*SD*	*M*	*SD*	
SNA [°]	79.17	4.92	78.08	4.99	0.492
Co–A [mm]	74.48	3.57	75.10	3.44	0.576
A-to-N perp [mm]	–1.49	3.15	–1.00	2.16	0.577
SNB [°]	79.33	4.26	78.92	3.37	0.738
SN–Pog [°]	79.40	4.43	79.21	3.31	0.877
Co–Gn [mm]	98.97	5.54	100.65	7.21	0.410
Pog-to-N perp [mm]	–2.73	6.12	–0.68	3.21	0.201
Wits appraisal [mm]	–6.59	2.29	–6.23	2.04	0.598
ANB [°]	–0.17	1.98	–0.84	2.69	0.368
SN–SPP [°]	10.00	3.41	9.61	2.93	0.698
SN–GoMe [°]	35.26	4.93	35.32	3.14	0.968
SPP–GoMe [°]	25.24	4.31	25.71	3.13	0.697
Björk's sum [°]	393.98	5.15	394.37	3.10	0.775
Y-axis [°]	66.52	4.42	67.13	3.18	0.624
ANS–Me [mm]	56.65	4.45	57.90	4.90	0.403
S–Go/N–Me [%]	62.44	3.77	62.06	2.31	0.707
U1–SPP [°]	108.93	6.61	111.84	6.02	0.155
U1-SN [°]	99.02	6.54	102.24	7.32	0.151
L1–GoMe [°]	89.07	5.07	90.58	3.73	0.295
L1–NB [°]	23.81	4.28	24.92	5.11	0.459
Overjet [mm]	–1.98	1.19	–1.58	1.48	0.352
Overbite [mm]	1.58	1.17	1.09	1.60	0.270
Ls–Esth [mm]	–2.98	2.24	–2.66	1.86	0.625
Li–Esth [mm]	0.05	2.13	0.28	1.73	0.707
Nasolab [°]	110.21	9.50	110.34	5.85	0.960
Mentolab [°]	133.57	17.75	138.55	15.98	0.359

* independent *t* test.

In terms of intermaxillary sagittal relationship changes, both groups changed significantly over time; however, ORTA introduced favorable changes (a mean change of Wits appraisal of 5.24 mm and of ANB of 3.12°), while the parameters for the controls worsened (–0.72 mm for Wits appraisal and –0.69° for ANB). Differences across the groups were significant (5.96 mm for Wits appraisal and 3.81° for ANB) (Table 3 and Table 4).

In terms of vertical relationship changes, the patients in the ORTA group had a significant clockwise rotation and a significant mean increase in the vertical dimension (SN–GoMe: 1.12°; Björk's sum: 2.40°). Conversely, the patients in UCG showed a non-significant anterior rotation (SN–GoMe: –0.85°; Björk's sum: –0.87°). The mean increases in the vertical dimension were significantly greater in the ORTA group than in the controls (SN–GoMe: 1.97°; Björk's sum: 3.27°), while no significant changes were found in SN–SPP and SPP–GoMe between the 2 groups (Table 3 and Table 4).

Table 3. Descriptive statistics of changes in the 2 groups and the results of significance tests

Cephalometric parameter	ORTA (n = 21)			p-value†	UCG (n = 19)			p-value†
	T1	T2	T2 – T1		T1	T2	T2 – T1	
SNA [°]	79.17 ±4.92	80.48 ±4.70	1.31 ±0.83	<0.001***	78.08 ±4.99	78.37 ±4.47	0.29 ±0.89	0.172
Co–A [mm]	74.48 ±3.57	77.40 ±3.61	2.92 ±1.66	<0.001***	75.10 ±3.44	75.76 ±2.89	0.66 ±2.21	0.215
A-to-N perp [mm]	−1.49 ±3.15	−0.08 ±3.44	1.41 ±1.45	<0.001***	−1.00 ±2.16	−0.98 ±2.24	0.02 ±1.35	0.948
SNB [°]	79.33 ±4.26	77.48 ±4.06	−1.85 ±1.06	<0.001***	78.92 ±3.37	79.89 ±3.07	0.97 ±1.06	0.001**
SN–Pog [°]	79.40 ±4.43	77.74 ±4.22	−1.66 ±1.02	<0.001***	79.21 ±3.31	80.05 ±3.16	0.84 ±1.16	0.005**
Co–Gn [mm]	98.97 ±5.54	99.55 ±4.70	0.58 ±2.20	0.239	100.65 ±7.21	102.26 ±6.83	1.61 ±2.51	0.012*
Pog-to-N perp [mm]	−2.73 ±6.12	−4.90 ±6.60	−2.17 ±3.28	0.006**	−0.68 ±3.21	0.82 ±4.86	1.50 ±2.60	0.021*
Wits appraisal [mm]	−6.59 ±2.29	−1.35 ±3.31	5.24 ±2.68	<0.001***	−6.23 ±2.04	−6.95 ±2.28	−0.72 ±1.09	0.010*
ANB [°]	−0.17 ±1.98	2.95 ±1.94	3.12 ±1.07	<0.001***	−0.84 ±2.69	−1.53 ±2.83	−0.69 ±0.77	0.001**
SN–SPP [°]	10.00 ±3.41	9.81 ±3.17	−0.19 ±1.75	0.623	9.61 ±2.93	8.58 ±2.86	−1.03 ±1.45	0.006**
SN–GoMe [°]	35.26 ±4.93	36.38 ±5.09	1.12 ±1.45	0.002**	35.32 ±3.14	34.47 ±2.84	−0.85 ±1.76	0.052
SPP–GoMe [°]	25.24 ±4.31	26.57 ±4.96	1.33 ±2.15	0.010*	25.71 ±3.13	25.84 ±3.24	0.13 ±2.15	0.793
Björk's sum [°]	393.98 ±5.15	396.38 ±4.92	2.40 ±2.27	<0.001***	394.37 ±3.10	393.50 ±2.65	−0.87 ±1.61	0.031*
Y-axis [°]	66.52 ±4.42	68.43 ±4.40	1.91 ±1.09	<0.001***	67.13 ±3.18	66.50 ±2.51	−0.63 ±1.42	0.069
ANS–Me [mm]	56.65 ±4.45	58.49 ±4.28	1.84 ±1.83	<0.001***	57.90 ±4.90	57.72 ±4.92	−0.18 ±1.55	0.616
S–Go/N–Me [%]	62.44 ±3.77	61.08 ±3.51	−1.36 ±1.62	<0.001***	62.06 ±2.31	62.82 ±2.09	0.76 ±1.19	0.013*
U1–SPP [°]	108.93 ±6.61	112.29 ±5.64	3.36 ±3.06	<0.001***	111.84 ±6.02	111.24 ±6.04	−0.60 ±2.83	0.363
U1-SN [°]	99.02 ±6.54	101.98 ±5.83	2.96 ±2.67	<0.001***	102.24 ±7.32	102.74 ±6.72	0.50 ±2.97	0.473
L1–GoMe [°]	89.07 ±5.07	81.69 ±5.46	−7.38 ±4.38	<0.001***	90.58 ±3.73	90.26 ±4.74	−0.32 ±1.98	0.496
L1–NB [°]	23.81 ±4.28	16.07 ±4.78	−7.74 ±4.37	<0.001***	24.92 ±5.11	24.45 ±6.19	−0.47 ±2.81	0.472
Overjet [mm]	−1.98 ±1.19	3.89 ±1.09	5.87 ±1.39	<0.001***	−1.58 ±1.48	−1.91 ±1.35	−0.33 ±0.74	0.062
Overbite [mm]	1.58 ±1.17	2.20 ±2.30	0.62 ±1.84	0.135	1.09 ±1.60	1.30 ±1.59	0.21 ±0.50	0.071
Ls–Esth [mm]	−2.98 ±2.24	−1.95 ±2.63	1.03 ±1.65	0.010*	−2.66 ±1.86	−3.40 ±2.49	−0.74 ±1.79	0.086
Li–Esth [mm]	0.05 ±2.13	−0.75 ±2.67	−0.80 ±1.58	0.030*	0.28 ±1.73	0.08 ±1.82	−0.20 ±0.98	0.369
Nasolab [°]	110.21 ±9.50	111.33 ±8.25	1.12 ±10.03	0.615	110.34 ±5.85	109.50 ±9.20	−0.84 ±8.20	0.660
Mentolab [°]	133.57 ±17.75	130.12 ±18.50	−3.45 ±15.39	0.316	138.55 ±15.98	140.34 ±14.43	1.79 ±4.95	0.132

T1 – at the beginning of the treatment or observation period; T2 – at the end of the treatment or observation period;
* $p \leq 0.05$; ** $p < 0.01$; *** $p < 0.001$; † paired t test.
Data presented as $M \pm SD$.

The maxillary incisors proclined in the ORTA group (U1–SPP: 3.36 ±3.02°; U1–SN: 2.96 ±2.67°), while no changes were observed in UCG (U1–SPP: −0.60 ±2.83°; U1–SN: 0.50 ±2.97°). Differences between the 2 groups were significant for maxillary incisor protrusion (U1–SPP: 3.96°; $p < 0.001$ and U1–SN: 2.45°; $p = 0.009$). The mandibular incisors retroclined significantly in the ORTA group (L1–GoMe: −7.38 ±4.38°; L1–NB: −7.74 ±4.37°), while no significant changes were observed in UCG (Li–GoMe: −0.32 ±1.98°; L1–NB: −0.47 ±2.81°). Differences in mandibular incisor retroclination were significant between the 2 groups (L1–GoMe: −7.06° and L1–NB: −7.27°; $p < 0.001$). Overjet improved significantly more in the ORTA group (6.20 mm; $p < 0.001$), whereas no significant differences were found in overbite in either group, nor between the 2 groups (Table 3 and Table 4).

Regarding soft tissues, the upper lip moved significantly forward in the ORTA group (Ls–Esth: 1.03 ±1.65 mm), whereas in the control group, the upper lip moved backward (Ls–Esth: −0.74 ±1.79 mm), resulting in a significant difference between the groups (Ls–Esth: 1.77 mm; $p = 0.002$) (Table 3 and Table 4).

Harm

No harm was encountered in the current research project.

Table 4. Descriptive statistics of differences between the 2 groups in the amount of change observed between T1 and T2, and the results of significance tests

Cephalometric parameter	ORTA ($n = 21$)		UCG ($n = 19$)		Difference	*t*-value	*p*-value†
	M	*SD*	*M*	*SD*			
SNA [°]	1.31	0.83	0.29	0.89	1.02	3.760	0.001**
Co–A [mm]	2.92	1.66	0.66	2.21	2.26	3.686	0.001**
A-to-N perp [mm]	1.41	1.45	0.02	1.35	1.39	3.123	0.003**
SNB [°]	−1.85	1.06	0.97	1.06	−2.82	−8.424	<0.001***
SN–Pog [°]	−1.66	1.02	0.84	1.16	−2.51	−7.306	<0.001***
Co–Gn [mm]	0.58	2.20	1.61	2.51	−1.03	−1.383	0.175
Pog-to-N perp [mm]	−2.17	3.28	1.50	2.60	−3.67	−3.906	<0.001***
Wits appraisal [mm]	5.24	2.68	−0.72	1.09	5.96	9.040	<0.001***
ANB [°]	3.12	1.07	−0.69	0.77	3.81	12.782	<0.001***
SN–SPP [°]	−0.19	1.75	−1.03	1.45	0.84	1.636	0.110
SN–GoMe [°]	1.12	1.45	−0.85	1.76	1.97	3.857	<0.001***
SPP–GoMe [°]	1.33	2.15	0.13	2.15	1.20	1.763	0.086
Björk's sum [°]	2.40	2.27	−0.87	1.61	3.27	5.199	<0.001***
Y-axis [°]	1.91	1.09	−0.63	1.42	2.54	6.363	<0.001***
ANS–Me [mm]	1.84	1.83	−0.18	1.55	2.02	3.742	0.001**
S–Go/N–Me [%]	−1.36	1.62	0.76	1.19	−2.12	−4.668	<0.001***
U1–SPP [°]	3.36	3.06	−0.60	2.83	3.96	4.241	<0.001***
U1-SN [°]	2.95	2.67	0.50	2.97	2.45	2.750	0.009**
L1–GoMe [°]	−7.38	4.38	−0.32	1.98	−7.06	−6.452	<0.001***
L1–NB [°]	−7.74	4.37	−0.47	2.81	−7.27	−6.172	<0.001***
Overjet [mm]	5.87	1.39	−0.33	0.74	6.20	17.309	<0.001***
Overbite [mm]	0.62	1.84	0.21	0.50	0.41	0.934	0.356
Ls–Esth [mm]	1.03	1.65	−0.74	1.79	1.77	3.267	0.002**
Li–Esth [mm]	−0.80	1.58	−0.20	0.98	−0.60	−1.413	0.166
Nasolab [°]	1.12	10.03	−0.84	8.20	1.96	0.673	0.505
Mentolab [°]	−3.45	15.39	1.79	4.95	−5.24	−1.419	0.164

* $p \leq 0.05$; ** $p < 0.01$; *** $p < 0.001$; † independent *t* test.

Discussion

To the best of our knowledge, this is the first randomized controlled trial evaluating the skeletal, dental and soft tissue changes following the use of ORTA in growing Class III patients, and comparing these changes with an untreated control group.

The analysis of homogeneity between the 2 groups in terms of age, gender distribution and cephalometric variables indicated that the 2 groups were very similar and the applied randomization procedure generated 2 well-matched groups.

Since this was the first time when ORTA was applied at the University of Damascus Postgraduate Orthodontic Clinics, it was necessary to conduct a pilot study. This study led to 2 important modifications in the treatment protocol: increasing the number of teeth with retentive ridges to ensure the stability of the appliance; and shortening the edges of the device to prevent gingival impingement. This may have provided better results as compared to those achieved with earlier designs.

Although still controversial, RME might disarticulate the maxilla and initiate a cellular response in the sutures, thereby allowing a more positive reaction to protraction forces, which may be beneficial in the early treatment of Class III malocclusion.[12–14] Therefore, in this study, RME was applied in every treated patient in order to release the circumferential maxillary sutures or to correct posterior cross-bites in case they were found, which also standardized the clinical intervention.

The mean treatment duration in the present study was 18.62 weeks (4.34 months), which was less than that in Moore's study (6.96 months).[10] The additional time in Moore's study could be attributed to the fact that records were not always taken at the application or removal of the appliance. Also, traction in Moore's study started following RME, which may have lengthened the overall treatment time, whereas traction in the current study started at the same time as using the RME appliance.

The orthodontic removable traction appliance was able to induce significantly greater advancement of the maxilla as compared to the control group, which means that ORTA had a favorable effect on the maxilla and contributed to the correction of Class III malocclusion. The amount of increase in SNA in the current study was approx. 3 times greater than that observed in Moore's study (an average increase of 0.4°).[10] The greater amount of movement in point A in this study could be attributed to the following reasons: the age range was 3.1–12.1 years in the previously published retrospective study, while it was 8–10 years in the present work (including younger children might have compromised compliance with appliance wear); the magnitude of the traction forces was not fixed at a specific level, but was adjusted to patients' age, while it ranged between 220 and 240 g in the present study; the fact that traction was applied after finishing RME in the previous study, while in the current study, traction was applied simultaneously with RME.

The amount of SNA increase observed in the present study was similar to that reported in a recent meta-analysis on the effects of RME + FM (an average increase of 1.39°).[15] Therefore, ORTA could be considered as an alternative modality to treat mild or moderate cases of retrusive maxilla; a conclusion that was arrived at in a recently published systematic review.[16] Increases in the control group in terms of mandibular sagittal growth and position were significantly unfavorable. These findings are in line with a previous study, which confirmed that in untreated patients with Class III malocclusion, the deformity increased over time.[2]

Although a difference between the 2 groups was not significant in terms of change in the length of the mandible (Co–Gn), that difference (–1.03 mm) indicated that the forces applied through the device played a role in reducing the growth of the mandible in the sagittal plane. This may suggest that ORTA not only helped in maxillary advancement, but also restrained mandibular growth to some extent. An insignificant increase in Co–Gn in the treatment group was found to be smaller than that reported by Majanni and Hajeer, regarding the groups treated with bone-anchored intermaxillary traction or the removable mandibular retractor (RMR).[17] This can be explained by the fact that their groups' age means were greater than those in the current study.

The sagittal relationship between the 2 jaws in the treatment group significantly improved as a result of the anterior movement of the maxilla and the posterior movement with a clockwise rotation of the mandible, which was reflected by significant increases in ANB (the average increase of 3.12°; $p < 0.001$) and Wits appraisal (the average increase of 5.24 mm; $p < 0.001$). This increase in ANB is consistent with previous studies by Ngan et al.[13] and Nienkemper et al.,[18] applying RME and protraction FM. Lin et al. in their meta-analysis showed that FM induced an improvement in the intermaxillary sagittal relationship with a mean ANB change of 2.92°.[19] An increase in ANB was also greater when using ORTA as compared to other devices, such as RMR[17] or the modified tandem appliance.[20]

When comparing the 2 groups, a decrease in SNB was approx. triple the amount of increase in SNA. In other words, ¾ of the improvement in ANB could be attributed to mandibular changes in the form of clockwise rotation. Therefore, Class III patients with mandibular prognathism that are able to tolerate a mandibular clockwise rotation as part of their treatment can be treated with ORTA, as such cases were included and successfully treated with the proposed protocol.

In this study, the mandible in the treatment group showed a significant clockwise rotation (a mean of 1.12°) and significant increases in the vertical dimension (ANS–Me: 1.84; $p < 0.001$ and Björk's sum: 2.40; $p < 0.001$). These changes may have been due to the molar extrusion caused by RME and the vertical effect of the force vector applied by elastics. These findings are similar to those from many previous studies.[13,20] It should be noted that changes in the glenoid fossa were not assessed in the current study; therefore we may need an in-depth analysis of such changes in future studies.

The upper incisors proclined significantly in the treatment group; a finding that is consistent with the previously published literature.[13,21] However, the lower incisors retroclined more than reported previously.[10] This amount of retrusion was greater than that reported in Moore's study (–1.40°).[10] This difference could be due to the difference in the amount of overjet correction achieved in the 2 studies, which was greater in the present work (a mean of 5.87 mm as compared to 1.88 mm in Moore's study).

The amount of protrusion of the upper incisors was similar to that reported in many previous studies.[13,21] However, the amount of retrusion of the lower incisors observed in the present study was almost double that reported in previous studies employing the RME procedure in conjunction with FM.[13,21] This could be explained by the underlying biomechanics of the 2 systems. In the FM therapy, the frontal and mental bony regions were used as extraoral anchorage units to advance the maxilla, whereas in the ORTA therapy, the maxilla was moved forward using intermaxillary traction based on the intraoral elastics resting on the lower dental arch as the anchorage unit. This led to extra forces being transferred to the lower teeth, pushing them further in the posterior direction.

Although the retrusion of the lower incisors noted in the treatment group contributed to the overjet correction, the final inclination of the lower incisors at the end

of the treatment was deemed unfavorable, as such severe retroclination may cause post-treatment relapse and possible dentoalveolar bony defects (e.g., fenestration or dehiscence).

Soft tissues improved significantly with the ORTA treatment, as both the upper and lower lips moved favorably, meaning that the upper lip moved forward and the lower lip backward, following dentoskeletal changes. This is similar to what was reported in previous studies.[22,23]

Limitations

One important limitation of the current study is its short-term evaluation period (i.e., patients were followed up for approx. 19 weeks). Therefore, the conclusions are confined only to the short-term perspective and future research work should focus on the prognosis of the achieved results. Another limitation is that the effect of gender on the treatment outcomes was not evaluated. Also, this study focused on 8–10-year-old patients and it would be interesting to see the skeletal and dentoalveolar effects in older age groups. More importantly, an analysis of patients' acceptance and of the levels of pain and discomfort associated with this treatment modality would be very valuable to clinicians.

Generalizability

As growth-related changes were filtered out by the reasonable homogeneity presented between the 2 groups in terms of age and type of malocclusion, it is expected that the results of this study reflect the effectiveness of the appliance, and hence could be generalized to all patients at the same age suffering from the same malocclusion. The short-term nature of the study does not allow us to make assumptions about the long-term stability of the results.

Conclusions

In the short-term, ORTA was an effective appliance to treat mild-to-moderate Class III malocclusion patients aged 8–10 years. The ORTA therapy led to a significant improvement in the intermaxillary relationship within 5 months of treatment, which was achieved by a forward movement of the maxilla as well as a backward and downward rotation of the mandible. In the current short period of observation, ORTA caused significant and favorable proclination of the upper incisors, and significant retroclination of the lower incisors, which was deemed undesirable.

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Clinical and radiographic evaluation of jumping distance management using a collagen matrix in flapless immediate implant placement

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Abstract

Background. Improvement in implant design has made implant dentistry a challenging treatment modality worldwide.

Objectives. This study aimed to investigate the efficacy of a xenogeneic collagen matrix in managing 3–4-millimeter gaps in flapless immediate implant placement.

Material and methods. Twenty-two patients received 39 immediate implants via the flapless approach. Patients with intact bony walls, buccal bone thickness ≥2 mm and a jumping distance of 3–4 mm were included in this study. The gap between the implant and the socket walls was filled with a xenogeneic collagen matrix (Collacone®). The final clinical and radiographic evaluations were performed at least 24 months following functional loading.

Results. There was no early or late failure, and the implants showed a 100% survival rate. The mean mesial (0.28 ±0.39 mm) and distal (0.28 ±0.39 mm) marginal bone loss (MBL) at the site of incisors was not significantly different from the values at the site of premolars and molars (0.30 ±0.42 mm and 0.34 ±0.48 mm, respectively). The evaluation of the implant success index (ISI) score revealed no difference between the mandible and the maxilla ($p = 0.700$), or incisors compared with premolars and molars ($p = 0.420$). The only significant difference was in terms of distal MBL, which was higher in the maxilla (0.39 ±0.49 mm) than in the mandible (0.12 ±0.23 mm) ($p = 0.040$).

Conclusions. Within the limitations of this study, it seems that the application of a xenogeneic collagen matrix to manage 3–4-millimeter gaps in carefully selected cases may bring promising outcomes.

Keywords: peri-implantitis, alveolar bone loss, collagen matrix, immediate dental implant

Cite as
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Introduction

The use of dental implants to replace the missing teeth was a great scientific breakthrough in the field of dentistry. Implant dentistry has evolved considerably, as the original protocol was modified to adopt one-stage surgery[1] and immediate implant placement protocols.[2] Although there have been some reports of peri-implantitis and implant failure, immediate dental implants can offer a success/survival rate comparable to implants placed with early and delayed protocols, as long as the existing guidelines are strictly followed.[3]

It has been well documented that implant placement in a fresh extraction socket does not counteract bone remodeling. Therefore, both vertical and horizontal dimensional changes may be expected.[4] Several factors affect the outcome of immediate implantation, such as the flap or flapless approach,[5] the thickness of the buccal bone,[6] the gingival biotype, the timing of restoration placement,[7] the distance from the implant platform to the crestal bone, implant surface topography, and the size of the gap between the implant and the alveolar socket walls.[6,8]

The distance between the socket walls and the implant surface may justify augmentation to predictably achieve bone–implant contact (BIC) and to prevent soft tissue collapse.[9] However, there has been controversy in the literature in this regard. Some preclinical and clinical studies have documented the regeneration of horizontal gaps smaller than 2 mm in the presence of a stable blood clot.[10,11] More recent studies have shown that gaps of more than 2 mm have a tendency to fill better, even without grafting material.[8] A previous study compared flap and flapless surgery for immediate implantation, and concluded that the flapless approach allowed for minimal surgical intervention with comparable bony changes and gap filling after a 6-month follow-up in areas with sufficient buccal bone support.[12]

Bone formation in jumping distances of various sizes remains a controversial topic. Moreover, there have been few investigations on the secondary healing of the implant–buccal bone interface, and the current evidence referring to post-extraction alveolar bone alterations in regard to the thickness of the buccal plate remains unclear. However, some studies have shown that the thickness of the buccal plate and the size of the jumping distance play critical roles in the filling of the gap.[6] This study assessed the clinical and radiographic outcomes of immediate implant placement with the use of a xenogeneic collagen matrix to fill the jumping distance in cases with a thick buccal plate (≥2 mm).

Material and methods

This study was conducted from September 2016 to February 2020 at the Department of Periodontics, Shahid Beheshti University of Medical Sciences, Tehran, Iran, in accordance with the Declaration of Helsinki for human studies. It was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.DRC.REC.1398.164), and written informed consent was obtained from all patients prior to their enrollment.

Study population

Twenty-two patients (11 males and 11 females) were included in this study. The inclusion criteria were as follows: patients between 20 and 40 years of age; having a hopeless tooth indicated for extraction (due to an unrestorable fracture or a carious lesion) with no active infection at the surgical site; at least a 4-millimeter distance between the tooth apex and the maxillary sinus floor; the absence of gingival inflammation; achieving adequate primary stability following immediate implant placement; buccal bone thickness ≥2 mm, measured using the NNT software (NewTom Company, Imola, Italy); intact socket walls following the extraction; gingival thickness ≥1.5 mm, measured using a periodontal probe; presenting for a visit after at least 24 months of functional loading; O'Leary's plaque index ≤20%; and class I dental socket based on a cone-beam computed tomography (CBCT) scan.[13] The exclusion criteria were as follows: poor oral hygiene or the lack of regular maintenance; compromised immune system, systemic diseases or an intake of medications; the use of orthodontic appliances; the presence of parafunctional habits (bruxism or clenching); external root resorption; a jumping distance >4 mm, measured using a periodontal probe; smoking; and anatomical limitations.

Study overview and interventions

All patients received phase I periodontal therapy and their hard tissue condition was evaluated preoperatively with CBCT. The patients rinsed their mouths with 0.2% chlorhexidine for 1 min right before local anesthesia administration (20 mg/mL lidocaine with 1:80,000 epinephrine). All steps were performed conservatively by an experienced periodontist (M.K.), with no soft tissue manipulation, using the flapless approach. Following tooth extraction, the socket walls were examined with a periodontal probe, and in case of fenestration or dehiscence, the patient was excluded from the study. The sockets were cleaned using a curette and rinsed with saline. Drilling was performed based on the manufacturer's instructions with palatal orientation and 2–3 mm apical to the extraction socket, according to the selected implant system: SPI® (Thommen Medical, Grenchen, Switzerland); SIC® (SIC invent, Basel, Switzerland); 3i (Zimmer Biomet, Warsaw, USA); BioHorizons (BioHorizons Implant Systems, Birmingham, USA); Euroteknika (Euroteknika, Sallanches, France); or Intra-Lock® (Intra-Lock International, Boca Raton, USA) (Table 1). Implants of different root forms were selected based on the implant site and bone condition. The implants were inserted 1 mm apical to the alveolar crest at 30–35 N/cm. A xenogeneic collagen matrix (Collacone®; Botiss Biomaterials, Zossen, Germany) was then applied into the jumping distance (Fig. 1). No sutures or other materials

Table 1. Patient information, implant data and the implant success index (ISI) scores

Characteristic	Description
Patient gender (*N* = 22)	female (*n* = 11) male (*n* = 11)
Implant system (*N* = 39)	SPI (*n* = 13) SIC (*n* = 2) 3i (*n* = 3) BioHorizons (*n* = 2) Euroteknika (*n* = 8) Intra-Lock (*n* = 11)
Implant location (*N* = 39)	maxillary incisors (*n* = 7) maxillary premolars (*n* = 18) maxillary molars (*n* = 6) mandibular premolars (*n* = 5) mandibular molars (*n* = 3)
Implant parameters	diameter: 3.3–5 mm length: 8–14 mm
ISI score (*N* = 39)	I (*n* = 22) II (*n* = 17)

The implant success index (ISI) according to Kadkhodazadeh M, Amid R. Evaluation of peri-implant tissue health using a scoring system. *JIACD*. 2012;4(1):51–57 (cf. Table 2).

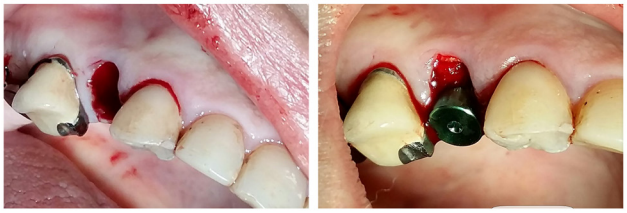

Fig. 1. Atraumatic tooth extraction performed without flap reflection and the application of a xenogeneic collagen matrix (Collacone®) into the gap between the socket wall and the implant surface following implant insertion

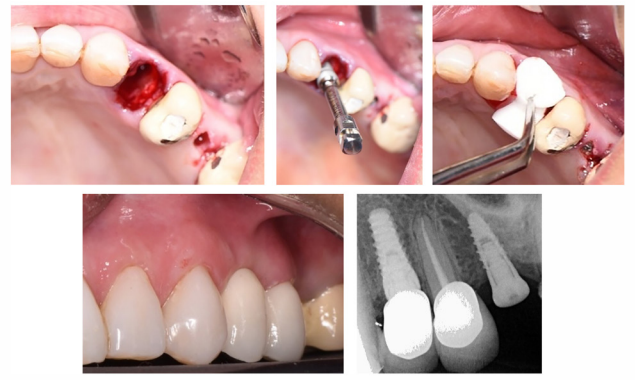

Fig. 2. Immediate implant placement with the use of a xenogeneic collagen matrix; 2-year clinical and radiographic follow-up demonstrates a well-shaped soft tissue contour and a stable marginal bone level

were applied to close the socket or to cover it. The healing abutment was screwed into all implants so that it was 2 mm coronal to the gingival margin. None of the implants were immediately restored.

The patients and their companions were provided with postoperative instructions, which included rinsing with a chlorhexidine mouthwash 3 times a day, 400 mg ibuprofen every 6 h, and 500 mg amoxicillin every 8 h for 1 week or an alternative in case of being allergic to penicillin. The patients were followed up weekly in the 1st month and monthly during the next 3 months. All final restorations were provided by the same prosthodontist and dental laboratory (after 3 months in the mandible and after 4 months in the maxilla).

The recall program was scheduled at 6-month intervals.[14] After at least 24 months of functional loading, the patients were recalled for clinical and radiographic examinations (Fig. 2). Periapical radiographs (the parallel technique) were obtained to assess the implants, the restorations and the surrounding tissues. Marginal bone loss (MBL) was measured relative to the implant shoulder with the use of digital software (Scanora™; KaVo, Biberach, Germany) and the probing depth (PD) was measured using a plastic periodontal probe. Next, the pink esthetic score (PES) was determined for all implants.[15] Clinical measurements were made at 4 points around each implant by an expert periodontist (M.K.) with an intra-rater agreement of 0.93 based on the intraclass correlation coefficient (ICC). Oral hygiene instructions were regularly reinforced at each session and professional cleaning was performed as required. All implants were evaluated based on the implant success index (ISI) proposed by Kadkhodazadeh and Amid (Table 2).[16]

Table 2. Implant success index (ISI)

Score	SL	HL	Clinical findings
ISI I	SL+, PPD ≤ 4 mm, BOP–	HL+	clinically healthy
ISI II	SL+, PPD ≤ 4 mm, BOP+	HL+	soft tissue inflammation
ISI III	SL+, PPD > 4 mm, BOP+	HL+	deep soft tissue pocket
ISI IV	SL+	HL–, RBL ≤ 2 mm (≤20%)	initiation of hard tissue breakdown
ISI V	SL–	HL–, RBL ≤ 2 mm (≤20%)	hard tissue breakdown and soft tissue recession
ISI VI	SL+	HL–, RBL: 2–4 mm (<40%)	notable hard tissue breakdown
ISI VII	SL–	HL–, RBL: 2–4 mm (<40%)	notable hard tissue breakdown and soft tissue recession
ISI VIII	–	RBL ≥ 40%	severe bone loss
ISI IX	–	clinical mobility	clinical failure

SL – soft tissue level; HL – hard tissue level; PPD – probing pocket depth; BOP – bleeding on probing; RBL – radiographic bone loss detected via the long cone paralleling peri-apical technique; + tissue level located at or coronal to the reference line; – tissue level located apical to the reference line; if the peri-apical area of implants has a bone loss/radiolucent view (retrograde peri-implantitis), it is identified by placing the letter R (e.g., ISI IR, etc.).
The Table is adapted from: Kadkhodazadeh M, Amid R. Evaluation of peri-implant tissue health using a scoring system. *JIACD*. 2012;4(1):51–57.

Statistical analyses

Data analyses were conducted using IBM SPSS Statistics for Windows, v. 22 (IBM Corp., Armonk, USA). The ISI scores were compared using the χ^2 test. The independent *t* tests were used to analyze the mean PD, MBL and PES values. A *p*-value <0.05 was considered statistically significant with a 95% confidence interval (*CI*).

Results

All the included patients were followed up for a period of 24–72 months. During the study period, all surgical sites healed uneventfully with no signs of gingival inflammation, infection or esthetic complications.

Table 3 presents PD, radiographic MBL as well as PES with regard to implant location. The PD and MBL scores at the site of incisors were compared with the corresponding values at the site of premolars and molars. The mean buccal PD was 2.29 ±0.49 mm at the site of incisors, and 2.25 ±0.44 mm at the site of premolars and molars. No significant difference was observed between the 2 groups (p = 0.850). The mean lingual PD at the site of incisors (2.14 ±0.38 mm) was not significantly different from the value measured at the site of premolars and molars (2.21 ±0.55 mm) (p = 0.860). The mean PD was not significantly different in the maxilla and the mandible (p = 0.850 for buccal PD and p = 0.890 for lingual PD).

Marginal bone loss was also evaluated at different implant locations and for both jaws. The mean mesial MBL was 0.28 ±0.39 mm at the site of incisors, and 0.30 ±0.42 mm at the site of premolars and molars, which showed no significant difference (p = 0.950). There was no significant difference in the mean distal MBL at the site of incisors (0.28 ±0.39 mm) in comparison with premolars and molars (0.34 ±0.48 mm) (p = 0.770). The mesial MBL was not significantly different in the maxilla and the mandible (p = 0.070); however, there was a significant difference in the distal MBL (p = 0.040), which was 0.39 ±0.49 mm in the maxilla and 0.12 ±0.23 mm in the mandible. The PES was also determined for each implant, and it showed no significant difference at different sites (p = 0.150) or jaws (p = 0.540).

The results of the ISI score evaluation revealed that there was no significant difference between the mandible and the maxilla (p = 0.700), and incisors compared with premolars and molars (p = 0.420).

Discussion

Although fewer surgical procedures, optimal cost-effectiveness and a shorter treatment time have made immediate implantation a desirable option, the inability to predict soft and hard tissue levels, difficulty in achieving primary stability, and the presence of the jumping distance intervening with direct BIC may jeopardize a favorable outcome.[17] Different biomaterials, including autogenous, allogenic and xenogeneic grafts, have been proposed in the literature to successfully fill the jumping distance.[18–20] However, there is concern that the residual particles may interfere with efficient BIC. In the present study, the aim was to find an alternative to biomaterials for 3–4-millimeter gaps; for this purpose, a xenogeneic collagen matrix was used to preserve the blood clot and prevent soft tissue collapse

Table 3. Probing depth (PD), marginal bone loss (MBL) and the pink esthetic score (PES) at different implant locations after at least 24 months of functional loading

Dependent variable	Implant location				
	incisors (n = 7)	premolars (n = 23)	molars (n = 9)	maxilla (n = 31)	mandible (n = 8)
PD buccal [mm]	2.29 ±0.49	2.21 ±0.42	2.33 ±0.50	2.26 ±0.44	2.25 ±0.57
p-value		0.850		0.850	
PD lingual/platal [mm]	2.14 ±0.38	2.26 ±0.54	2.11 ±0.60	2.26 ±0.57	2.20 ±0.00
p-value		0.860		0.890	
MBL mesial [mm]	0.28 ±0.39	0.23 ±0.33	0.44 ±0.58	0.33 ±0.43	0.12 ±0.23
p-value		0.950		0.070	
MBL distal [mm]	0.28 ±0.39	0.28 ±0.42	0.50 ±0.61	0.39 ±0.49	0.12 ±0.23
p-value		0.770		0.040*	
PES	9.86 ±0.38	9.52 ±0.59	9.78 ±0.44	9.68 ±0.47	9.50 ±0.76
p-value		0.150		0.540	

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

(although slightly). Collacone is a moldable xenogeneic collagen matrix designed to support the natural healing of extraction sockets. Its application supports the stabilization of the formed blood clot, helps to control bleeding, and protects the wound area from food residue and bacteria. Collacone resorbs completely in about 2–4 weeks with no remnants; thus, it does not seem to interfere with BIC.

After at least 24 months of functional loading, all implants were osseointegrated with minimal bone loss. As all restorations were cement-retained, the measurements were conducted with the presence of the restorations. The PD scores were within the normal range and were similar to those reported in other studies in which implants were placed immediately or delayed.[21]

Marginal bone loss is among the most significant variables, as it may predispose implants to peri-implantitis and result in implant failure.[22] Since immediate implants are often placed apical to the alveolar crest, some researchers have reported that they may compromise accurate bone level measurements. As previously emphasized, the available supporting bone is an important parameter to consider.[23] In this study, bone loss relative to the implant shoulder was ≤1 mm (the mesial MBL was 0.28 ±0.39 mm at the site of incisors, and 0.30 ±0.42 mm at the site of premolars and molars, while the distal MBL was 0.28 ±0.39 mm at the site of incisors compared with 0.34 ±0.48 mm at the site of premolars and molars). Although there was a difference in terms of distal MBL between the maxilla and the mandible, it did not seem to be clinically significant. In addition, the high standard deviation (*SD*) values mean that the numbers are more spread out. Therefore, further studies with larger sample sizes are advocated to avoid errors from the testing of possibly atypical samples. More importantly, most previous studies, as well as the present one, which examined MBL with the use of the parallel radiographic technique evaluated only the mesial and distal surfaces; however, significant changes may also occur at the buccal surface in the long term, which may adversely affect the esthetic outcome.[22] Nevertheless, considering our strict inclusion criteria (buccal bone thickness ≥2 mm), we concluded that there was no need to evaluate the buccal bone by means of three-dimensional (3D) radiography during follow-up visits. Furthermore, we included teeth with a thick gingival biotype, which has been shown to improve soft and hard tissue stability in immediate implantation.[24]

Soft tissue considerations, specifically midfacial recession, is another important issue regarding immediate implant placement.[17] Peri-implant soft tissue management can influence implant success and prevent peri-implantitis. It has been documented that adequately keratinized gingiva around implants is especially important in the esthetic zone to provide a more natural soft tissue drape. In the case of adopting the non-submerged protocol, the use of xenogeneic collagen materials such as Collacone may resolve the concern.

Socket closure and soft tissue management are among other controversial topics in immediate implant placement. Attempts to stabilize the peri-implant tissue after tooth extraction and immediate implant placement include a variety of wound closure techniques that use different types of flaps. Tarnow et al. evaluated changes in the facial and palatal ridges during flapless immediate implant placement and showed less bone resorption with the use of bone graft material along with a provisional restoration,[25] even though a recent study showed that the placement of an immediate provisional restoration would not significantly improve the esthetics.[7]

The absence of infection at the site of immediate implant placement is another critical factor that affects long-term success and prevents postoperative complications.[26] Some studies have reported retrograde peri-implantitis following immediate implant placement in the extraction sockets of teeth with periapical lesions.[27] However, meticulous socket debridement may decrease the risk of retrograde peri-implantitis. Furthermore, the type of dental socket, and the proper selection of the diameter and length of the implant are of paramount importance in implant stability.[28]

Another noteworthy issue is that proper oral hygiene and regular recall visits maintain the treatment results and prevent adverse consequences. Therefore, this study included patients with adequate plaque control, who followed a strict oral hygiene routine and attended follow-up assessments.[29]

The favorable results of the current study might be partially related to the applied flapless technique for immediate implant placement. However, the available evidence in the literature is not yet conclusive regarding the superiority of performing immediate implant placement in a flapless manner.[5]

The thickness of the buccal plate and the size of the gap have been shown to be the most influential factors in gap filling.[8] In a randomized clinical trial, it was shown that the thickness of the buccal plate was the most determinant factor in the resorption of the alveolar bone following extraction[30]; hence, randomized clinical trials are needed to compare the method applied in the present study with spontaneous healing in cases with a buccal bone thickness of more than 2 mm. Also, the effect of filling the gap in sockets with thinner buccal plates needs further investigation.

Limitations

As with any investigation, the present study has a number of limitations. The analyzed radiographs were not standardized, which potentially might have led to measurement errors. However, the calibration of radiographs by using known implant dimensions minimized this limitation.

Conclusions

Implant success/failure is the most frequently reported outcome measure in the literature; however, it is more favorable to evaluate and compare peri-implant health and disease condition, as discussed in the proposed ISI.[16] Our results showed a 100% success rate, healthy surrounding tissues and minimal bone level alterations for immediate implants placed in sockets with buccal plates ≥2 mm. Despite the limitations of this study, it seems that the application of a xenogeneic collagen matrix without bone grafting particles may provide promising outcomes in the management of 3–4-millimeter jumping distances in carefully selected cases.

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Comparison of the results of the treatment of enophthalmos in orbital blowout fracture in children/adolescents and adults

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Abstract

Background. Orbital fractures are common injuries in adults and children. Although the mechanism of blowout fracture is generally similar regardless of age, due to differences in anatomy, clinical symptoms of these fractures vary in the 2 groups of patients. Numerous articles describe the methods of orbital reconstruction leading to enophthalmos correction; however, the current literature lacks articles presenting the comparison of enophthalmos treatment results in adults and children with orbital blowout fracture.

Objectives. The aim of this study was to compare the results of the treatment of enophthalmos in orbital blowout fracture in children/adolescents and adults with regard to the location of the fracture, the time from the injury to surgical treatment, the type of surgical procedure, and the donor location of an autogenous bone graft.

Material and methods. The treatment results of 2 groups were compared: 530 adults (patients over 18 years of age; 18–77 years; average age: 34 years); and 200 children/adolescents (4–18 years; average age: 12.1 years). Data was obtained retrospectively through a review of the medical history of patients treated for a fracture of the orbital floor and/or medial wall in our department in the years 1975–2015.

Results. In patients with post-traumatic enophthalmos, the correct positioning of the eyeball was achieved in 313 adults (59.1%) and 139 children (69.5%), improvement in 159 adults (30%) and 49 children (24.5%), and no improvement in 58 adults (10.9%) and 12 children (6%). Recovery after surgical treatment was achieved in 311 adults (60.9%) and 94 children (52.8%), improvement in 120 adults (23.5%) and 59 children (33.1%), and no improvement in 80 adults (15.7%) and 25 children (14%).

Conclusions. The relationship between post-traumatic enophthalmos and the location of the fracture was more significantly marked in the adult group. In cases that required bone graft reconstruction, better results were achieved in adults.

Keywords: enophthalmos, orbital blowout fracture, orbital fracture, diplopia

Cite as
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Introduction

In adults as well as in children, orbital fractures are quite common among the injuries of the facial part of the skull. Depending on classification (isolated fractures of the orbit, or part of maxillo-zygomatic or naso-orbital fractures), orbital fractures constitute 4–50% of fractures.[1–3] Pure orbital blowout fracture is defined as a fracture of the orbital floor and/or medial wall with intact margins of the orbit. Enophthalmos is one of the main symptoms accompanying orbital fracture. Enophthalmos greater than 2 mm is clinically detectable, and may lead to esthetic and functional disorders (Fig. 1, Fig. 2, Fig. 3). As part of orbital fracture, enophthalmos may be a result of changes in the volume of the orbit, or muscle and/or fat atrophy due to ischemia. Numerous articles describe the methods of orbital reconstruction leading to postoperative enophthalmos correction; however, the current literature lacks articles presenting the comparison of enophthalmos treatment results in adults and children with orbital blowout fracture. Isolated fracture of the orbital floor, owing to its pathomechanism, is limited to the orbital area, and its characteristic symptoms are unique to this type of facture. Due to differences in the proportions of the facial and cerebral parts of the skull, the degree of paranasal sinus development, and the flexibility of the bone, the appearance of orbital blowout fracture in adults and children varies.[4,5] Typical symptoms of pure blowout fracture of the orbit include diplopia, enophthalmos and the lack of sensation in the suborbital area, usually accompanied by soft tissue swelling. In the case of orbital fracture in pediatric patients, limited eyeball movement is predominant, very often with the lack of or very discreet symptoms of soft tissue swelling.[6] In adults, blowout fracture with the loss of bony structures of the orbital floor or medial wall, and the herniation of periocular tissues into the maxillary or ethmoid sinus is quite common.[7] In contrast, white-eyed fracture, which is very often not evident in the images of the bone fracture, and the predominant impairment of eyeball movement is quite typical in children.[8–12] Due to its location and symptoms, orbital blowout fracture often requires collaboration among clinical teams, consisting of ophthalmologists, radiologists and maxillofacial surgeons.[13–18]

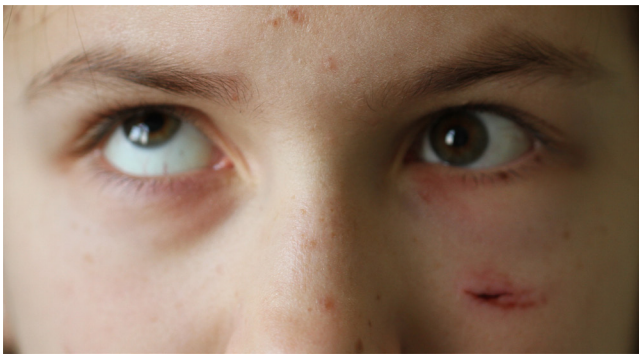

Fig. 1. Girl with blowout fracture of the left orbit and enophthalmos

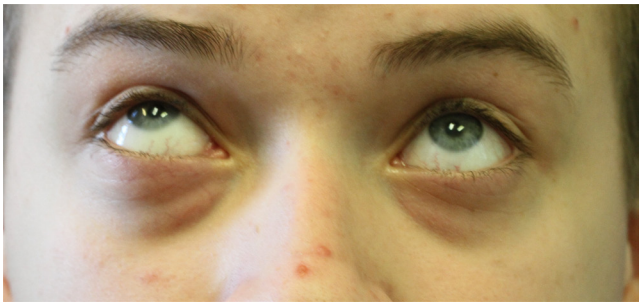

Fig. 2. Patient with blowout fracture of the left orbit and enophthalmos

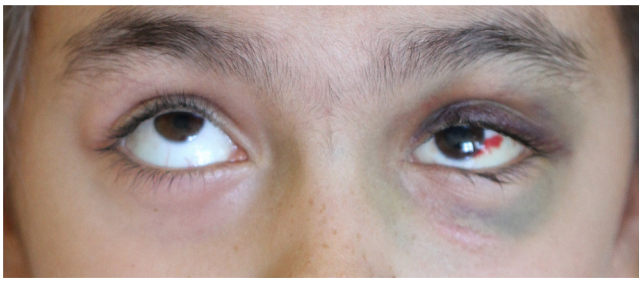

Fig. 3. Girl with blowout fracture of the left orbit and enophthalmos

Objectives

The aim of this study was to compare the results of enophthalmos treatment in orbital blowout fracture in children/adolescents and adults with regard to the location of the fracture, the time from the injury to surgical treatment, the type of the surgical procedure used, and the site of autogenous bone graft harvest.

Material and methods

The treatment results of the following 2 groups were compared: adults (patients over 18 years of age; 18–77 years; average age: 34 years) and children/adolescents (4–18 years; average age: 12.1 years). Data was obtained retrospectively through a review of the medical history of patients treated for a fracture of the orbital floor and/or medial wall in our department between 1975 and 2015. The study included patients with pure orbital blowout fracture without a coexisting fracture of other parts of the facial skeleton (Fig. 4). Data on enophthalmos was obtained from the records of ophthalmological examinations, which had been carried out at the beginning of treatment, after surgery, and repeatedly, depending on indications, during postoperative observation in the outpatient mode. Similarly, data on diplopia was obtained. Double vision was evaluated on a 5-point scale: in upgaze (type I), in upgaze and downgaze (type II), in straight and upgaze (type III), in straight and downgaze (type IV), or in the whole scope of view (type V). The indications for surgical treatment in both groups were as follows: persistent double vision with no tendency to subside; limited mobility of the eyeball; enophthalmos above 2 mm; and an extensive fracture of the orbital floor and/or medial wall.

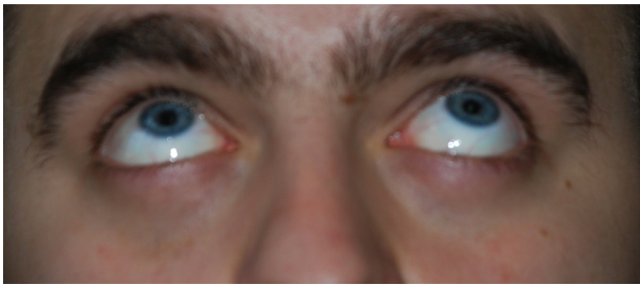

Fig. 4. Patient with blowout fracture of the right orbit

Surgical procedures included the revision of the fracture site with the removal of the herniated tissues in the case of linear fractures, or revision combined with tissue release and defect reconstruction with autogenous bone transplantation in fractures with a bone defect. The procedures were performed under general anesthesia. Passive eye movement was tested (the forced duction test) at the beginning and end of the procedure. The access of choice was the transconjunctival incision, or in the case of fracture with soft tissue damage around the injury, access through the wound.

The following recovery criteria were selected: the lack of diplopia; full eyeball movement; and enophthalmos lesser than 1 mm. Improvement was defined as a decrease in enophthalmos after the surgical procedure, a reduction in the area of diplopia and improvement in eyeball movement. The lack of improvement was indicated by persistent diplopia, and no improvement in enophthalmos and eyeball movement.

Statistical analysis

The statistical analysis was performed in R, v. 3.6.1. (the R Foundation, the R Project for Statistical Computing; https://www.R-project.org/). The relationships between the scales were analyzed using the χ^2 test and differences between the groups were evaluated using the χ^2 test with Bonferroni's correction. In addition, the Kruskal–Wallis tests were performed for the ranking scales referring to the time from trauma to surgery and enophthalmos after trauma, and Dunn's test with Bonferroni's correction and the Jonckheere–Terpstra trend test were used to compare both groups. A p-value less than 0.05 was considered statistically significant and a p-value less than 0.01 was considered highly significant.

Results

In the adult group, the most common cause of injury was an assault – 265 patients (50%), followed by a fall – 88 patients (16.6%). In the child group, the most common causes of injury were an accidental hit to the periorbital area – 74 children (37%), and sports – 47 children (23.5%). Individual causes of injury in the adult and child groups are presented in Table 1.

Table 1. Characteristics of the study groups

Characteristic	Children/ adolescents $N = 200$	Adults $N = 530$	p-value
Sex			
female	38 (19.0)	90 (16.9)	0.596
male	162 (81.0)	440 (83.1)	
Cause of injury			
assault	35 (17.5)	265 (50.0)	<0.001*
fall	19 (9.5)	88 (16.6)	
accidental hit to the periorbital area	74 (37.0)	65 (12.3)	
road traffic accident	17 (8.5)	49 (9.2)	
sports	47 (23.5)	35 (6.6)	
work accident	0 (0.0)	14 (2.6)	
other	8 (4.0)	14 (2.6)	
Location of fracture			
floor	176 (88.0)	434 (81.9)	0.018*
floor and medial wall	14 (7.0)	77 (14.5)	
medial wall	10 (5.0)	19 (3.6)	
Enophthalmos after injury [mm] vs location of fracture			
floor	1.15 ±0.95 ($n = 176$)	1.53 ±1.21 ($n = 434$)	0.001* (children/ adolescents)
floor and medial wall	0.36 ±0.50 ($n = 14$)	1.91 ±1.41 ($n = 77$)	<0.001* (adults)
medial wall	0.40 ±0.52 ($n = 10$)	0.37 ±0.68 ($n = 19$)	
Type of fracture intraoperatively	$N = 178$	$N = 511$	
with a bone defect	129 (72.5)	438 (85.7)	<0.001*
linear	49 (27.5)	73 (14.3)	
Diplopia			
after injury			0.914
– lack of diplopia	24 (12.0)	67 (12.6)	
– diplopia	176 (88.0)	463 (87.4)	
after treatment			0.262
– lack of diplopia	119 (59.5)	341 (64.3)	
– diplopia	81 (40.5)	189 (35.7)	
after injury			
– type I	21 (11.9)	121 (26.1)	
– type II	43 (24.4)	119 (25.7)	
– type III	14 (8.0)	38 (8.2)	
– type IV	5 (2.8)	46 (9.9)	
– type V	93 (52.8)	139 (30.0)	
after treatment			
– type I	47 (58.0)	95 (50.3)	
– type II	24 (29.6)	55 (29.1)	
– type III	2 (2.5)	10 (5.3)	
– type IV	5 (6.2)	22 (11.6)	
– type V	3 (3.7)	7 (3.7)	
Enophthalmos			
after injury			<0.001*
– 0 mm	68 (34.0)	128 (24.2)	
– 1 mm	65 (32.5)	134 (25.3)	
– 2 mm or more	67 (33.5)	268 (50.6)	
after treatment			0.020*
– 0 mm	139 (69.5)	313 (59.1)	
– 1 mm	49 (24.5)	159 (30.0)	
– 2 mm or more	12 (6.0)	58 (10.9)	
General symptoms			
loss of consciousness	31 (15.5)	94 (17.7)	0.545
cerebral concussion	32 (16.0)	96 (18.1)	0.575
brain contusion	3 (1.5)	11 (2.1)	0.768
nausea and headache	72 (36.0)	104 (19.6)	<0.001*

* statistically significant.
Data presented as number (percentage) (n (%)) or as mean ± standard deviation ($M \pm SD$).

The most common location of the fracture was the orbital floor, which regarded 434 patients (81.9%) in the adult group and 176 patients (88%) in the child group. Individual fracture locations are presented in Table 1. The relationship between the location of the fracture and post-traumatic enophthalmos was assessed. In the adult group, the greatest enophthalmos occurred in the case of a fracture of the orbital floor and medial wall, in contrast to the child group, where the greatest enophthalmos occurred with a fracture of the orbital floor. The results for individual groups are presented in Table 1. In the adult group, 438 patients (85.7%) had an orbital fracture with a bone defect and 73 (14.3%) had a linear fracture. In the child group, a fracture with a bone defect occurred in 129 patients (72.5%), others had a linear fracture of the orbital floor. Individual types of fractures are presented in Table 1.

The injury was connected with the loss of consciousness in 94 patients (17.7%) in the adult group and 31 patients (15.5%) in the child group, cerebral concussion occurred in 96 patients (18.1%) and 32 patients (16%) in the adult and child groups, respectively, and 11 adults (2.1%) and 3 children (1.5%) suffered from brain contusion. Other general symptoms, such as nausea and headache, occurred in 104 adults (19.6%) and 72 children (36%).

The relationship between the time from the injury to surgery and the treatment outcome was evaluated. In surgically treated patients, 311 adults (60.9%) and 94 children (52.8%) were cured, 120 adults (23.5%) and 59 children (33.1%) showed improvement, while 80 adults (15.7%) and 25 children (14%) showed no improvement. In the adult group, a significant relationship between the time from the injury to surgery and the treatment outcome was found ($p < 0.001$). In general, the time from the injury to surgical treatment was shorter in the complete recovery group as compared to the improvement and no improvement groups. In the child group, no significant relationship between the time from the injury to surgery and the treatment outcome was found ($p = 0.598$). The results are presented in Table 2 and Table 3.

Post-traumatic enophthalmos occurred in 402 adults (75.8%) and 132 children (66%). Enophthalmos ranged from 1 mm to 6 mm. After treatment, the proper positioning of the eyeball (enophthalmos less than or equal to 1 mm) was achieved in 313 adults (59.1%) and 139 children (69.5%), improvement was observed in 159 adults (30%) and 49 children (24.5%), and there was no improvement in 58 adults (10.9%) and 12 children (6%). Changes in the size of enophthalmos were compared with respect to the type of surgical treatment that was used. In the group which underwent bone graft reconstruction, enophthalmos after injury was generally greater than in the group in which tissue release was used. A statistically significant relationship was found ($p < 0.05$). A reduction in enophthalmos was more significant in the bone graft reconstruction group. No statistically significant difference was observed between those 2 surgical methods in the child group. The results are summarized in Table 4 and Table 5.

Table 4. Relationship between a decrease in enophthalmos and the type of the surgical procedure applied in the adult group ($N = 511$)

Type of surgical procedure	Decrease in enophthalmos [mm]			*p*-value
	M ±*SD*	*Me*	quartiles	
Tissue release $N = 54$	0.57 ±0.60	1	0–1	0.001*
Bone graft reconstruction $N = 457$	1.08 ±1.03	1	0–2	

M – mean; *SD* – standard deviation; *Me* – median;
* statistically significant.

Table 5. Relationship between a decrease in enophthalmos and the type of the surgical procedure applied in the child group ($N = 178$)

Type of surgical procedure	Decrease in enophthalmos [mm]			*p*-value
	M ±*SD*	*Me*	quartiles	
Tissue release $N = 46$	0.80 ±0.75	1	0–1	0.001*
Bone graft reconstruction $N = 132$	0.77 ±0.78	1	0–1	

Table 2. Relationship between the time from the injury to surgical treatment and the treatment outcome in the adult group ($N = 511$)

Treatment outcome	On the day of accident $N = 8$	2–14 days $N = 92$	15–30 days $N = 202$	1–3 months $N = 152$	4–6 months $N = 24$	>6 months $N = 33$	*p*-value
Complete recovery	7 (87.50)	67 (72.83)	138 (68.32)	78 (51.32)	9 (37.50)	12 (36.36)	<0.001*
Improvement	1 (12.50)	16 (17.39)	39 (19.31)	46 (30.26)	5 (20.83)	13 (39.39)	
No improvement	0 (0.00)	9 (9.78)	25 (12.38)	28 (18.42)	10 (41.67)	8 (24.24)	

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

Table 3. Relationship between the time from the injury to surgical treatment and the treatment outcome in the child group ($N = 178$)

Treatment outcome	On the day of accident $N = 4$	2–14 days $N = 28$	15–30 days $N = 70$	1–3 months $N = 58$	4–6 months $N = 11$	>6 months $N = 7$	*p*-value
Complete recovery	1 (25.00)	16 (57.14)	37 (52.86)	34 (58.62)	5 (45.45)	1 (14.29)	0.598
Improvement	2 (50.00)	9 (32.14)	24 (34.29)	17 (29.31)	3 (27.27)	4 (57.14)	
No improvement	1 (25.00)	3 (10.71)	9 (12.86)	7 (12.07)	3 (27.27)	2 (28.57)	

Data presented as *n* (%).

The results of blowout fracture treatment in adults and children were compared with respect to the type of the surgical procedure used. Regardless of the type of surgery, similar effects were obtained in both adults and children. The results are presented in Table 6 and Table 7.

Table 6. Relationship between the type of the surgical procedure applied and the treatment outcome in the adult group ($N = 511$)

Treatment outcome	Type of surgical procedure		*p*-value
	tissue release $N = 54$	bone graft reconstruction $N = 457$	
Complete recovery	30 (55.56)	281 (61.49)	0.667
Improvement	15 (27.78)	105 (22.98)	
No improvement	9 (16.67)	71 (15.54)	

Data presented as *n* (%).

The treatment outcome was assessed with respect to the site of autogenous bone graft harvest. In the adult group, the best results were obtained in the patients who underwent reconstruction with a donor graft taken from the anterior wall of the maxillary sinus, with 74% recovery, but in children, no statistically significant relationship was found. Detailed results for individual groups are presented in Table 8 and Table 9.

Table 7. Relationship between the type of the surgical procedure applied and the treatment outcome in the child group ($N = 178$)

Treatment outcome	Type of surgical procedure		*p*-value
	tissue release $N = 46$	bone graft reconstruction $N = 132$	
Complete recovery	22 (47.83)	72 (54.54)	0.371
Improvement	19 (41.30)	40 (30.30)	
No improvement	5 (10.87)	20 (15.15)	

Data presented as *n* (%).

Post-traumatic double vision occurred in 463 adults (87.4%) and 176 children (88%). In both adults and children, diplopia was most common in the entire field of view (type V) – 139 adults (30%) and 93 children (52.8%). Individual types of double vision are shown in Table 1. The relationship between the diplopia type and the treatment outcome was assessed. In the adult group, the best outcomes were achieved in the case of type I diplopia (77.69% recovery) and the worst in the case of type V (43.07%). Type III diplopia was associated with the best prognosis in children (85.71% recovery) and the worst results were obtained in the case of double vision in the entire scope of view (40.22%). Detailed results are presented in Table 10 and Table 11.

Table 8. Relationship between the bone graft donor site and the treatment outcome in the adult group ($N = 457$)

Treatment outcome	Bone graft donor site			*p*-value
	iliac bone $N = 78$	skull cover $N = 94$	anterior wall of the maxillary sinus $N = 285$	
Complete recovery	39 (50.00)	31 (32.98)	211 (74.04)	<0.001*
Improvement	20 (25.64)	32 (34.04)	53 (18.60)	
No improvement	19 (24.36)	31 (32.98)	21 (7.37)	

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

Table 9. Relationship between the bone graft donor site and the treatment outcome in the child group ($N = 132$)

Treatment outcome	Bone graft donor site			*p*-value
	iliac bone $N = 42$	skull cover $N = 47$	anterior wall of the maxillary sinus $N = 43$	
Complete recovery	28 (66.67)	19 (40.43)	25 (58.14)	0.068
Improvement	7 (16.67)	19 (40.43)	14 (32.56)	
No improvement	7 (16.67)	9 (19.15)	4 (9.30)	

Data presented as number *n* (%).

Table 10. Relationship between the type of post-traumatic diplopia and the outcome after surgical treatment in the adult group ($N = 511$)

Treatment outcome	No diplopia $N = 53$	Type I $N = 121$	Type II $N = 118$	Type III $N = 38$	Type IV $N = 44$	Type V $N = 137$	*p*-value
Complete recovery	45 (84.91)	94 (77.69)	70 (59.32)	17 (44.74)	26 (59.09)	59 (43.07)	<0.001*
Improvement	6 (11.32)	15 (12.40)	25 (21.19)	19 (50.00)	10 (22.73)	45 (32.85)	
No improvement	2 (3.77)	12 (9.92)	23 (19.49)	2 (5.26)	8 (18.18)	33 (24.09)	

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

Table 11. Relationship between the type of post-traumatic diplopia and the outcome after surgical treatment in the child group ($N = 178$)

Treatment outcome	No diplopia $N = 4$	Type I $N = 21$	Type II $N = 43$	Type III $N = 14$	Type IV $N = 4$	Type V $N = 92$	*p*-value
Complete recovery	0 (0.00)	16 (76.19)	26 (60.47)	12 (85.71)	3 (75.00)	37 (40.22)	
Improvement	2 (50.00)	4 (19.05)	11 (25.58)	2 (14.29)	1 (25.00)	39 (42.39)	0.005*
No improvement	2 (50.00)	1 (4.76)	6 (13.95)	0 (0.00)	0 (0.00)	16 (17.39)	

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

Discussion

Comparing the most common causes of orbital fracture in children and adults, there were some clear differences. In children, accidental hits to the periorbital area dominated, probably related to physical activity, which increases with the age of the child, and the 2nd most common cause was an injury due to sport, which coincides with the results of other authors.[8,9] In contrast, the main cause of injury in adults was an assault as a result of interpersonal violence. Road traffic accidents, which are often mentioned by other authors as the main cause of injury,[19,20] ranked 4th in the examined group.

Based on the available literature, intrabulbar injuries are associated with 3–18% of orbital fractures.[13–18] In the child and adult groups, eyeball injuries constituted 6.5% and 16% of all cases, respectively; they were mainly cases of retinal concussion. In some cases, the rupture of the pupillary sphincter and anterior chamber hemorrhage were noted. In such situations, surgical treatment was postponed until symptoms subsided to avoid sight-threatening complications during the surgical procedure.

According to numerous authors, typical blowout fractures are quite rare in children and are dominated by trapdoor fractures.[21–23] "A child is not a small adult" due to anatomical differences as well as differences in bone elasticity and periosteal thickness. In children, fractures with small displacement of hard tissue and a dominating picture of tissue herniation in the fracture area, with limited mobility of the eyeball, are often encountered, whereas in adults, due to fully developed paranasal sinuses, different proportions between the facial and cerebral parts of the skull, and thus greater exposure of the facial part to trauma, the most common orbital fracture is a fracture with tissue defects within the orbital floor.[24,25] In our study groups, both children and adults presented with the typical picture of blowout fracture, regardless of age. It should be emphasized that the average age of children in our study was greater than 12 years, hence the type of fracture may differ from those in younger children. This is in line with the reports of other authors.[26–28]

Discussions on the most appropriate time interval between the injury and surgical treatment remain open. For children, the prevailing view is that the faster the treatment, the better the result.[3,29,30] This scheme mainly applies to trapdoor fractures, in which prolonged entrapment of soft tissues, both muscle and intraorbital fat, can lead to irreversible changes, permanently impairing the mobility of the eyeball and resulting in permanent enophthalmos due to the atrophy of orbital fat. In adults, some authors point out that only the resolution of post-traumatic soft tissue edema allows for an accurate examination of enophthalmos and diplopia, and enables the proper qualification of the patient for conservative or surgical treatment.[20,31] Exceptions to these patterns are a fracture with the occurrence of an oculo-cardiac reflex or the development of a retrobulbar hematoma, which may lead to post-traumatic optic neuropathy, requiring urgent surgical intervention.[10,11,23] In our group of adults, there was a statistically significant relationship between the time from the injury to surgical treatment and the treatment outcome. The treatment results for the patients who underwent surgery up to 30 days after the injury were better than those of the patients who waited longer. There were no differences in the treatment outcomes in the patients who waited for treatment longer than 30 days after the injury (up to 3 months or more than 3 months after the injury). Missing the optimal time for surgical orbital reconstruction can lead to esthetic and functional disorders, such as permanent enophthalmos, eye globe depression and double vision. Postponed surgical treatment is intended for patients who develop double vision and enophthalmos later than 2 weeks after the injury as a result of orbital fibrosis. According to some authors, surgical reconstruction performed up to 14 days after the injury decreases the risk of late diplopia and enophthalmos. There was no statistically significant difference in the child group. Similar treatment effects were obtained regardless of the time from the injury to treatment; the only observed trend was better treatment outcome with earlier treatment.

Enophthalmos greater than 2 mm is clinically noticeable and, apart from being an esthetic defect, can cause functional disturbances in the form of double vision or impaired tear drainage.[1,32] In the adult group, post-traumatic enophthalmos was more common, occurring in 402 adult patients (75.8%), compared with 132 children (66%). The goal of surgical treatment is to restore the proper position of the eyeball in the orbit, either by releasing the herniated tissues or restoring the continuity of the orbital walls to regain the proper function of the supporting structures of the eyeball (Fig. 5, Fig. 6, Fig. 7, Fig. 8).

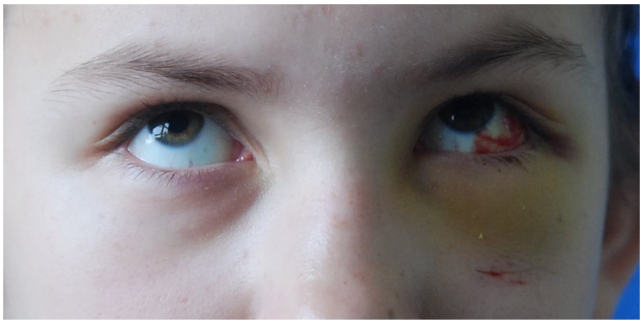

Fig. 5. The same girl as in Fig. 1, after surgery

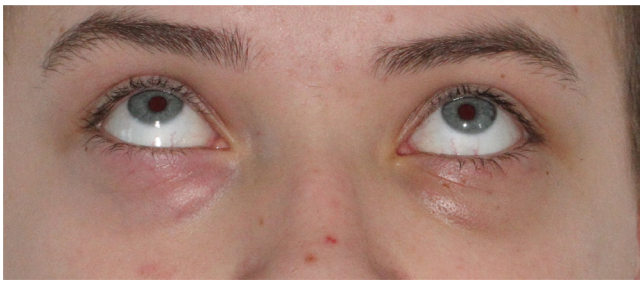

Fig. 6. The same patient as in Fig. 2, after surgery

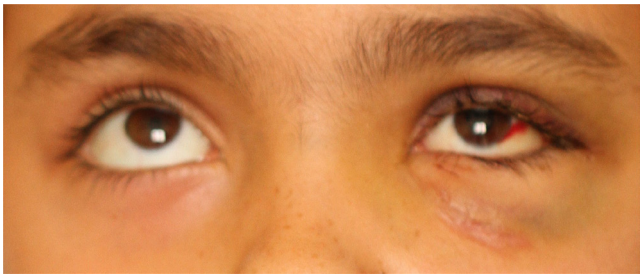

Fig. 7. The same girl as in Fig. 3, after surgery

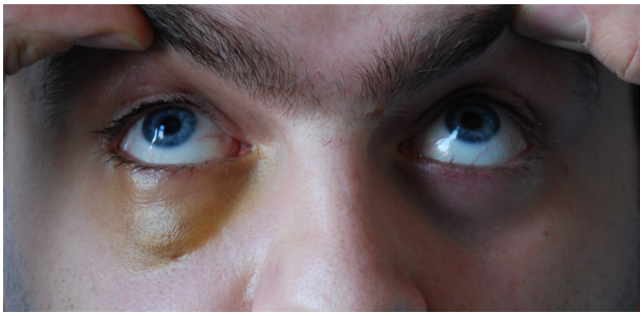

Fig. 8. The same patient as in Fig. 4, after surgery

According to Choi et al., patients with an orbital fracture involving the floor and medial wall are at greater risk of developing post-traumatic enophthalmos.[33] This is mainly due to the loss of eyeball support in the lower-medial quadrant of the orbit. Fractures involving more than 1 orbital wall are also associated with a correspondingly greater disorder of the relationship between the orbital volume and the structures which make up its content.[34] These findings are consistent with the data from our adult group, in which the greatest enophthalmos was noted in the group with orbital floor and medial wall fractures. In contrast, in the child group, the greatest enophthalmos was associated with fractures of the orbital floor. In both groups there were differences in the incidence of enophthalmos, 75.8% of adult patients, compared with 66% of pediatric patients. Post-traumatic enophthalmos in orbital fracture may have different etiology – either changes in the orbital volume or the loss of periocular fat due to the entrapment of soft tissue in the fracture line. Various surgical methods have been described to restore the correct anatomy of the orbit, including reconstruction with the use of auto- and xenografts as well as corrective osteotomies.[33,35,36] Nowadays, in adults, orbital reconstruction with the use of titanium mesh, or patient-specific or customized implants is becoming more popular.[37] In children, resorbable materials are widely used. In our groups of patients, an autogenous bone graft was the reconstruction material used in all patients who required the reconstruction of the orbital floor. In the adult group, the best results were obtained with the use of the anterior maxillary sinus wall graft, and in children, with grafts from the iliac bone; however, the most frequently used donor site was the skull. For children under 12–13 years of age, the use of a transplant from the anterior wall of the maxillary sinus is impossible due to the presence of permanent teeth buds. The use of autogenic orbital reconstruction material reduces the risk of inflammatory complications that may occur with artificial materials. The use of autogenic bone, despite inevitable and not completely predictable graft resorption, provides an opportunity to restore proper support for the eyeball, preventing the development of late enophthalmos.

Conclusions

The relationship between post-traumatic enophthalmos and the location of the fracture was more significantly marked in the adult group. After surgical treatment, the proper positioning of the eyeball (enophthalmos less than or equal to 1 mm) was achieved in a similar percentage of patients in the adult and child groups. In cases requiring bone graft reconstruction, better results were achieved in the adult group. The causes of injury differed between adults and children. However, general symptoms accompanying the injury did not differ significantly between the 2 groups. Due to differences in the clinical picture of orbital floor fractures in children and adults, the diagnosis and treatment of orbital fracture in children may be more challenging.

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Evaluation of the color stability of temporary materials produced with CAD/CAM

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Abstract

Background. If a temporary restoration is in the esthetic area and needs to be worn for a long time, the color stability of temporary materials becomes an important factor.

Objectives. The aim of this in vitro study was to evaluate the long-term effects of various staining solutions on the color stability of different temporary materials produced with the computer-aided design and computer-aided manufacturing (CAD/CAM) technology.

Material and methods. In the study, the following materials were used: VITA CAD-Temp® (group 1); Ceramill® Temp (group 2); and Telio® CAD (group 3). Forty disk-shaped specimens (10 mm in diameter, 2 mm in thickness) of each material ($N = 120$) were produced with a CAD/CAM system. Staining solutions – of tea (A), of coffee (B) and cola (C) – and distilled water (D, control) were used, and color was evaluated before and after storing the samples in the solutions. Measurements were taken with a spectrophotometer and the color parameters (L*, a*, b*, and ΔE) were calculated according to the Commission internationale de l'éclairage system (CIELab). The results were evaluated with the two-way analysis of variance (ANOVA) and Tukey's tests ($\alpha = 0.05$).

Results. Clinically perceivable ($\Delta E00 > 0.8$) and statistically significant ($p < 0.001$) color differences were detected in all specimens. The highest ΔE00 value was found in the Ceramill Temp specimens. In addition, the highest ΔE00 values were noted for the specimens stored in cola and the coffee solution for all groups. The lowest ΔE00 value was observed for the groups stored in the tea solution.

Conclusions. Clinically perceivable color changes were observed in all the specimens kept in the solutions. Color changes were greater for cola and coffee as compared to tea.

Keywords: CAD/CAM, coloring, temporary dental prosthesis

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Introduction

Temporary restorations are important to protect the prepared teeth, to restore the lost function, phonetics and esthetics, and to prevent tooth sensitivity.[1] Polymethylmethacrylate (PMMA) is the most commonly used traditional material for temporary restorations. Among available dental resins, this compound has excellent physical properties, including durability, color stability and marginal adaptation. Recently, high-density blocks and disks with highly cross-linked PMMA acrylic resin have been introduced for processing with the computer-aided design and computer-aided manufacturing (CAD/CAM) technology. These products have been recommended for temporary restorations in long-term dental treatment, including preparing implant-supported prostheses,[2,3] as they have better properties as compared to traditional materials.[4,5] If a temporary restoration is in the esthetic area and needs to be worn for a long time, the color stability of temporary materials becomes an important factor.[6] In such areas, a temporary restoration should not only have an initial color match, but also provide an esthetic appearance throughout its use.[7] As dental resins absorb liquid regardless of their chemical composition, discoloration may occur when the material is exposed to solutions such as coffee, tea, red wine, chlorhexidine, or bleaching agents.[8–11] In the Commission internationale de l'éclairage color system (CIELab), the degree of color change is expressed as ΔE, and the following formula is used (Equation 1):

$$\Delta E = \frac{(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2}{2} \quad (1)$$

where:
ΔL*, Δa*, Δb* – differences in the color parameters.

A value of zero for ΔE indicates that 2 colors are identical, while a value other than zero indicates a color change.[12] In previous studies, color differences between 2 specimens have been clinically evaluated using the CIELab color system.[13] However, the system has limitations, including tone values.[14] Therefore, other CIELab-based color difference formulas have been developed.[15] A recent study suggested that CIEDE2000 could better evaluate color differences.[16] This formula includes specific corrections for the interaction between chroma and color differences in the blue region as well as a modification of the CIELab coordinate that affects colors with low chroma.[17]

Objectives

The aim of this study was to investigate the effects of various solutions on the long-term color stability of different types of prefabricated disk materials for CAD/CAM systems. The null hypothesis was that the solutions used would affect the long-term color stability of prefabricated disk and block materials for CAD/CAM systems.

Material and methods

Three types of prefabricated temporary restoration disks for CAD/CAM systems were tested (Table 1):

- VITA CAD-Temp® blocks (VITA Zahnfabrik H. Rauter, Bad Säckingen, Germany) consisting of a microparticle filler, fiber-free, homogeneous, high-molecular-weight and cross-linked acrylate polymer; this structure is referred to by VITA as the MRP (Microfilled Reinforced Polyacrylate) material and contains 14% SiO_2 microparticles as fillers[18];
- Ceramill® Temp (Amann Girrbach, Koblach, Austria) made of PMMA and methacrylic acid ester-based cross-linked polymers that can be easily processed[19]; and
- Telio® CAD blocks (Ivoclar Vivadent, Schaan, Liechtenstein) consisting of 99.5% cross-linked PMMA and 0.5% pigment; these blocks have a high material homogeneity and do not exhibit polymerization shrinkage, as they are produced industrially like other CAD/CAM blocks.[20]

Table 1. Materials used in the study

Product name	Manufacturer	Composition
VITA CAD-Temp	VITA Zahnfabrik, Bad Säckingen, Germany	acrylate polymer
Ceramill Temp	Amann Girrbach, Koblach, Austria	PMMA and methacrylic acid ester-based cross-linked polymers
Telio CAD	Ivoclar Vivadent, Schaan, Liechtenstein	PMMA

PMMA – polymethylmethacrylate.

A wax pattern, 2 mm in thickness and 10 mm in diameter, was prepared and scanned in a CAD system, and the obtained images were transferred to digital media as a stereolithography (STL) file. VITA shade 1M2, corresponding to A1, was used for VITA CAD-Temp, and for Telio CAD and Ceramill Temp – a light disk corresponding to shade A1.

The specimens were divided into 3 groups according to the different temporary materials used. A total of 120 specimens (*N*) were milled, with 40 specimens for each group. These groups were further divided into 4 subgroups for different solutions, including the control group (n = 10). For the analysis of color stability, distilled water and 3 different staining solutions were prepared: tea (Yellow Label Tea; Lipton, Rize, Turkey); coffee (Nescafé Classic; Nestlé, Vevey, Switzerland); and cola (Coca-Cola; Coca-Cola Co., Istanbul, Turkey) (Table 2). For the tea solution, 1 teabag was placed in 200 mL of boiled water for 10 min. The coffee solution was prepared by pouring 15 g of coffee powder into 500 mL of boiled water, followed by mixing. The front surfaces of the specimens were polished under water cooling for 10 s with 400-, 800-, 1,200-, and 2,400-grit SiC abrasive papers, respectively.

Table 2. Composition of the solutions

Solution	Manufacturer	Product/Composition
Tea	Lipton Rize, Turkey	Yellow Label Tea black tea
Coffee	Nestlé, Vevey, Switzerland	Nescafé Classic instant coffee
Cola	Coca-Cola Co., Istanbul, Turkey	carbonated water, high-fructose corn syrup, sugar, caffeine, phosphoric acid, citric acid, caramel color, and natural flavors
Distilled water	–	H_2O

For initial color measurements, a clinical spectrophotometer device (VITA Easyshade® Advance; VITA Zahnfabrik H. Rauter) utilizing the CIELab color system was used. The instrument was calibrated before each measurement, and the specimens were individually numbered after being washed with distilled water and dried. The CIELab values were obtained with the spectrophotometer, with 3 different points measured for each specimen and the mean value calculated. Color measurements were taken before soaking the specimens in the solutions and after 21 days of storage in the solutions. Measurements were done in a single-tooth mode at the same time of day, under the same conditions, on a white background. They were performed by a single investigator and the CIELab parameters were recorded.

The solutions were exchanged every 2 days to prevent plaque formation during soaking, and the specimens were cleaned with a conventional toothbrush (Macleans® brand toothbrush; GlaxoSmithKline, Brentford, UK) and toothpaste (Aquafresh® brand toothpaste, mild and minty flavor; GlaxoSmithKline). Color differences were converted to CIEDE2000 and recorded as ΔE00. Recently, some studies established 50:50% color difference thresholds in dentistry.[21,22] The CIELab 50:50% perceptibility threshold (PT) was ΔEab = 1.2 and 50:50% acceptability threshold (AT) was ΔEab = 2.7, whereas the CIEDE2000 (ΔE00) 50:50% PT was ΔE00 = 0.8 and 50:50% AT was ΔE00 = 1.8.[21,22] These values were included in the ISO/TR 28642:2016[23] and should be applied to all issues related to the quality of tooth color matching in dentistry. They can serve as quality controls to guide the selection of esthetic dental materials, evaluate their clinical performance, and interpret visual and instrumental findings in clinical dentistry, dental research, and subsequent standardization.[24] Thus, in this study, PT ΔE00 > 0.8 was accepted.

Results

Color differences (ΔE00) for different materials before and after soaking in the solutions are shown in Fig. 1. The ΔE values for the specimens kept in different solutions were compared via the two-way analysis of variance (ANOVA). The analysis showed that the Ceramill Temp specimens had the highest statistically significant ΔE00 values ($p < 0.001$). The clinical color matching in all specimens was ΔE00 > 0.8; therefore, all were classified as clinically perceivable. The two-way ANOVA indicated statistically significant differences in the ΔE00 values for the material and solution types ($p < 0.010$). In addition, the interaction between the material type and the solution type was statistically significant ($p < 0.010$). The results represent the ΔE00 values for different material specimens stored in different solutions. According to this, the mean ΔE00 value for the specimens kept in distilled water was found to be 1.67; thus, it was a perceivable change as well (ΔE00 > 0.8).

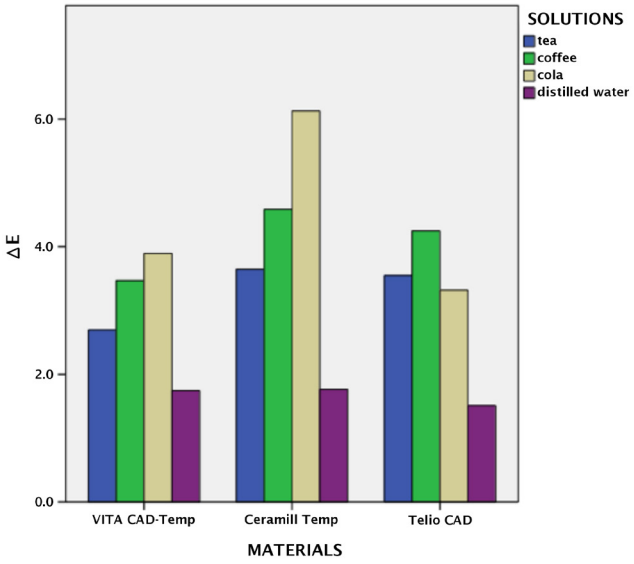

Fig. 1. Color differences in the specimens following soaking in different solutions

ΔE – color change.

The mean ΔE00 value for the specimens kept in tea was 3.29, the mean ΔE00 value for the specimens kept in coffee was 4.10, and the mean ΔE00 value for the specimens stored in cola was 4.44. According to these results, the color change of the specimens kept in tea was less significant than of those kept in coffee and cola (Fig. 2).

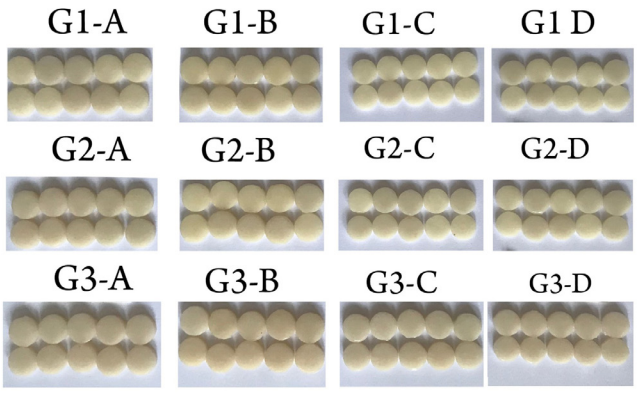

Fig. 2. Color change in the specimens

Materials: G1 – VITA CAD-Temp; G2 – Ceramill Temp; G3 – Telio CAD; solutions: A – tea; B – coffee; C – cola; D – distilled water.

Discussion

The hypothesis of the current study was accepted. Color stability is an important criterion for the selection of materials, especially for temporary restorations to be used for a long time in the anterior region.[25] Although there are studies in the literature that examine the color stability of different types of temporary materials,[26–28] no studies have been found where the current CAD/CAM-produced temporary materials are evaluated together.

Bayindir et al. studied the color change of autopolymerizing temporary prosthetic materials in various solutions.[1] The highest ΔE value reported in this study was for the groups kept in coffee.[1] Guler et al. investigated the color change of autopolymerizing and light-polymerized composite resin temporary restorations, reinforced microfill and microhybrid composite resins in various solutions.[29] The lowest ΔE value was reported for the water, cola and cherry juice solution groups, while the highest ΔE value was observed in the materials stored in red wine. In addition, the highest color change was observed for a light-polymerized composite resin.[29]

Prefabricated, pre-polymerized resin blocks for the CAD-CAM technique have been introduced recently.[30] These blocks are manufactured under more favorable and controlled production conditions, are used for temporary fixed dental prostheses, and have better properties than autopolymerizing temporary materials.[31,32] VITA CAD-Temp is an acrylic resin-based material, and Ceramill Temp and Telio CAD have PMMA content. In our study, the highest ΔE value was observed for the Ceramill Temp specimens containing PMMA.

Sham et al. also examined the color stability of 5 temporary restoration materials by immersing them in distilled water or coffee for 20 days.[33] In their study, the minimum color change was observed for the materials containing bis-acryl methacrylate. In addition, it was reported that the materials containing poly(ethylmethacrylate) and PMMA stored in coffee showed a lesser color change as compared to those containing bis-acryl methacrylate.[33] Haselton et al. also investigated the color change of 12 different temporary prosthetic materials in artificial saliva and the artificial saliva-coffee solution.[9] The highest ΔE value was found for the bis-acryl resin-containing specimens stored in the artificial saliva-coffee solution for 4 weeks, and the lowest ΔE value – for the specimens with PMMA content.[9]

Interim crowns made by means of conventional methods were compared with those made with CAD/CAM by Almohareb et al., and it was found that those made with CAD/CAM were more color-stable.[26] Telio CAD had the lowest ΔE value in all solutions and showed better color stability than other materials.[26]

Lauvahutanon et al. measured the ΔE values of CAD/CAM blocks after soaking in coffee and water.[27] No significant color change was found for the specimens in water, while the specimens in coffee had an increased ΔE. Similarly, we observed a clinically perceivable color change for the specimens held in coffee. Two recent studies also reported a strong color change in temporary materials due to coffee.[26,34] This was attributed to the smaller molecular size along with the water absorption property of the tested materials.[26,34] Also, it was reported that coffee was a more coloring solution, whereas cola mostly influenced roughness.[35]

Stawarczyk et al. also measured the color change of resin blocks for CAD/CAM systems in the coffee, black tea and red wine solutions.[28] Similar to the results of our study, color changes were observed in all groups. VITA CAD-Temp and the other CAD/CAM resins showed similar color stability.[28] These findings indicate that prefabricated blocks produced for CAD-CAM systems have better physical properties than conventional materials. In the present study, such a comparison could not be made, as we did not use any temporary crown material polymerized by means of conventional methods. Another limitation of the current study is that the oral environment is different from in vitro conditions. Food, thermal and mechanical stresses, and their interactions may increase the color change in vivo.

Conclusions

According to the results of this study, the color stability of fixed temporary restorations depends on the type of the material used and the type of beverage. Although the color change of the specimens kept in tea was lesser than of those kept in coffee and cola, all changes were perceivable. Thus, the color stability of prefabricated temporary blocks for CAD/CAM systems needs to be improved.

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Comparative evaluation of the shear bond strength of ceramic brackets of three different base designs bonded to amalgam and composite restorations with different surface treatment

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Abstract

Background. Nowadays, due to the increasing number of adult orthodontic applicants, who also have multiple dental restorations, it is important to have the ability to bond an orthodontic appliance to restoration surfaces.

Objectives. The aim of this paper was to determine the shear bond strength of ceramic brackets of 3 different base designs bonded to amalgam and composite restorations after using different surface treatment methods in vitro.

Material and methods. In an in vitro study, the surfaces of 180 amalgam and composite specimens were prepared by using sandblasting and the erbium, chromium-doped yttrium, scandium, gallium, and garnet (Er,Cr:YSGG) laser irradiation. Ceramic brackets of 3 base designs, including Star, Cross and Slot, for upper central teeth were bonded to amalgam and composite surfaces by using Transbond™ XT Light Cure Adhesive. All specimens were incubated at a temperature of 37°C for 1 week, and then subjected to shear bond strength tests after 1,000 cycles of thermal cycling. The bond strength of the groups was analyzed by means of the one-way and two-way analysis of variance (ANOVA), and the comparison of the 2 groups was made with Tukey's test. Residual adhesives were also determined by a 4-part criterion (0–3) in different groups and the results were analyzed with the χ^2 test.

Results. There was a significant difference in the shear bond strength of brackets of 3 base designs bonded to amalgam and composite surfaces with different surface treatment.

Conclusions. According to the results of this study, all surface treatment methods and different bracket base designs were able to provide sufficient shear bond strength on composite and amalgam surfaces. As far as the bracket base design is concerned, the use of each of the 3 base designs in the amalgam group brought desirable results in terms of the adhesive remnant index (ARI) and shear bond strength values; the use of the Star base design in the composite group proved to be suitable.

Keywords: shear bond strength, orthodontic brackets, adhesive remnant index

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Introduction

In contemporary orthodontic treatment, establishing a successful clinical bond between the bracket and the tooth surface is essential. Currently, the number of patients applying for orthodontic treatment is on the rise, and adults' treatment has also grown rapidly. Orthodontic treatment for both clinical and cosmetic purposes has long been popular among teenagers, but in recent times, middle-aged patients and seniors have also sought orthodontic treatment more frequently than previously. These patients commonly received amalgam or metal restorations in their earlier dental treatment. At least 1 amalgam restoration was found in 50–85% of the population.[1] Recent orthodontic treatment requires bonding orthodontic appliances to restoration surfaces, including resin, amalgam and porcelain composites, and thus achieving a reliable bond to restoration surfaces is important. As adults tend to look esthetic, they use ceramic brackets and have dental restorations, many studies have been conducted on the bond strength of orthodontic brackets on restoration surfaces, such as amalgam or porcelain. It should be high enough to maintain the orthodontic brackets during orthodontic treatment[2] and to withstand the forces caused by occlusion, chewing and wire stressing as well as biomechanical forces. On the other hand, bond strength must not be too high so that to avoid causing damage to the tooth surface during debonding at the end of the treatment.[3]

To be accepted, a bracket bond system must be able to withstand the forces of orthodontic wires as well as those of the oral environment. Bond strength testing is one of the most popular analyses used in dental material evaluation. The force used in these tests is often of tensile or shear type. In a comparison between tensile, shear and torsional forces, it has been identified that shear forces are the most common and destructive type of forces, which cause bracket debonding in the mouth.[4,5]

Things get even tougher when we want to bond brackets on dental restorations, and not on the enamel. Various surface preparation methods as well as different kinds of physical and chemical retention are used to do this.[6]

Some research has been carried out on the results of various surface preparation methods, such as diamond milling, sandblasting or etching with phosphoric acid and hydrofluoric acid.[7] Sandblasting or aerating is a method of combining aluminum oxide particles with air pressure to increase bond strength to gold, porcelain, amalgam, and composite resins. Other clinical applications of sandblasting include removing the composite from the surface of the debonded bracket, increasing orthodontic band retention and making the surface of the primary teeth rough.[8] Sandblasting is the most common way of surface preparation and increases bond strength by creating scratch-like irregularities.[9]

Recently, the Er,Cr:YSGG laser system has also been considered for surface preparation, and it has been determined that this type of laser produces a rough surface, similarly to the conventional acid-etching technique, on the enamel and the dentin.[9] Limited studies have evaluated the effects of laser irradiation on the surface of metal restorations and it has been found that Er,Cr:YSGG lasers can partially cause abrasion on amalgam surfaces.[10]

Ceramic brackets are a type of orthodontic brackets made of non-metal minerals that are almost colorless. This type of brackets is used for people who want the orthodontic appliances on their teeth to be almost unnoticeable, not attracting the attention of others. Currently, all the available ceramic brackets are made of aluminum oxide. These brackets are divided into 2 types at the manufacturing stage – polycrystalline and monocrystalline, and the main difference is in the transparency of the brackets; single-crystal brackets are more transparent than polycrystalline ones. Fortunately, both single-crystal and polycrystalline brackets are resistant to staining and discoloration.[11]

Mechanical bonding is caused by the clogged spots and surface roughness, and the locking of the materials. The amount of the created microscopic retention indicates the strength of the bond. Almost all dental bonding consists in mechanical bonding. Chemical bonding is also possible, but this type of bond often accounts for a small share of the total bond strength.[12] For mechanical bonding, various bracket base designs, such as microcrystalline, mechanical, button, and polymer bases are available.[13] Different bracket base designs are used to achieve proper mechanical retention and bonding of orthodontic appliances to different dental surfaces or restorative materials; it has been shown that different bracket base designs show different bond strength.[14,15]

Bracket failure is divided into 2 groups with regard to its location: cohesive failure, which occurs inside the adhesive; and adhesive failure, which occurs at the site of the tooth–adhesive or bracket–adhesive interface.

The adhesive remnant index (ARI) is used to classify the bond failure location.[2] Based on the material outlined and the availability of 3 different base designs (Star base, Cross base and Slot base), we intended to use both the sandblasting and laser surface treatment methods, due to their frequent application, to examine the bond strength of ceramic brackets with these 3 different base designs on amalgam and composite restorations.

Material and methods

This in vitro study was conducted on 180 samples of amalgam and composite in 12 groups of 15 (for each of the 3 bracket base designs, each kind of surface – amalgam or composite, and each method of surface preparation – sandblasting or laser). There were 3 groups of 60

for each bracket base design; half of the specimens were bonded to amalgam surfaces and the other half to composite surfaces. The grouping was done randomly.

To simulate the amalgam restoration cavities, 2 grooves, 3.5 mm in diameter and 6 mm in width, with smooth baffles and parallel walls perpendicular to the surface were cut on brass ingots. This was accomplished by using a milling machine and a cylindrical turning machine. For composite samples, 90 Filtek® Z250 composite discs (3M ESPE, St. Paul, USA) of color A2, a 10-millimeter diameter and a 2-millimeter thickness were prepared by the operator and, using the Ortholux® LED device (3M Unitek, Monrovia, USA) with radiometer adequacy, they were illuminated at a moderate intensity for 40 s on both sides.[16] The head was at a 90° angle to the surface of the discs. They were then evaluated ophthalmologically for the absence of cracks or any defects.

In the sandblasting group, the amalgam and composite surfaces were sandblasted with the DENTO-PREP™ microbeader (Rønvig Dental, Daugård, Denmark) using 50-micrometer aluminum oxide particles, at air pressure of 3 kg/cm^2 at a distance of 10 mm for 4 s. A plaster facade after washing and drying amalgam and composite surfaces was considered as a criterion for finishing the sandblasting operation.[17]

In the laser group, an Er,Cr:YSGG laser machine (Biolase Europe, Floss, Germany) with a G-type 600-micron tip was used to prepare the surface. This laser system produces photons with a wavelength of 2.78 μm, with a duration of 140–200 μm and a repetition rate of 20 Hz. The output power varies 0 to 6 W. In this study, a power of 1 W (20% air level and 10% water level) was used. The rays were irradiated perpendicular to the surface at a distance of 1 mm with a radiation time of 5 s for the amalgam and composite surfaces. The droplet size was 0.228 mm and the energy density of the laser was 17.7 J/cm. After irradiation, the samples were rinsed with distilled water and finally dried.[5]

Upper central incisor ceramic brackets (0.022-inch slot size) and a base of a surface area of 12.25 mm^2 were bonded to the center of the amalgam and composite surfaces of the specimens from 12 groups. The Transbond® XT bonding agent and Transbond XT Light Cure Adhesive (3M Unitek) containing 45–55% of bisphenol A diglycidyl methacrylate (Bis-GMA) and 45–55% of triethylene glycol dimethacrylate (TEGDMA) were used for bonding attachments. The Transbond XT bonding agent was applied to the amalgam and composite surfaces with the help of a microbrush, dried with a slight pressure of air spray (no water or oil) and left to dry for 10 s. Transbond XT Light Cure Adhesive was applied on the back of the bracket, and then the bracket was compressed on the amalgam and composite surfaces with the use of an orthodontic gage. Excess composite was removed by using the sharp tip of an explorer. After making sure that the desired condition was reached, the curing operation of the composite was carried out with a medium-intensity light-curing apparatus,[8] in which the light was spun for 40 s perpendicular to the surface of the ceramic bracket face.[18]

All samples were stored in the Pars Azma incubator (Pars Azma Co. Tehran, Iran) at 37°C and 95% humidity for 1 week, and then thermocycled for 10,000 rounds, using a thermal cycler (Dorsa, Tehran, Iran). They were placed in 5°C in cold water for 20 s and in 55°C in warm water for 20 s in each cycle, and were kept for 5 s out of the water container, between the 2 containers.[10] Because of the fact that orthodontic adhesives are routinely exposed to thermal changes in the oral cavity, it is paramount to establish whether these changes introduce stress in the adhesive that might affect bond strength. Thermal cycling is an in vitro process through which the adhesive resin is subjected to temperature extremes compatible with the oral cavity environment.[19]

In order to mount the samples in acrylic resin for bond strength testing, wax boxes were fabricated and the brackets were placed on top of the boxes (5 per each row) with 0.019×0.025-inch wire ratchets, using elastomeric ligatures in such a way that they were parallel to the longitudinal margins of the box. Auto-polymerizing acrylic resin was poured into the box up to the upper margin of composite discs. The samples were embedded in the acrylic resin. The contact of the acrylic resin and the bracket was prevented as such, and a proper stub was obtained for the placement of the samples in a universal testing machine.[16] To measure shear bond strength, the samples were placed in the universal testing machine (STM-20; SANTAM Engineering Design Co. Ltd., Tehran, Iran) with pooling tools of a 0.02-inch ligature wire. The ligature wire was modified and connected with the bracket as a shear tool, and a direct force was applied at a speed of 1 mm/min until the bracket fell apart. The load at fracture was recorded in newtons. By dividing the load [N] by the cross-sectional area of the bracket [mm^2], the shear bond strength of the brackets was calculated [MPa]. The samples were evaluated under a stereomicroscope (Carl Zeiss, Jena, Germany) at ×10 magnification to determine the mode of failure. The ARI score was also calculated based on the amount of adhesive remaining on the surface, using a 4-point scale as follows[3]:

– score 0: no adhesive remained on the restoration surface;
– score 1: less than 50% of the adhesive remained on the restoration surface;
– score 2: more than 50% of the adhesive remained on the restoration surface;
– score 3: all the adhesive remained on the restoration surface.

The IBM SPSS Statistics for Windows software, v. 20, was used for data analysis. For this purpose, the mean (*M*) and standard deviation (*SD*) of shear bond strength values for 12 sample groups were calculated and reported. The data was analyzed by means of one-way and two-way

analysis of variance (ANOVA), and Tukey's test for paired comparisons. Also, the ARI scores after debonding were compared among the groups with the χ^2 test. A p-value <0.05 was considered statistically significant.

Results

In this study, according to one-way ANOVA, significant differences were noted in shear bond strength between the 12 experimental groups.

The comparison of shear bond strength in the amalgam – composite groups, sandblast – laser groups and 3 bracket base design groups revealed significant differences (Table 1).

The comparison of shear bond strength in the composite group with sandblast and laser surface treatment revealed no significant difference, but in the amalgam group with sandblast and laser surface treatment, there was a significant difference (Table 2).

The comparison of shear bond strength in the composite group with 3 bracket base designs revealed a significant difference, but in the amalgam group with 3 bracket base designs, there was no significant difference (Table 3).

Adhesive remnant index

According to the results shown in Table 4, the difference in the ARI scores between the composite and amalgam groups was significant at the 0.05 level of probability. Most composite specimens (71.1%) had an ARI score of 3 (100% of the adhesive remained on the restoration) and most amalgam samples (88.8%) showed an ARI score of 0 (no adhesion remained on the restoration). The highest fracture incidence in the composite base was observed in the case of the Cross base design of the composite groups. In the composite + laser + Star group, fractures in the composite base were observed in 2 samples.

Table 2. Distribution and comparison of the mean shear bond strength [MPa] in the composite and amalgam groups with sandblasting and laser surface preparation

Restorative material	Surface preparation	*M*	*SD*	*p*-value
Composite	sandblasting	9.22	5.32	0.400
	laser	10.15	5.15	
Amalgam	sandblasting	8.46	2.48	0.001*
	laser	4.64	1.47	

* statistically significant.

Discussion

One of the difficulties in fixed orthodontic treatment is peeling off the brackets from the tooth surface. In other words, the repeated removal of orthodontic attachments is a major problem in orthodontics. On the other hand, with an increasing number of adults requesting orthodontic treatment with multiple restorations and the interest of these patients in ceramic brackets, further studies are needed. Although a low bond strength is a disadvantage in the use of metal brackets, it can be a relative advantage when using ceramic brackets. One drawback of ceramic

Table 1. Distribution and comparison of the mean shear bond strength [MPa] in different groups

Groups		*M*	*SD*	Min	Max	*p*-value
Restorative material	composite	9.68	2.44	2.77	22.06	0.001*
	amalgam	6.55	1.61	1.89	14.22	
Surface preparation	sandblasting	8.84	2.06	2.77	22.06	0.030*
	laser	7.40	1.99	1.89	19.53	
Bracket base design	Star	8.84	2.46	3.58	13.71	0.001*
	Cross	11.46	5.47	1.89	22.6	
	Slot	5.29	2.18	2.60	12.51	

M – mean; *SD* – standard deviation; min – minimum; max – maximum; * statistically significant.

Table 3. Distribution and comparison of the mean shear bond strength [MPa] in the composite and amalgam groups with different bracket base designs

Restorative materials	Bracket base design	*M*	*SD*	Min	Max	*p*-value
Composite	Star	8.82	2.10	8.03	9.60	0.001*
	Cross	15.63	3.18	14.44	16.82	
	Slot	4.61	2.30	3.74	5.47	
Amalgam	Star	6.40	2.22	5.57	7.23	0.180
	Cross	7.28	3.82	5.85	8.71	
	Slot	5.97	1.85	5.28	6.66	

* statistically significant.

Table 4. The adhesive remnant index (ARI) scores in 12 groups

Group			Score 0 *n* (%)	Score 1 *n* (%)	Score 2 *n* (%)	Score 3 *n* (%)	Fracture in the composite base *n* (%)	*p*-value
restorative material	surface preparation	base design						
Composite	sandblasting	Star	0	0	0	15 (100.0)	0	<0.001*
		Cross	0	0	7 (46.7)	4 (26.7)	4 (26.7)	
		Slot	0	0	0	15 (100.0)	0	
	laser	Star	0	0	0	13 (86.7)	2 (13.3)	
		Cross	0	7 (46.7)	2 (13.3)	2 (13.3)	4 (26.7)	
		Slot	0	0	0	15 (100.0)	0	
Amalgam	sandblasting	Star	9 (60.0)	0	0	6 (40.0)	0	
		Cross	15 (100.0)	0	0	0	0	
		Slot	13 (86.7)	2 (13.3)	0	0	0	
	laser	Star	15 (100.0)	0	0	0	0	
		Cross	15 (100.0)	0	0	0	0	
		Slot	13 (86.7)	2 (13.3)	0	0	0	

* statistically significant.

brackets is the high bond strength with the adhesives due to the chemical bond. As a result, the risk of damage to the enamel increases when the brackets are removed.[20]

According to the results of this study, the mean shear bond strength value for the composite groups was 9.68 MPa and 6.55 MPa for the amalgam groups, and there was a significant difference between the 2 groups ($p < 0.05$). In fact, a lower bond strength was recorded at the amalgam surfaces as compared to the composite surfaces. The results obtained by Eslami Amirabadi et al. regarding the bond strength of stainless steel brackets bonded to porcelain and amalgam with Transbond XT and Assure® Universal Bond Resin are consistent with the current finding; the authors reported lower bond strength values on amalgam surfaces than on porcelain.[21]

Ebert et al. investigated the shear bond strength of ceramic and metal brackets bonded to composite, ceramic and amalgam restorative surfaces.[22] The results showed that the shear bond strength of ceramic and metal brackets to amalgam surfaces was significantly lower than in other groups.[22]

In recent studies, the bond strength values at amalgam surfaces were significantly lower than at the enamel.[4–10] However, considering a range of 5–8 MPa as the acceptable bond strength values in clinical conditions,[8] the reported bond strength range in the amalgam and composite groups was acceptable in all our study groups except for 3 groups: composite + sandblasting + Slot; amalgam + laser + Star; and amalgam + laser + Cross.

According to the results of the present study, the mean shear bond strength value in the case of surface preparation with sandblasting was 8.84 MPa, and 7.40 MPa for the laser group, and there was a significant difference between the 2 groups ($p < 0.05$). The mean shear bond strength value in the composite group with sandblasting and laser surface preparation were 9.22 MPa and 10.15 MPa, respectively, which showed no significant difference; both groups provided adequate and sufficient bonds. The mean shear bond strength value in the amalgam group with sandblasting and laser surface preparation were 8.46 MPa and 4.64 MPa, respectively, which showed a significant difference, and only sandblasting provided an adequate and sufficient bond. Therefore, both in the composite and amalgam group, sandblasting surface preparation provided a sufficient and appropriate bond. The results of the research by Sperber et al., who studied the effects of different amalgam surface preparation methods, are consistent with the current finding; they reported higher shear bond strength values when preparing amalgam surfaces through sandblasting.[10]

A study by Espinar-Escalona et al. also confirms a higher shear bond strength for sandblasting surface preparation.[23] Tayebi et al. evaluated different methods of com-

posite surface preparation by sandblasting and rough diamond milling.[16] Their results showed that the brackets bonded to composite surfaces had a higher shear bond strength in the sandblasted samples as compared to the surfaces prepared by means of a bur, although the difference was not statistically significant.[16]

Laser use in dentistry is currently increasing.[24] Previous studies have shown that surface preparation by sandblasting is clinically acceptable and is recommended for bracket bonding on amalgam surfaces. In a similar study by Zaheer et al., the shear bond strength of amalgam samples was reported to be 16.30 MPa with sandblasting surface preparation and 10.04 MPa with diamond bur prparation.[25] Machado et al. studied the effects of different surface preparation methods, such as diamond bur or sandblasting, on amalgam samples that were packed inside composite cylinders.[26] The sandblasted amalgam samples showed a higher bond strength than other groups.[26] Another study was conducted to investigate the sandblasting and laser techniques for bonding metal brackets on amalgam surfaces.[5] According to its results, sandblasting provided a higher bond strength in comparison with the control group, although there was no statistically significant difference.[5]

According to the results of this study, the average shear bond strength was 8.84 MPa for the Star base design, 11.46 MPa for the Cross base design and 5.29 MPa for the Slot base design. Significant differences were observed when comparing the bond strength values in different groups of Star, Cross and Slot base designs.

The results obtained by Kukiattrakoon and Samruajbenjakul, who studied the shear bond strength of ceramic brackets with 3 base designs bonded to fluorapatite and aluminum ceramics, are consistent with the current finding; the researchers showed that there was a significant difference in shear bond strength for different bracket base designs.[15]

The results of Hudson et al.'s study are consistent with ours.[27] According to the authors, the different base designs of metal and ceramic brackets bonded to porcelain surfaces affect shear bond strength.[27] Wang and Lu concluded that the bracket base design could be one of the factors influencing the shear bond strength of brackets.[28]

In the present study, in most of the amalgam groups (88.8%), no adhesive remained on the restoration (ARI = 0) and in most of the composite groups (71.1%), all the adhesive remained on the restoration (ARI = 3). There was a significant difference in the ARI score between the 2 groups ($p < 0.001$). The 0 score indicates that the fracture occurred at the adhesive–restoration interface, while the 3 score indicates that the fracture site was between the adhesive and the bracket base. The amount of the remaining adhesive is estimated in various studies based on ARI. However, it is not possible to compare the results of different research in this field, as some studies have modified the ARI index and reported different results. Still, in most previous studies, the bond failure of the majority of samples was at the amalgam–adhesive interface (ARI = 0),[29] which is consistent with our results.

The study by Tayebi et al. also provided similar resluts.[16] The researchers showed that most composite samples had an index of 2 and 3, and some had a fracture in the composite base.[16] This is due to the high bond strength of the adhesive to the prepared surface of the composite, which prevents a fracture at the composite–adhesive interface and causes a fracture at the adhesive–bracket base.

In the current study, the comparison of the ARI scores between the 3 groups of base design, including Star, Cross and Slot, showed that in the composite groups, the Star and Slot base designs had the highest amount of adhesive remaining on the restoration surfaces after debonding, and most cases of bond failure between the adhesive and the restoration occurred for the Cross base design. This base design causes more damage on the restoration surface than other designs. In the amalgam groups, the Cross base design showed more adhesive remnants on the restoration surfaces after debonding than other designs. In accordance with the current study, it has been stated in previous studies that the type of base design has a large impact on ARI.

In a study by Ahangar Atashi et al., the comparison of the ARI scores between 2 groups with the anchor pylon base design and the mesh base design showed that in 20% of the mesh base design samples, bond failure occurred at the adhesive–enamel interface and they also indicated the highest amount of adhesive remaining on the tooth surface after debonding.[14] Bond failure between the adhesive and the enamel occurred most frequently for the anchor pylon base design. This base design leads to more stress being transferred to the enamel during debonding and causes more damage to the enamel surface than the mesh base design.

In a study by Ansari et al., the ARI scores in 4 groups of ceramic brackets and 1 group of metal brackets bonded to the enamel surface with different base designs were investigated.[13] The groups with different base designs showed significant differences in terms of ARI, which is consistent with the present study.

In the current study, the shear bond strength test was performed using the looped ligature wire method, which is different from the usual blade method. Force from the testing machine was transferred to the upper jaw and the bracket by forming a ligature wire and connecting one end of the wire to the upper jaw and the other end to the bracket.

The crosshead speed in the current study was 1 mm/min. A crosshead speed of 0.1–10 mm/min have been used for shear bond strength testing; however, these values do not correspond to the values in the clinical oral environment, because the speed of mastication is in range of 81–100 mm/s or 4,860–6,000 mm/min with a frequency of 1.03–12 Hz.[30]

Storage media in previous investigations were water or normal saline.[4] The storage temperature was 37°C and the shelf life also varied from 24 h to 10 weeks. In the present study, the samples were stored in an incubator at 37°C and 95% humidity for 1 week, and then subjected to 10,000 thermal cycles for artificial aging. They were soaked in 5°C cold water for 20 s and placed in 55°C warm water for 20 s in each cycle.[10] This may be one of the reasons for differences in the results of various studies. Undoubtedly, simulating oral conditions will never be fully possible in vitro.

Conclusions

The results of the study are limited by the laboratory conditions and further studies should be performed in a clinical setting. Within the limitations of this in vitro study, all surface treatment methods and different bracket base designs were able to provide sufficient shear bond strength on composite and amalgam surfaces. Considering bond strength in all groups, surface treatment by sandblasting is recommended in clinical activity due to its availability, lower cost and less injuries while working. In terms of bracket base design, according to ARI and bond strength, the use of each of the 3 base designs in the amalgam group and the use of the Star base design in the composite group are suitable.

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Retention of a telescopic overdenture on customized abutments after the simulation of 1 year in function

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Abstract

Background. Telescopic implant-retained overdentures are considered one of the most common treatment modalities for edentulous patients.

Objectives. The aim of the study was to evaluate the retention of a BioHPP (biocompatible high-performance polymer) telescopic overdenture supported by customized abutments made from 2 different materials after the simulation of 1 year in function.

Material and methods. Twelve models of a completely edentulous mandible were three-dimensionally (3D)-printed. Two implants and 2 groups of customized abutments – group Bio: BioHPP ($n = 6$) and group Ti: titanium ($n = 6$) – were used to support BioHPP telescopic overdentures. A vertically dislodging force was applied to each denture until its separation before and after 240,000 cycles of chewing simulation and 1,440 iterations of cyclic dislodgement for the simulation of 1 year in function in order to measure maximum tensile loads needed to dislodge the overdenture. Student's *t* test and the paired *t* test were used for the statistical analysis ($a = 0.05$).

Results. The initial and final retentive forces of the Ti group were significantly higher than in the case of the Bio group. A significant decrease in the retentive forces within the 2 groups after chewing simulation was observed and it was higher in group Ti; however, there was no statistically significant difference between the 2 groups.

Conclusions. The retentive force values for implant-retained telescopic overdentures significantly decreased after the simulation of 1 year of overdenture use. Both BioHPP and titanium are considered suitable abutment materials to retain telescopic overdentures.

Keywords: dental implants, titanium, overdenture, software design

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Introduction

Implant overdentures are the most common treatment modality for edentulous patients due to their efficacy in increasing retention, stability and masticatory performance, especially with the noted increased success rate in dental implant placement.[1] Among different types of overdenture attachments, the telescopic attachments used with implant overdentures are considered interesting and unique, as they give the dental practitioner the possibility of achieving more esthetic results while using fewer implants with less restricted implant location, better access for oral hygiene measures,[2,3] better horizontal stability due to their parallel wall design and exerting less torque, and better load distribution on the abutments due to their circumferential relation to the outer coping.[4] Telescopic overdentures are classified according to their mechanism of retention into 3 categories: parallel, conical and hybrid telescopic with an added retentive feature. In the 1st category, they gain retention through the friction of the parallel-milled surfaces. In the 2nd category, they obtain retention through friction, but only after their final seating with the so-called 'wedging effect'. In hybrid telescopic systems, an added retentive feature, such as the TC-SNAP system (the Marburg double-crown system), is used.[5,6]

The materials used for manufacturing implant abutments should have desirable biological, mechanical and esthetic properties. Titanium, gold and zirconium are the most well-known materials used in prefabricated abutments.[7] Titanium is considered the gold standard and is most frequently used, although it has several disadvantages, such as grayish color, corrosion susceptibility and oversensitivity reactions.[8] Gold abutments are not used nowadays despite their great biocompatibility due to their high cost and poor attachment to the soft tissue collar around implant platforms,[9] while zirconia abutments suffer from the risk of fracture of their apical part,[10] inconsistent long-term survival[11] and fretting wear.[12]

With the evolution of the computer-aided design and computer-aided manufacturing (CAD/CAM) technology, customized abutments are now easier to produce. The CAD/CAM process can optimally control the geometry of the abutment and adjust it to the optimum design to overcome the drawbacks of prefabricated abutments.

Customized abutments may be in the two-piece form (hybrid abutments); this type consists of a customized ceramic abutment that is cemented on a prefabricated titanium insert,[13] providing the titanium-to-titanium contact for a better fit. Unfortunately, bonding these customized abutments to their titanium bases is technique-sensitive.[14] Pre-milled abutments, which have been recently introduced into the dental market, are another option for abutment customization that could overcome the problems of previous offerings. These abutments are used in the digital production of CAD/CAM workflow, allowing the milling of implant abutments to a customized design with a pre-milled implant connection.

High-performance polymers are used nowadays in the fabrication of hybrid and pre-milled abutments. Biocompatible high-performance polymer (BioHPP) is one of such polymers; it offers a lot of unique properties, which makes it an interesting alternative to ceramic abutments. Its biocompatibility and excellent polishability[15] have a great impact on preserving bone height and soft tissues, which results in better anchorage.[16] It also has high mechanical and flexural strength, along with elasticity similar to bone.[17] BioHPP can be fabricated via pressing or milling. The material properties of pressed and milled BioHPP are virtually identical.[18]

Unfortunately, there is little previous research comparing these new materials as telescopic abutments for the retention of implant overdentures. This study was conducted to evaluate the retention of a BioHPP telescopic overdenture supported by titanium pre-milled abutments and BioHPP customized abutments after the simulation of 1 year in function.

The null hypothesis of this study was that there is no difference between titanium pre-milled abutments and BioHPP customized abutments in the retentive force of the overdenture before and after the simulation of 1-year function.

Material and methods

Model fabrication

A three-dimensional (3D) model of a completely edentulous mandible was designed with 2 implant beds in the canine region, equidistant from the midline and perpendicularly aligned to the ultimate occlusal plane to accommodate two 4.2 mm × 10 mm implants. A layer of a 2-millimeter thickness was removed from the surface of the model to be replaced with mucosa-simulating material later on. Twelve models were printed by means of an additive manufacturing technology. Two 4.2 mm × 10 mm implants were cemented at their planned sites in each model with a delicate layer of cyanoacrylate adhesive cement.

Mucosa simulation

A wax build-up was done on the model over the designed space for mucosa simulation. Then, the duralay resin pattern (Pi-Ku-Plast® HP 36; Bredent Medical, Senden, Germany) was adapted on the wax layer to act as a matrix. Wax elimination was performed and silicone-based soft tissue-replicating material (Multisil-Mask® soft; Bredent Medical) was applied, while the matrix was fixed on the model. After the material was completely set, a scalpel was used to finish and trim the excess of the soft tissue material.

Abutment fabrication

The Uni.fit scan abutments (Bredent Medical) were seated tightly on each implant and were scanned with a desktop scanner (InEos® X5; Sirona Dentsply, York, USA) to transfer the 3D implant position to the CAD software (Exocad, Darmstadt, Germany). In the CAD software, the design of the abutments was made, 4 mm in length with a wall taper angle of 2 degrees and a chamfer finish line. For the Bio group, wax was used for milling the abutments, which were invested and burnt out, and then BioHPP granules were pressed onto the titanium base, using the for-2-press system (Bredent Medical) to produce customized hybrid BioHPP abutments. For the Ti group, titanium prefab blanks (Bredent Medical), a type of pre-milled abutments, were used for milling. Six pairs from each group were fabricated and each pair was completely seated on the model. Figure 1 shows the final abutments on the model.

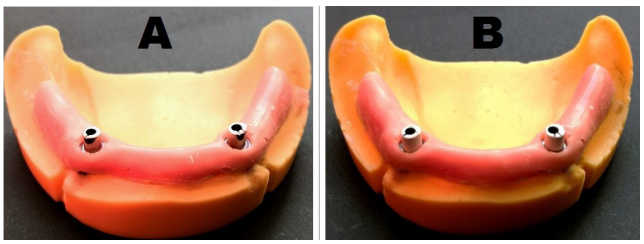

Fig. 1. Final abutments on the model
A – titanium; B – biocompatible high-performance polymer (BioHPP).

Framework fabrication

A wax pattern of a telescopic overdenture extending from the right first molar site to the left first molar site, including the secondary copings, was done for each model. The wax patterns were then invested and burnt out, and then BioHPP pellets were pressed using the for-2-press system to produce BioHPP frameworks. Each framework was finished and polished, and then returned to its model. Figure 2 shows the final BioHPP telescopic overdenture framework.

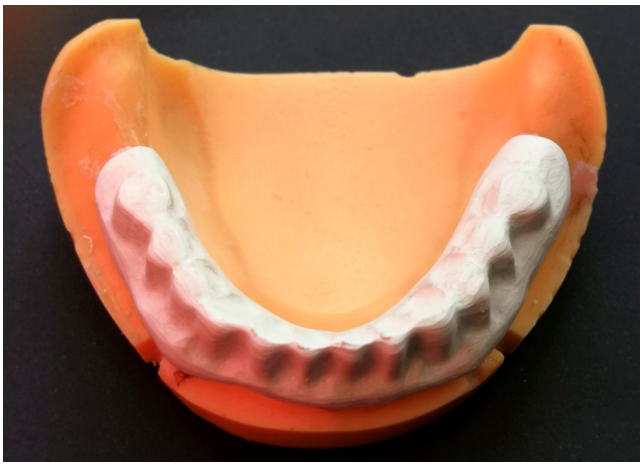

Fig. 2. Final BioHPP telescopic overdenture framework

Testing

A universal testing machine (Lloyd Instruments, Bognor Regis, UK) was used to apply vertical dislodging forces on a horizontal metal plate. A central hook was attached to the occlusal surface of each overdenture at a position 13 mm distal to the line passing through the implant center until it was elevated from its seating position. All groups were tested under the same conditions, i.e., moistening of the abutments and the fitting surface of the overdenture with artificial saliva (Glandosane®; STADAPHARM, Laichingen, Germany), as recommended by Bayer et al.,[19] and loading the overdenture with a compressive pre-weight of 50 N for 20 s. The machine was set at a constant crosshead speed of 50 mm/min. The initial pull-off test was done and maximum tensile loads needed to dislodge the overdentures from the cast model were calculated in newtons. Three measurements were performed for each overdenture and their mean was considered as the initial retentive value. Figure 3 shows the initial pull-off test.

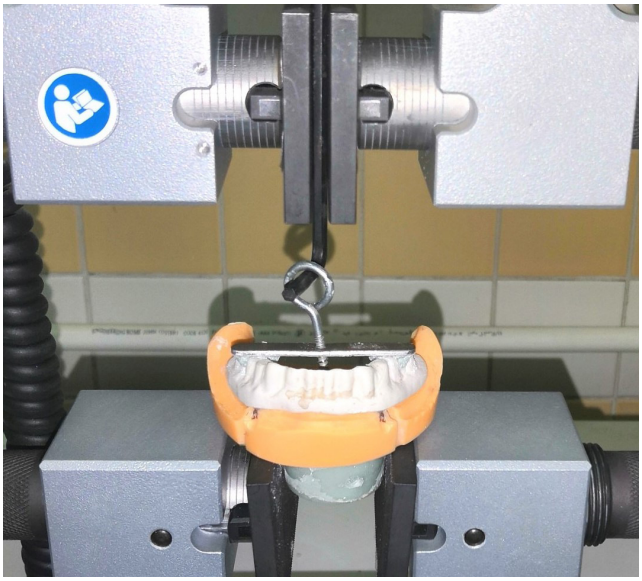

Fig. 3. Initial pull-off test

A chewing simulator (CS-4.4; SD Mechatronic, Munich, Germany) was used to apply dynamic/cyclic loading to each overdenture. The exact point of load application was marked at the center of the horizontal metal plate which was attached to the occlusal surface of each overdenture, as shown in Fig. 4. All groups were tested under the same conditions, i.e., filling the specimen chamber with artificial saliva and load settings of 49 N. The software parameters were set at 60 mm/s, 3 mm vertical path, 0.7 mm horizontal path, and 1.6 Hz according to the settings used in the previous studies which used implant-retained overdenture models.[20,21] Each overdenture was subjected to bi-axial cyclic loading for a total of 240,000 cycles in wet conditions at room temperature.

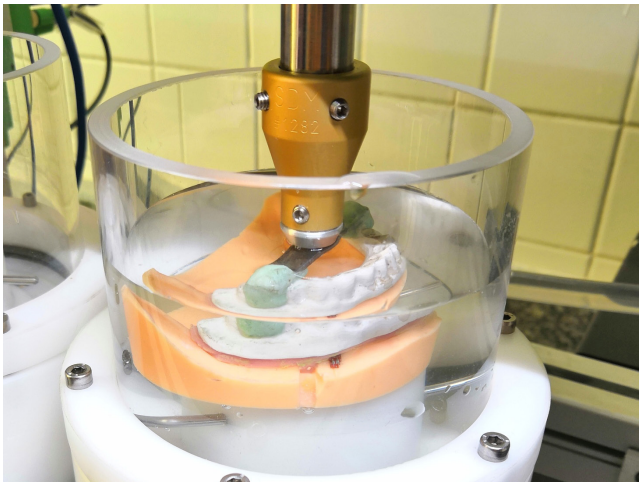

Fig. 4. Point of load application in the center of the metal plate

Each overdenture was inserted and removed 1,440 times, and mounted again in the universal testing machine to measure the final retentive force. Three additional measurements were performed for each overdenture and their mean was considered as the final retention value after the simulation of 1 year of overdenture use.

Data analyses were carried out using Student's *t* test and paired *t* test for comparisons between the 2 groups as well as to study changes within each group before and after the simulation of 1-year use. The significance level was set at $p \leq 0.05$.

Results

The retentive values calculated before chewing simulation were considered as the initial retentive forces, while those recorded after chewing simulation and cyclic dislodgment were considered as the final retentive forces. The mean reduction in the retentive forces in the 2 groups was calculated as percentage.

The mean initial retentive force for the Bio group was 6.19 N and for the Ti group – 16.64 N. The mean final retentive force for the Bio group was 5.26 N and 12.92 N for the Ti group. The mean percentage of the retention force reduction after the simulation of 1 year in function was 15.02% in the Bio group and 22.44% in the Ti group. The mean (*M*) and standard deviation (*SD*) values of the retentive forces in both groups are listed in Table 1. Figure 5 and Fig. 6 show the minimum, maximum and mean values of the retentive forces as well as the mean percentage reduction in the retention forces for both groups.

The statistical analysis showed that the initial and final retentive forces in the Ti group were significantly higher as compared to the Bio group ($p < 0.001$ and $p = 0.001$, respectively). There was a statistically significant decrease in the retentive forces after the simulation of 1 year in function in both groups (group Bio: $p = 0.041$; group Ti: $p = 0.004$). A higher percentage of reduction in the retention force was observed in the Ti group as compared to the Bio group, but there was no statistically significant difference between the 2 groups ($p = 0.216$). The results of Student's *t* test and the paired *t* test for changes in the retention force values for each group are listed in Table 2.

Table 1. Retention force values in the 2 groups

Variable	Abutment	*M* ±*SD*	*SEM*
Initial retentive value [N]	BioHHP (*n* = 6)	6.1933 ±2.01288	0.82175
	titanium (*n* = 6)	16.6367 ±3.38784	1.38308
Final retentive value [N]	BioHHP (*n* = 6)	5.2633 ±1.98457	0.81020
	titanium (*n* = 6)	12.9217 ±3.31107	1.35174
Percentage of reduction [%]	BioHHP (*n* = 6)	15.0245 ±10.15311	4.14499
	titanium (*n* = 6)	22.4444 ±9.30491	3.79872

M – mean; *SD* – standard deviation; *SEM* – standard error of mean.

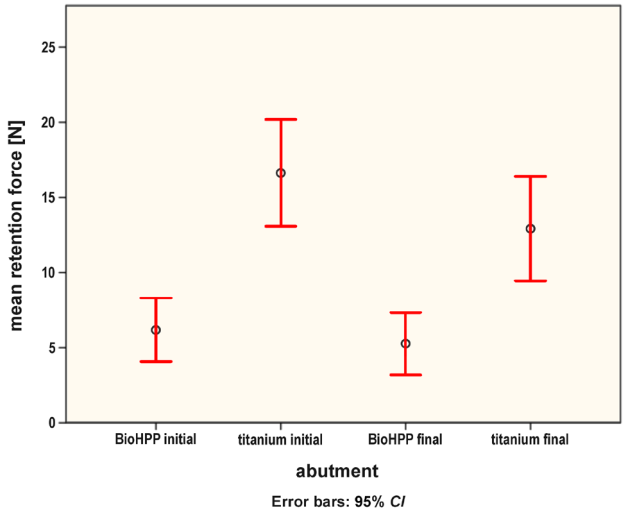

Fig. 5. Error bar showing the minimum, maximum and mean initial and final retention force values in the 2 groups

CI – confidence interval.

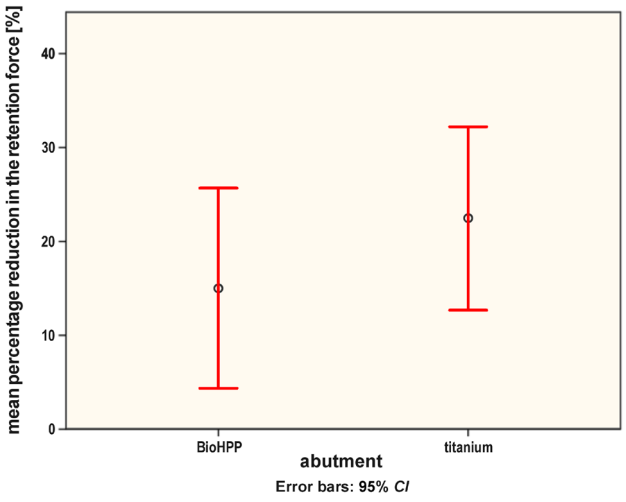

Fig. 6. Error bar showing the minimum, maximum and mean percentage reduction in the retention force values in the 2 groups

Table 2. Results of Student's *t* test and the paired *t* test

Retention force	*t*	df	*p*-value	95% *CI* of the difference	
				lower	upper
Initial (BioHPP * titanium)	–6.491	10	0.000	–14.02793	–6.85874
Final (BioHPP * titanium)	–4.860	10	0.001	–11.16977	–4.14690
Percentage of reduction in the retention force (BioHPP * titanium)	–1.320	10	0.216	–19.94736	5.10754
BioHPP (initial * final)	2.739	5	0.041	0.05719	1.80281
Titanium (initial * final)	4.943	5	0.004	1.78296	5.64704

df – degrees of freedom.

Discussion

The experimental models in this study were manufactured using the 3D printing technology, as it offers the operator freedom in choosing every detail in the model, including the location of implant beds.[22] The abutments of the 1st group were fabricated from pressed BioHPP on a titanium base. It has been established that BioHPP can be used as an alternative material for the fabrication of abutments and prosthetic restorations, as it has a modulus of elasticity similar to human bone and a hardness value of 30–40 HV,[23] in addition to its good mechanical properties.[17] Titanium pre-milled abutments were chosen in the 2nd group. Titanium is considered the gold standard abutment material; it is characterized by high mechanical and wear resistance with a hardness value of 350–370 HV.[23] Besides, pre-milled abutments allow for free customization of the abutment design.

The design of the abutments was prepared with a wall taper angle of 2 degrees and a chamfer finish line for better adaptation and fitting between the copings, and to increase the retention forces.[24] Glandosane was used as artificial saliva due to its unique effect on the retention force of the telescopic attachment and its role in simulating real oral conditions – specifically its tri-biological effect on the materials and the removal of debris from the wear and tear of the materials.[18,19,25] To simulate 1 year of function, the number of chewing cycles in this study was 240,000, which was based upon the average number of chewing cycles expected in a year.[26] Accordingly, the overdentures were inserted and removed 1,440 times, as if they were placed and removed 4 times per day for a year.[27]

Our results rejected the null hypothesis, as they revealed higher initial and final retentive force values in the Ti group over the Bio group. The difference in the initial retentive forces could be attributed to the pressing process of BioHPP abutments, which was complicated, with many potential sources for errors. Also, the higher final retentive force values in the Ti group could be due to the already higher initial retentive forces as compared to the Bio group.

It has been postulated that any attachment system is subjected to functional loads; it can be attributed to the friction between the telescopic copings, which leads to lowering the retentive force values. Several studies reported a decrease in the retentive force values of different telescopic attachments at the end of the experimental procedures, which supports the results of the present study.[19,24,28] Also, it has been postulated that the retentive force should be at a level that will not damage the implants or the bone. Furthermore, it has been recommended that the retentive forces in telescopic overdentures should be kept within the range of 5–10 N.[25] Both groups in our study attained their final retentive force values within the recommended range.

A decline in the retentive force values after the simulation of 1 year of overdenture use was higher in the Ti group as compared to the Bio group. This may have resulted from the wear which occurred in the fitting surfaces of the framework after the simulated functional use in the Ti group due to a difference in the hardness values between the 2 materials. In the Bio group, mechanical adaptation between the primary and secondary copings with the same hardness values resulted in less wear, in addition to strong wedging action between the 2 copings after functional use.[25,29] However, there was no significant difference in the decrease of the retentive force values after the simulation of 1 year of overdenture use between the 2 groups.

Conclusions

Within the limitations of the study, it can be concluded that in implant-retained telescopic overdentures supported by 2-degree angle abutments, the retentive force values significantly decreased after the simulation of 1 year of overdenture use. BioHPP and titanium are both considered suitable materials for customized abutments to retain BioHPP telescopic implant overdentures.

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Effect of different geometric changes in the dental implant abutment body on the amount of residual excess cement and retention in a cemented implant-supported prosthesis

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Abstract

Background. Fixed implant-supported restorations are mainly used in dental implantology. In comparison with screw-retained implants, cement-retained prostheses have the following advantages: the ease of splinting implants; increased passive casting; and procedural similarity to conventional tooth-supported fixed partial dentures. Furthermore, they show reduced fracturing of components with better esthetic outcomes and an improved force direction, along with a reduced cost and less chairside time.

Objectives. The aim of this study was to evaluate the effect of different geometric changes in the dental implant abutment body on the amount of residual excess cement (REC) and the retention of cemented implant-supported prostheses.

Material and methods. Seventy-two straight abutments were categorized into 4 groups: vertical groove; 1 horizontal groove; 2 horizontal grooves; and ccontrol (with no geometric changes in the abutment). The access hole was partially filled and the cast copings were cemented using Temp-Bond™ NE, a non-eugenol cement. The difference in weight before and after removing the excess cement was considered as REC. Furthermore, the retention of the cast coping was measured as the force that was required to separate the cemented cast coping from the abutment.

Results. The mean REC values of the groups with 1 and 2 horizontal grooves were significantly different as compared to the control group ($p < 0.05$).

Conclusions. This study shows that the presence of 1 or 2 horizontal grooves in the abutment body significantly reduces the amount of REC in comparison with control.

Keywords: dental implants, cement, abutment type

Introduction

Implant-supported fixed dental prostheses are a good treatment choice, which has developed into a standard of care in dentistry. This achievement may be due to the osseointegration process and the improved stability of the interfaces between the implants, the abutments and the dental prosthesis.[1] Fixed implant-supported restorations are usually retained on abutments with screws or cement.[2] Both abutment types have their own benefits and drawbacks. It is the clinician's responsibility to decide on the most suitable technique for each individual case.[1] A recent systematic review found that the retention type (cement or screws) might not have a critical effect on the general survival of the prosthesis, but rather was responsible for the development of certain complications.[3] In comparison with the screw-retained type, cemented prostheses have the following advantages: the ease of splinting implants; increased passive casting; and procedural similarity to conventional tooth-supported fixed partial dentures.[4] Additionally, they show reduced fracturing of components with better esthetic outcomes and an improved force direction, along with a reduced cost and less chairside time.[2,5,6] Investigators have concluded that the cement retention method is preferred over the screw-retained abutment type in the following cases: short-span prostheses with margins at or above the mucosa level; inappropriately inclined implants; and narrow-diameter crowns.[1]

The main disadvantage of cemented prostheses is residual excess cement (REC), which can cause the inflammation of soft tissues around the implant.[7,8] Multiple research studies have shown that REC around the implant can result in a rough surface and facilitate plaque accumulation, and consequently damage soft tissues around the implant due to bacterial colonization.[6] Several techniques have been proposed to reduce the amount of REC, such as minimizing the amount of cement used,[9] creating a vent hole,[9,10] using cements of higher viscosity, applying modified cementation methods, or the selective removal of the abutment walls.[11,12]

Changing the design of the abutment body is another method explored in some studies.[6,13] Various modifications in the geometric design of the abutment body have been investigated, like the creation of a vent hole or a groove. Such changes made to the abutment body can act as an internal vent that may reduce REC.[6,8]

Unreliable retention is another concern about cemented restorations.[14] To circumvent this drawback, the following methods to increase the retention rate have been proposed: changes in the abutment surface texture; modified cementation methods; and the selective removal of the abutment walls.[13,14] The abutment surface can be changed by creating grooves. Such changes can reduce REC and improve the retention of the prosthesis.[12]

Objectives

The aim of the present study was to investigate how different geometric changes in the dental implant abutment body influence the amount of REC and the retention of cement-retained implant restorations. The null hypothesis stated that all of these modifications could reduce REC and increase the retention of cement-retained implant restorations.

Material and methods

Abutment modification

The sample size was calculated with the Power and Sample Size Calculator (PS) software, v. 3.1 (https://ps-power-and-sample-size-calculation.software.informer.com/3.1/) as 13 samples per group (n = 13). This was based on the results of a study by Wadhwani et al.,[6] with α = 0.05 and a power of 80%. To increase the validity of the study, 18 samples were considered for each group, resulting in a total of 72 samples. The straight abutments (OSSTEM®; Osstem Implant, Busan, South Korea) used in this study were 5.5 mm in length, 4.5 mm in diameter and 1 mm in gingival height.

Coping fabrication

In order to mold the coping crown, the access holes of the abutments were carefully blocked out with wax during the laboratory procedures. For uniformity between the study groups, a three-dimensional (3D) printer was used to design the coping patterns. Since the abutments were similar prior to implementing the changes, one of the abutments was scanned using a Maestro® 3D scanner (AGE Solutions, Pontedera, Italy), and then designed with the Exocad software (Exocad, Darmstadt, Germany), considering a cement space relief of 50 µm. After that, the scanned and designed copings were made with a 3D printer (Prodent® 3D printer; Bonyan Mechatronic, Tehran, Iran) and a light-curing moldable 3D resin (Freeprint® cast; Detax, Ettlingen Germany), and casted with base metal alloys (Sankin®, non-beryllium; Dentsply Sirona, Tokyo, Japan). The cast copings were examined under an optical microscope (Nikon, Tokyo, Japan) at ×20 magnification to assist in adaptation to their corresponding abutments and any irregularities were removed with a milling round of ½. A vertical mark was created on the copings in the corresponding area of the flat side of the abutments to guide the placement of the copings on the abutments.

The abutments were tightened with the ratchet of the OSSTEM system by using a torque of 25 N·cm on the fixture analogs of the same system and mounted

in acrylic blocks to help with the operation. Each of the 4 study groups contained 18 individual abutments with the indicated modifications. In group 1, each abutment had a vertical groove measuring 0.5 mm × 0.5 mm from the occlusal surface of the abutment up to 1 mm above the finish line; it was created with a bur (KaVo Dental, Biberach, Germany). Each abutment of group 2 had a horizontal groove (0.5 mm × 0.5 mm) that was created at a distance of 3 mm from the occlusal edges. The abutments of group 3 had 2 horizontal grooves (0.5 mm × 0.5 mm) with a 1-millimeter distance. The control group (group 4) consisted of 18 abutments with no changes in the abutment body.

Cementation

Before cementation, the abutment screw access channel was filled up to 1 mm on the occlusal surface with Coltosol® (Coltène/Whaledent, Altstätten, Switzerland). To measure the amount of REC, the weight of coping/abutment/analog/acrylic block was determined with an A&D scale (EK-300i; A&D Company, Tokyo, Japan). A dental cement (Temp-Bond™ NE; Morris Dental Company, Dublin, Ireland) was mixed according to the manufacturer's instructions and applied to the intaglio surface until the coping was filled in approx. 75%. The weight of coping/abutment/analog/acrylic block with cement was then measured before placing the coping on the abutment. Next, the copings were placed – initially by finger pressure – on the mounted abutments, followed by a pressure of 5 kg for 7 min with a universal testing machine (model HSK-S; Hounsfield Test Equipment, Redhill, UK). The excess cement was then removed with a plastic scaler and coping/abutment/analog/acrylic block was weighted again after cleaning (Fig. 1).

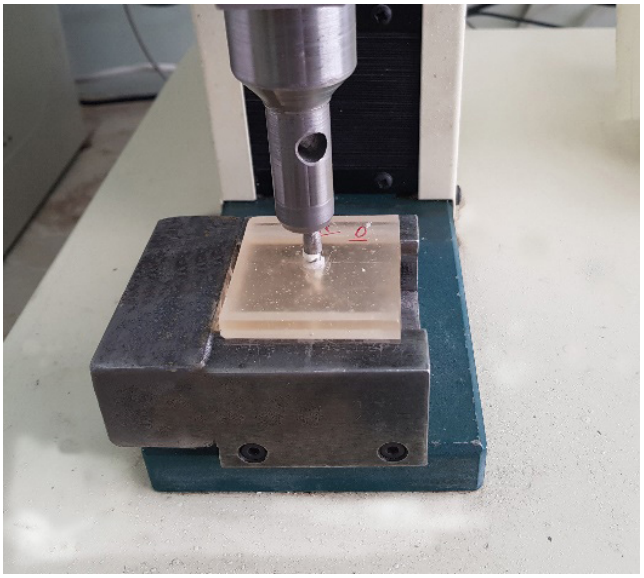

Fig. 1. Cementation process

REC evaluation

The following formula was used to measure REC (Equation 1):

$$\begin{aligned} \text{REC} = {} & (\text{weight of coping/abutment/analogue/acrylic block after cementation and removing excess}) \\ & - (\text{weight of coping/abutment/analogue/acrylic block with cement before cementation}) \end{aligned} \quad [\text{gr}] \ (1)$$

Evaluation of retention

The samples were then incubated at 37°C and 100% relative humidity for 24 h. The specimens were assembled in a universal testing machine and subjected to a pull-out test (retention) at a crosshead speed of 1 mm/min. The force required to remove the copings was recorded in newtons (Fig. 2).

Fig. 2. Evaluation of the retention

Statistical analyses

Data was analyzed using descriptive statistical methods (mean (*M*) ± standard deviation (*SD*)), and then compared between the groups. The normality of data was analyzed with the Kolmogorov–Smirnov test. Statistically significant differences between the studied groups in the mean REC values were investigated with the Kruskal–Wallis test. Statistically significant differences between pairs of groups were analyzed using the Mann–Whitney *U* test. The statistical analyses were carried out by means of the SPSS Statistics for Windows, v. 17.0 (SPSS Inc., Chicago, USA), and a p-value <0.05 was considered statistically significant.

Results

The *M* and *SD* values for the 2 variables – REC and retention – in the study groups are presented in Table 1. We found that the mean REC value was the highest in the 'no groove' control group. Group 3 (2 horizontal grooves) showed the lowest mean REC value. The mean retention value was the highest in group 3 (2 horizontal grooves) and the lowest in group 1 (vertical groove).

Table 1. Residual excess cement (REC) and retention in the study groups

Variable	Group	*M*	*SD*	*p*-value
REC [gr]	vertical groove	0.0450	0.01295	0.002[1]*
	1 horizontal groove	0.0406	0.01349	
	2 horizontal grooves	0.0367	0.01029	
	no grooves	0.0544	0.01464	
	total	0.0442	0.01432	
Retention [N]	vertical groove	103.8444	13.37945	0.102[2]
	1 horizontal groove	111.3833	25.33394	
	2 horizontal grooves	119.1944	19.39701	
	no grooves	108.4944	13.95609	
	total	110.7292	19.10013	

M – mean; *SD* – standard deviation; [1] Kruskal–Wallis test; [2] one-way ANOVA; * statistically significant.

The normal distribution of the 2 variables – REC and retention – was analyzed using the Kolmogorov–Smirnov test and we found that the distribution of the REC variable was not normal; therefore non-parametric tests were used to examine the associated hypotheses ($p < 0.05$). Additionally, we found that the distribution of the retention variable was normal, and therefore parametric tests were used to examine the associated hypotheses ($p < 0.05$). Figure 3 shows REC for the study groups and Fig. 4 shows retention for the study groups. To examine if there was any statistically significant difference between the studied groups in the mean REC values, the Kruskal–Wallis test was used. The results showed a statistically significant difference in the REC means between the study groups ($p < 0.05$) (Table 1). The Mann–Whitney *U* test was then used to compare the groups with each other; the results are presented in Table 2. There were statistically significant differences in the REC means between the 'no grooves' control group and groups 2 and 3 – with 1 and 2 horizontal grooves, respectively. The mean REC value in the 'no grooves' group was higher than the means in those 2 groups ($p < 0.05$). The mean REC value in the 'vertical groove' group was significantly higher as compared to the group with 2 horizontal grooves ($p < 0.05$). There were no statistically significant differences in the REC means between other

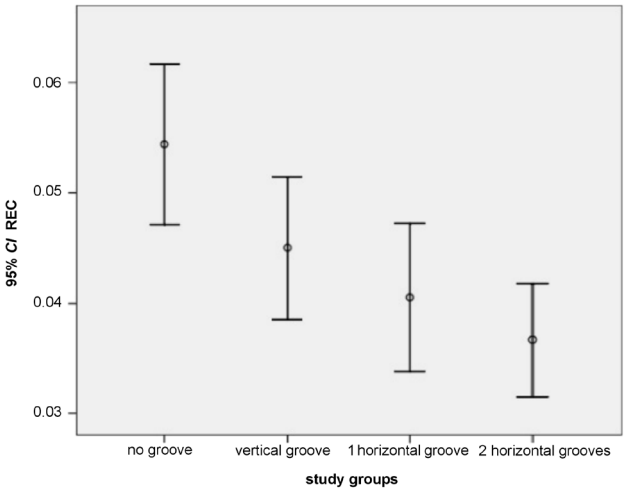

Fig. 3. Residual excess cement (REC) in the study groups
CI – confidence interval.

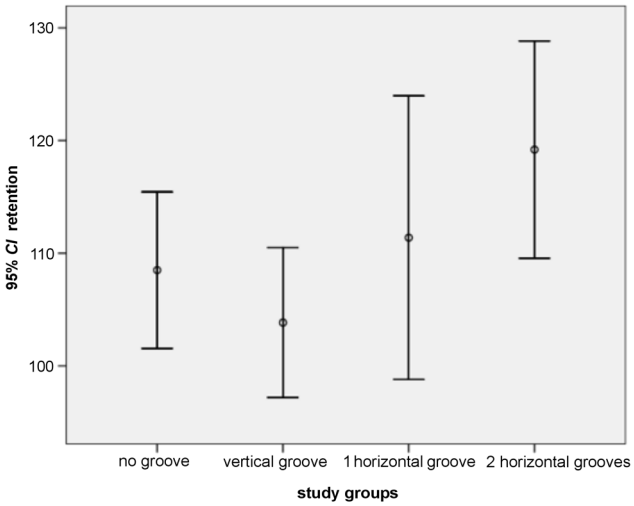

Fig. 4. Retention in the study groups

study groups. To test any statistically significant difference in the mean retention between the study groups, the one-way analysis of variance (ANOVA) was used. There was no statistically significant difference in the mean retention between the study groups (Table 1).

Table 2. Comparison of the mean amount of residual excess cement (REC) among the study groups (Mann–Whitney *U* test)

Group comparisons		*p*-value
No grooves	vertical groove	0.060
	1 horizontal groove	0.007*
	2 horizontal grooves	<0.001*
Vertical groove	1 horizontal groove	0.256
	2 horizontal grooves	0.043*
1 horizontal groove	2 horizontal grooves	0.489

* statistically significant.

Discussion

Implant treatment can be a challenging clinical condition, which requires a high level of communication between the surgeon, the technician and the restoring dentist.[15,16] Today, cement-retained implant-supported prostheses are widely used. However, they might have disadvantages in comparison with screw-retained ones, including REC and unreliable retention after cementation. The present study aimed to introduce modifications in the abutment that would address these problems.[17–19]

The main disadvantage of cement-retained implant-supported prostheses is REC, which can cause the inflammation of soft tissues around the implant.[5,7,8] Various studies have shown that REC around the implant may result in a rough surface and facilitate plaque accumulation, and damage soft tissues around the implant due to bacterial colonization.[5,7] A cohort study found that the direct cause of damage in 80% of the soft tissues surrounding the implant was due to the colonization of bacteria on the excess cement.[6] For this reason, numerous studies have investigated methods that reduce REC.

In this study, the null hypothesis about the effect of the changes made in the abutments on the amount of excess cement was rejected, and we found that only the addition of horizontal groove(s) to the abutment body resulted in reduced excess cement. On average, the amount of excess cement in the group with 1 horizontal groove was 0.0406 gr, while it was 0.0367 gr in the group with 2 horizontal grooves. Both values were statistically significantly different as compared to the control group (0.0544 gr; $p < 0.05$). We propose that perhaps horizontal grooves act as a reservoir and because of the circumferential shape around the abutment, they house some excess cement during the insertion of the coping. However, a vertical groove is created only in a specific area, and its function is limited and localized. Additionally, the groove might facilitate cement exit before filling the superior space of the screw hole.

Based on the reports, creating a groove in the abutment body can increase the retention of the crown and reduce the amount of REC without weakening the abutment.[6,8] However, in this study, we found that the mean retention was higher in the group with 2 horizontal grooves as compared to other groups and lower in the 'vertical groove' group. Nonetheless, this failed to reach statistical significance when analyzed using the one-way ANOVA. This may be explained by the dimensions of the created grooves. Lewinstein et al. designed grooves during the construction of the abutment, which allowed them to design larger grooves.[13] However, in this study, the abutments were prefabricated, and therefore it was not possible to create a deep groove without affecting the abutment body resistance. The use of cements of higher fracture strength in these conditions might reveal the effect of creating such grooves on increasing retention. In recent years, some studies reported the importance of creating grooves together with other modifications. In a recent study by Shrivastav, the influence of different surface modifications on the retention of a zinc phosphate cement-retained implant was investigated.[20] The work investigated the effects of circumferential grooves with sandblasting (group 1) and with a bur modification (group 2) against control (group 3). It was shown that modifications in group 2 resulted in improving the retention of a bridge cemented on implant abutments.[20] Sahu et al. reported that abutments with the milled and sandblasted modifications exhibited the highest retention, followed by abutments with retentive grooves, and then by abutments with the milled surfaces once the cast copings were cemented to implant abutments with a polymer-based cement.[21]

There are no specific guidelines available on the appropriate amount of cement to be used. Using a minimal amount of cement might decrease the cement rejection rate, but this method can result in problems such as inadequate retention and leakage.[5,9,14] Similarly, excessive amounts of cement can cause problems such as the inappropriate placement of the coping and high REC values.[14] However, the amount of cement used in this study was greater than the amount needed for flooding the relief space between the coping and the abutment. Although various methods have been proposed to adjust the appropriate cement amount, for clinicians, the control of the cement amount during the clinical stages is uncertain.[22] Moreover, the amount of cement used in this study is the most commonly used for the cementation process by clinicians.[10] Modified cementation methods are another option to reduce REC.[11,12] Such methods, despite being effective in reducing REC, might not be clinically feasible due to their time-consuming nature, especially in cases with higher number of implants. One method is to seat the restoration filled with cement on a mock abutment (an analog abutment) extraorally. This abutment could be a stock analog or a customized analog made from polyvinyl siloxane.[14] Recently, Chee et al. explored 4 cementation methods for their effect on the amount of excess cement.[12] They studied the cementation of the internal marginal area of the crown (group 1), cementation on the apical half of the axial walls of the crown (group 2), cementation to all axial walls of the interior surface of the crown, excluding the occlusal surface (group 3), and in group 4 – the crown filled with cement, and then seated on the putty index formed to the internal configuration of the restoration (a cementation device). The least amount of excess cement was found in group 4. The authors concluded that this method led to a uniform layer of the luting agent, which might be due to the internal surface of the crown leaving minimal excess cement when the restoration was seated.[12]

The creation of a vent hole in the restoration surface is also proposed to reduce REC.[8,13] Although this modification was introduced initially to reduce the seating discrepancies in tooth-supported restorations, it was found

to have a negative effect on the integrity of the crown structure. Additionally, complex laboratory procedures are needed for its construction, after which it requires to be restored again by the dentist in the clinic.[14] In a study by Wadhwani et al., a change in the abutment body as 2 opposite double-sided holes in the axial wall of the abutment was more effective than a normal abutment in decreasing REC, as the hole was used as a means to transfer cement to the abutment screw access space.[6] In a finite element study by Rodriguez et al., an abutment design with 8 holes in the abutment margin area improved the pattern of the flow of cement into the abutment screw access space, thereby decreasing the rejection rate of the cement.[8] Recently, Chen et al. tested the effect of a vent hole on the retentive force of a restoration. They showed that the retentive force of restorations with a vent hole was equal to or better than of those without a vent hole.[23]

Different methods have been proposed to block the abutment screw access hole, but there are currently no guidelines in this regard. Studies have shown that the partial filling of the screw access channel can act as a reservoir for excess cement and can also increase the retention of the restorations cemented with a temporary cement.[24] In this study, some space within the abutment was preserved to prevent further rejection of cement and increase the retention, in addition to relative re-accessible blocking.

Unreliable retention is another concern about cemented restorations. The main factors affecting retention include abutment dimensions, framework properties and the characteristics of the cement used.[14] In some circumstances, like small occlusogingival dimensions, where procedures are limited, other methods, such as changing the surface of the abutment body, are used.[14]

Changing the abutment surface texture by sandblasting also increases the retention of the crown, but this method is not quite feasible in commonly used implants. Additionally, the selective removal of the abutment walls increases retention by decreasing taper and creating vertical walls.[10,13,14] However, this method increased the odds of abutment body weakening.

Conclusions

The purpose of the current study was to assess how different geometric changes in the dental implant abutment body influence the amount of REC and the retention of cemented implant-supported prostheses. It was found that the REC means in groups 2 (1 horizontal groove) and 3 (2 horizontal grooves) were statistically significantly different from control group 4 (no grooves) ($p < 0.05$). There was a significant difference between the lowest mean REC value (group 1) and the highest mean REC value (group 3) ($p < 0.05$). However, 1 and 2 horizontal grooves in the abutment body effectively reduced REC in comparison with other groups.

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One year into the COVID-19 pandemic – temporomandibular disorders and bruxism: What we have learned and what we can do to improve our manner of treatment

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has drastically changed the routine way of life and challenged the ways in which health and dental services are provided. During the 1st lockdown, practiced in most of the countries, routine dental procedures were suspended. Even after the lockdown was eased, visiting crowded dental clinics was still considered health-threatening, especially among populations at high risk of developing a severe reaction to COVID-19. Regretfully, in most cases, temporomandibular disorders (TMD) and bruxism were not included under the definition of emergency, leaving many patients without the possibility of consulting their dentists.

A literature search, performed about 10 months after the declaration of the pandemic, found only a few studies dealing with TMD and bruxism during COVID-19. Most of the studies indicate adverse effects on subjects' psycho-emotional status (stress, anxiety, depression), which in turn lead to the intensification of subjects' TMD and bruxism symptoms, and increased orofacial pain. Unlike other oral pathologies, which require manual interventions, chronic orofacial pain can be addressed, at least at its initial stage, through teledentistry and/or consultation.

Remote first aid for patients suffering from orofacial pain includes various kinds of treatment, such as the self-massage of tense and painful areas, stretching, thermotherapy, drug therapy, relaxation techniques, meditation, and mindfulness, all of which can be administered through the phone and/or the Internet. Relevant legal and ethical issues should be considered while using remote modes for the triage, diagnosis and treatment of chronic orofacial pain patients.

Keywords: bruxism, temporomandibular disorders, orofacial pain, COVID-19, teledentistry

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Introduction

About a year ago, the World Health Organization (WHO) was informed of cases of pneumonia of unknown cause in Wuhan, China. A novel coronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified as the cause.[1] On March 11th, 2020, due to a rapid increase in the number of cases outside China, WHO announced that the outbreak could be characterized as a pandemic. By mid-March 2020, the WHO European region had become the epicenter of the respiratory coronavirus disease 2019 (COVID-19) epidemic, reporting over 40% of the globally confirmed cases.[1] At the time of this review being written, COVID-19 cases worldwide reached 78,065,178, causing the death of over 1,716,170 people.[2]

Following WHO's declaration of pandemic and due to uncertainty about the ways of spread, efficient treatment and the lack of vaccine, most countries adopted social distancing policies and partial to total lockdown.[3] Routine everyday life was drastically altered and has not gone back to normal yet. This situation gave rise to severe health threats, economic uncertainty and social isolation, each of them with a potential of severe deleterious effects on both the physical and mental health of people.[3]

The COVID-19 pandemic has challenged the existing healthcare systems across the globe in general, and in particular, the way dental care is provided. The primary mode of spread of the virus is via respiratory droplets, which puts dentists at the spearhead of infection.[4] As a result, during the 1st lockdown, routine dental procedures were suspended in most countries. Only emergency dental procedures, specified by WHO and the American Dental Association (ADA), were authorized.[5] In most countries, dentists were instructed to limit their practices to emergency and urgent dental care.[6] Regretfully, temporomandibular disorders (TMD) and bruxism were not considered as such, leaving many patients without the possibility to consult their dentists in moments they might have needed them the most.

Temporomandibular disorders and bruxism are often associated with psychosocial factors, such as stress, anxiety, depression, and catastrophizing.[7–16] The TMD-related pain affects the daily activities and quality of life of numerous individuals worldwide.[17]

Bruxism (at daytime and/or during sleep) poses similar problems. A recent review demonstrated that patients with high levels of stress were almost 6 times more likely to report awake bruxism. Researchers explained the sustained muscle contraction as a fight-or-flight reaction and implicated that awake bruxism could be part of the defense behavior occurring in times of stress and anxiety.[18]

Undoubtedly, the COVID-19 pandemic has caused significant distress to billions of individuals worldwide. The most common psychosocial responses to the pandemic are stress, anxiety and depression.[3]

Objective

The aim of the study was to review the initial existing literature on TMD, bruxism and orofacial pain during the COVID-19 pandemic – signs and symptoms, triage, diagnosis, and management during times of psychological tension, immediate health hazards and social isolation.

Method

A data search was performed using the PubMed and Quertle databases, applying the following keywords: "COVID-19" and/or "coronavirus" in combination with "TMD", "bruxism", "orofacial pain", and "teledentistry".

The selection criteria were original research and/or review articles in the English language, published between March 1, 2020 and November 30, 2020, and relevant publications extracted from them. The final review was based on 13 items fulfilling the inclusion criteria.

Results and discussion

A cross-sectional online survey conducted in Israel and Poland during the 1st lockdown period showed adverse effects on the psycho-emotional status of both Israeli and Polish populations, and the intensification of subjects' TMD and bruxism symptoms, leading to increased orofacial pain.[19] Data arising from the COVID-19 literature supports the aggravation of signs and symptoms of TMD and bruxism among the general population and TMD patients.[19–21]

A survey conducted in China, which compared TMD patients to the general population and a population of orthodontic patients, concluded that during the pandemic, TMD patients exhibited higher levels of psychological distress than the other 2 populations.[22] Factors such as young age, female gender, concerns about isolation, psychological barriers, and distrust were found to be associated with a high level of psychological distress and TMD pain.[22] The authors suggested that their findings were due to higher levels of sympathetic activity and the release of adrenocortical steroids, leading to vasoconstriction and increased peripheral vascular resistance, triggered by the emergency and threatening situation caused by the pandemic.[22] The autonomic impairment may have also led to increased sympathetic drive and the hyperarousal sensation, which create and perpetuate sleep disturbances, and this in turn may explain the aggravation of sleep bruxism.[23] Additionally, a case–control study conducted among ambulatory non-hospitalized patients, who were quarantined in a designated hotel for COVID-19 patients, found that facial pain was more common among women than men.[24]

According to Almeida-Leite et al., orofacial specialists should be aware of a greater risk of developing, worsening and perpetuating TMD and bruxism (mainly awake bruxism) due to COVID-19.[20] The authors suggest that guidelines for patient education, self-management, home care, and relaxation techniques, which are already available on the Web, can be useful tools in times of isolation.[20]

Unlike other oral pathologies, which require immediate manual interventions (i.e., caries, pulpitis, a periapical abscess, etc.), chronic orofacial pain originating from TMD and/or bruxism can be addressed, at least at its initial stage, through teledentistry and/or consultation.

Telemedicine refers to the use of information-based technologies and communication systems to deliver healthcare across distances.[25] Teledentistry is not a new concept in dentistry and was used by the US military as early as in 1994.[26] Video communication was found to be feasible and effective in chronic disease management.[27]

Today, software such as WhatsApp, Zoom, Skype, and many others may help triage, diagnose and treat various conditions.[28] Lv et al. suggested video conferencing guidelines and a flow chart to help dentists in decision-making at times when face-to-face consultation is prohibited and crowded waiting rooms are health-threatening, as during COVID-19.[28] Patel et al. developed an algorithm to utilize guidance from the Centers for Disease Control and Prevention (CDC), which can help decide if in-office consultation is essential or a telehealth visit is sufficient.[29]

As most of the instruments for the initial diagnoses of TMD and bruxism are already carried out via self-report questionnaires,[30–32] teledentistry may provide additional visual parameters, such as the verification of the range of motion, indicating painful areas, etc.

First aid for TMD patients can include conservative kinds of treatment, such as the self-massage of tense and painful areas of the masticatory muscles, which can be demonstrated via teledentistry or a link to a video demonstrating such exercises may be provided. Other techniques may include mandibular relaxation and coordination exercises, stretching, and thermotherapy.[33] Drug therapy, relaxation techniques, meditation, and mindfulness can all be administered through the phone and/or the Internet, and help subjects deal with the painful condition, reduce catastrophizing and improve quality of life.[34–36]

One accepted mode to manage bruxism is based on increasing the patient's awareness of the syndrome (especially for awake bruxism). The methods include monitoring via the Ecological Momentary Assessment (EMA) applications for smartphones, such as the BruxApp application,[37] which can help monitor the bruxing behavior and act as biofeedback. All of these can be easily administered through video communication, namely, teledentistry.

Telemedicine and teledentistry are relatively new entities, which have expanded substantiality during the pandemic. Unfamiliar legal and ethical issues may arise. Chang et al. point out that patients should be acknowledged that, even if slight, a possibility exists that the transmitted information can be intercepted.[38]

Another issue, which should be addressed, is that of informed consent. As nothing replaces the gold standard evaluation of a clinical examination, informed consent should cover not only the traditional consent text, but also the possibility of the inherent risk of improper diagnosis and/or treatment. Furthermore, medico-legal, copyright, fiscal, and taxation issues should also be considered concerning the information exchange.[39,40]

Hopefully, the mass vaccination of the population has already started, bringing hope for a better and healthier year to come. Nevertheless, there are lessons to be learned from the pandemic. Dentists and orofacial pain specialists should adopt at least some of the new strategies, technologies and guidelines for remote treatment. This will not only ease the provision of treatment to remote populations, who lack immediate access to dental clinics, but also make us better prepared for possible future health crises. Further research should focus on providing clear guidelines for the triage, diagnosis and treatment of chronic orofacial pain, TMD and bruxism through teledentistry.

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The COVID-19 pandemic, heart and cardiovascular diseases: What we have learned

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Abstract

In 2020, the coronavirus disease 2019 (COVID-19) pandemic overwhelmed the world, temporarily paralyzing healthcare and economic systems. Until now, we have learned a lot about the symptoms, pathophysiology, and complications of the disease as well as about the laboratory findings concerning the disease, and we are rapidly acquiring new data on the influence of COVID-19 on other aspects of human health beside its effects on the respiratory system. Patients with co-existing cardiovascular diseases (CVD) are more frequently hospitalized, more likely to be treated in an intensive care unit (ICU) and have poorer prognoses.

In this article, we discuss the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on CVD, starting from the mechanisms connected with the renin–angiotensin–aldosterone system (RAAS) and the angiotensin-converting enzyme 2 (ACE2) receptors, and then describing the main pathologies in the heart and vessels detected in patients with COVID-19. Additionally, we comment on the problem of acute coronary syndrome (ACS), which may be triggered by viral infection. Finally, we discuss how, in some countries, the pandemic has changed treatment patterns, lowering the rate of invasive diagnostics and even falsely reducing the prevalence of CVD as a result of patients' fear of being admitted to hospital.

Keywords: cardiovascular diseases, COVID-19, SARS-CoV-2

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Introduction

Since December 2019, when the first case of viral pneumonia was reported in Wuhan, China, coronavirus disease 2019 (COVID-19) has become a global pandemic. As of December 17, 2020, there were 45,942,902 confirmed cases of COVID-19, including 1,192,644 deaths worldwide according to the World Health Organization (WHO).[1] In Poland alone, as of December 17, 2020, there were 62,731 confirmed cases of COVID-19, including 5,631 deaths.[2] COVID-19, which is caused by a novel RNA coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is primarily associated with severe acute respiratory syndrome (SARS), yet the respiratory system is not the only system affected. Studies have shown that many patients have comorbidities, such as hypertension, other cardiovascular diseases (CVD), diabetes, and chronic obstructive pulmonary disease (COPD), which contribute to a poorer prognosis.[3]

The relationship between CVD and COVID-19 is important for many reasons; at first glance, it is clear that COVID-19 patients with pre-existing CVD show a higher mortality rate than those without CVD.[4] Patients with various cardiac disorders are also hospitalized and receive treatment in an intensive care unit (ICU) more often. Wang et al. reported that 58.3% of patients hospitalized due to COVID-19 had been previously diagnosed with hypertension and 25% had heart disease.[5] Additionally, the presence of CVD risk factors, such as obesity, increases mortality because of COVID-19, which is 3–5-fold higher in obese patients.[6,7] On the other hand, some studies reported that 7.2–12% of COVID-19 patients suffered from newly detected acute cardiac injury with an increase in the troponin I concentration and 16.7% developed arrhythmias.[5,8] Moreover, some authors suggest that COVID-19 patients may present symptoms of acute coronary syndrome (ACS), including individuals without pre-existing cardiac conditions.[9] Furthermore, symptoms of pre-existing CVD, such as heart failure and coronary artery disease, may overlap with symptoms typical of COVID-19, as in the case of dyspnea, which is a key feature of heart failure.[10]

In patients with coronary artery disease, the inflammatory state may destabilize atherosclerotic plaques, which may worsen a patient's condition and prognosis.[11,12] In some COVID-19 patients, the so-called 'cytokine storm' was detected, with higher levels of cytokines in blood, which could potentially be one of the pathophysiological factors that induce further cardiac complications.[8,13]

Some authors suggested that COVID-19 was associated with myocarditis, as the post-mortem biopsies of the individuals infected with SARS-CoV-2 revealed scarce amounts of mononuclear inflammatory infiltrates in the interstitial space of the myocardium.[14] However, data is still limited, as the diagnosis of myocarditis in patients is mainly based on cardiovascular magnetic resonance imaging (CMR) and echocardiography.[15,16] Myopericarditis in COVID-19 patients sometimes leads to cardiac tamponade in the course of ACS and even in cases of unobstructed coronary arteries.[17,18] This problem is still under investigation, and different tests, not only employing the histological analysis, but also identifying changes in the CMR images of the heart, should be recommended, as endomyocardial biopsies are not available in most COVID-19 cases.

The angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed in the heart, has been found to have a strong binding affinity for the SARS-CoV-2 spike protein.[19,20] This has led to the hypothesis that ACE2 may mediate cardiac injury in COVID-19 patients; however, recent studies on the hospitalized patients with hypertension showed a lower risk of all-cause mortality in the group of ACE inhibitor (ACEI)/angiotensin receptor blocker (ARB) (drugs that act through the abovementioned receptors) users as compared to non-users.[21]

Research studies are being conducted rapidly and new data is published nearly every week, yet key questions remain unanswered, including questions regarding the relationship between tissue and biochemical changes and the clinical condition of patients. We performed a systematic analysis of research articles published in medical journals between February 2020 and December 2020, searching the PubMed, Google Scholar and ScienceDirect databases with the use of keywords such as "COVID-19" OR "SARS-CoV-2" AND "cardiovascular disease", "ACE2 receptor", "heart", "obesity", "myocarditis", "arrhythmia", "atrial fibrillation", "acute coronary syndrome", "thromboembolism", and "hypertension". Then, we studied the current available data about patients suffering from various cardiological disorders in the era of the lasting pandemic, with a particular focus on the potential impact of the virus on the heart. The aim of this review was to provide an up-to-date synopsis of the influence of COVID-19 on the heart and its interactions with CVD by analyzing the SARS-CoV-2 pathogenesis, clinical complications and prognosis in patients with and without co-existing CVD.

General symptoms and pathologies of SARS-CoV-2

The incubation period of the novel coronavirus is estimated to be between 3–7 days and up to 2 weeks in some cases. Like other respiratory viruses, SARS-CoV-2 spreads primarily through respiratory droplet transmission as well as through hands and surfaces. The initial infection may be manifested through fever, dry cough, fatigue, dyspnea, myalgia, sore throat, headache, and conjunctivitis; hyposmia and dysgeusia are sometimes reported, and diarrhea, nausea and vomiting also occur in rare instances.[10,22,23] Most patients demonstrate mild

flu-like symptoms; some develop pneumonia and, in around 5% of cases, severe acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. However, the disease may also be asymptomatic.[22,24] Indeed, it has been found that in about 80–90% of infected people, symptoms are mild or not present at all.[22] Additionally, it has been shown that the majority of individuals with symptoms and more severe clinical patterns have 1 or more co-existing medical conditions, including hypertension, other CVD, diabetes, and chronic lung diseases.[23,24] The mortality rate for COVID-19 is usually between 3% and 5%, and out of the hospitalized patients, 10–20% are admitted to ICU, 3–10% require intubation and 2–5% die, as determined by Guan et al.[25]

Mounting evidence suggests that COVID-19 simultaneously causes multiple changes in other organ systems. Abnormal liver test results and liver damage are highly associated with severe pneumonia.[10,22,24,25] Jaundice has been noted as a long-term complication of the SARS-CoV-2 infection, and nausea, vomiting, diarrhea, and abdominal pain are also common in COVID-19 patients, yet these gastrointestinal symptoms are not correlated with the severity of the disease. The positive results of the real-time polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 in patients' stools raised suspicion for fecal-oral transmission. Moreover, even after obtaining a negative throat swab test result, the virus was still detectable in feces.[26] This possible route of transmission remains to be examined. It is also known that the mortality rate is directly proportional to age, reaching almost 30% fatality in patients over 80 years old, although death can occur at any age, including children and newborns.[3,22,24,25,27,28]

In laboratory tests from COVID-19 patients, we find leukocytosis or leukopenia, often with lymphopenia, which is an effective indicator of the severity of the infection. The alanine aminotransferase, aspartate aminotransferase and C-reactive protein (CRP) levels are increased as well.[3,10,22,24,25,28] Furthermore, increased troponin levels were also reported in 7% of patients who died from fulminant myocarditis, and some authors suggested it was a strong prognostic indicator of mortality, similar to the CRP level. In addition, the D-dimer and ferritin levels were elevated in numerous patients.[8,25,27,29,30]

Possible pathophysiological mechanisms of cardiovascular complications in COVID-19 patients

The mechanisms through which SARS-CoV-2 affects the cardiovascular system are still under investigation. However, there is some data on its interactions with the renin–angiotensin–aldosterone system (RAAS). Angiotensin-converting enzyme 2 has been identified as crucial in facilitating the entry of SARS-CoV-2 into the host cell and it is highly expressed in alveolar epithelial type 2 (AT2) cells. The virus exhibits binding to the cell-associated and soluble ACE2 receptors, expressed in numerous organs, such as the heart, kidneys, intestine, lung, brain, and liver,[31,32] which may explain why COVID-19 patients manifest a spectrum of symptoms, including gastrointestinal, cardiac and renal injury, along with neurological and respiratory symptoms.[33] Through the respiratory tract, SARS-CoV-2 reaches AT2 cells, which are responsible for surfactant production.[34] Once the virus enters the host cell, its mediators activate macrophages to release cytokines and chemokines, which increase vasodilation and vascular permeability. Excess plasma compresses alveoli and impairs surfactant production; thus, alveoli collapse and the gas exchange is not fully efficient. Angiotensin-converting enzyme 2, which is widely expressed throughout the body, normally shows protective effects against CVD by transforming angiotensin II into beneficial angiotensin 1-7.[35,36] The binding of SARS-CoV-2 to the ACE2 receptor induces the endocytosis of the complex, and thereby downregulates enzyme expression so that it is unable to exert organ-protective effects, which ultimately results in the reduction of the beneficial anti-inflammatory properties and vasodilation associated with ACE2.[31,37]

Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), the virus responsible for the SARS epidemic in 2002–2004, and SARS-CoV-2 both act via RAAS through ACE2, an enzyme that physiologically counters the activation of RAAS, but also functions as a receptor for both SARS viruses. These effects have been discussed primarily in the context that widely used ACEI and ARB drugs could potentially enhance the spread of SARS-CoV-2 in alveoli and myocardial cells. However, the RAAS blockade has been shown to limit exposure to the SARS-CoV-1 spike protein, which normally induces acute lung injury in experimental mouse models; furthermore, data suggests that ACEI and ARB therapy may be protective and result in lower levels of interleukin 6 (IL-6), and increased CD3 and CD8 T cell counts in blood.[31,38–41] Vaduganathan et al. claim that the withdrawal of RAAS inhibitors may be harmful in certain high-risk patients with known or suspected COVID-19, but globally, it is widely accepted that we do not yet have a complete understanding of the pathophysiological mechanism of the SARS-CoV-2 infection and lack clear therapeutic implications; moreover, the data referring to humans is too scarce to support or refute these hypotheses and concerns.[37]

The activation of RAAS ultimately stimulates the secretion of transforming growth factor beta (TGF-β), which is involved in fibrosis, cardiomyocyte apoptosis and cardiac enlargement.[42] In some cases, viral infection with SARS-CoV-2 leads to the so-called 'cytokine storm', and higher concentrations of IL-6, interleukin 8 (IL-8), interleukin 10 (IL-10), and tumor necrosis factor alpha (TNF-α) were reported in deceased patients as compared

to those who recovered.[43,44] Usually, the immune system counterbalances abrupt cytokine release through the activation of the ACE2/Mas receptor (MasR) axis; however, in COVID-19, this mechanism is diminished due to ACE2 downregulation.[45] As a result of the previously mentioned RAAS imbalance, SARS-CoV-2 leads to endothelial dysfunction,[46] as the endothelium lines the lumen of blood vessels, and is constantly exposed to direct viral invasion and massive cytokine release. The resulting endothelial injury impairs nitric oxide synthesis, which enhances vasoconstriction and thrombosis, and generally promotes CVD and atherosclerosis. Further examinations should be continued, as our understanding of the pathological mechanisms concerning COVID-19 is still limited.

Heart and cardiovascular diseases in times of pandemic

The impact of COVID-19 on the cardiovascular system has been widely reported. As summarized by Dhakal et al., cardiac complications in COVID-19 include acute myocardial injury, arrhythmias, cardiogenic shock, and even sudden death.[33] In addition, drug interactions with COVID-19 therapy may cause arrhythmias, cardiomyopathy and sudden death.[33]

Generally, patients with chronic diseases, such as CVD, are at higher risk of developing serious complications and dying from COVID-19, and the risk increases with age. Elderly patients with co-existing comorbidities are more likely to require admission to ICU and the cardiac manifestations of CVD may contribute to higher overall mortality.[47,48] Cardiovascular pathologies are present in 8–25% of COVID-19 patients, with a higher proportion of patients with a worse prognosis.[49] In Chinese studies of 1,527 hospitalized COVID-19 patients, about 17% showed hypertension, 14.4% had cardio-cerebrovascular diseases and 8–10% had diabetes[30]; similarly, in other studies, 2/3 of patients had diabetes, CVD or cancer.[30]

The link between smoking and COVID-19 is interesting. There is no doubt that tobacco smoke causes the inflammation of the airways and is a major risk factor for CVD, yet articles on the relationship between smoking and COVID-19 are limited and ambiguous. There is, for example, evidence that active smoking does not correlate with the severity of COVID-19; however, another systematic review points out that current or former smoking is associated with a poorer prognosis than in the case of non-smokers.[50–52]

COVID-19 patients with diabetes and obesity more commonly have respiratory dysfunction due to low muscle strength, and are more prone to infections; therefore, they often require mechanical ventilation. Diabetes and pre-diabetes are also important risk factors in COVID-19 patients, as the high glucose levels and various additional conditions observed in this group of patients, such as increased thrombosis, inflammation and reduced lung capacity, significantly increase the risk of lethal outcomes as compared to non-diabetic patients. Additionally, a study published in "The Lancet" points to a mutual interaction – patients with diabetes are at greater risk of severe infection, and COVID-19 exacerbates hyperglycemia and can even cause diabetes de novo.

Myocardial injury and COVID-19

Elevated cardiac biomarkers, and especially an elevated level of troponin I in the high-sensitivity cardiac troponin test, are the main diagnostic values that determine admission to ICU. Various studies had been analyzed and it was found that myocardial injury, defined as an elevation in the cardiac troponin concentration above the 99th percentile of the upper reference limit, was observed in 7–17% of the hospitalized COVID-19 patients.[23,33,51] Moreover, the incidence of myocardial injury increases with the severity of the SARS-CoV-2 infection, rising to 22.2% of patients needing ICU care and 59% of patients who die from the disease. Additionally, in ICU patients, the hypersensitive troponin I concentration was statistically significantly higher than in the non-ICU group.[5,23] In studies of early cases of COVID-19 in China, Wang et al. showed that among 138 patients, the most common cardiac complications during hospitalization were arrhythmia (23 patients) and acute cardiac injury (10 patients).[5]

Acute coronary syndrome

In the context of ACS, viral infections (e.g., influenza) are considered the potential triggers of ST-elevation myocardial infarction (STEMI). It is believed that the same applies to the SARS-CoV-2 infection. Chest pain and electrocardiogram (ECG) changes typical of ACS are among the initial manifestations of COVID-19, and diagnoses range from STEMI to Takotsubo cardiomyopathy.[23,33,53,54] In a retrospective study performed in Lombardy, Italy, 28 cases of SARS-CoV-2-positive patients with confirmed STEMI were investigated.[55] In 24 of the cases, the first clinical symptom was ST-elevation, which was detected before patients received the results of their SARS-CoV-2 tests. The rest (4 patients) developed ST-elevation during hospitalization.[55] Data acquired from New York hospitals presented 18 patients with COVID-19 and STEMI, and out of this group, 10 patients were diagnosed at the time of admission and 8 patients had myocardial infarction later during hospitalization.[53] Additionally, 33% of patients did not have significant changes within the coronary arteries and were included in the non-coronary myocardial injury group; the mean age was 63 years.[53]

The pandemic has also changed the dynamics of cardiovascular procedures. During the first weeks of the contagion, reduced admission of STEMI patients was observed, and data also suggests increased mortality, which was related not only to COVID-19.[55] The example of Madrid shows us that the newest situation lowered the number of percutaneous coronary interventions (PCIs) by half and increased the usage of fibrinolysis.[56] In Saudi Arabia, the weekly and monthly hospitalization rates were significantly cut down as compared to previous years.[57]

With regard to the pathophysiological mechanism, it is possible that myocardial ischemia and infarction could be secondary to the plaque rupture triggered by the virus-induced stress response or the exaggerated tendency to coagulation due to general infection, which is similar to the situation observed in the complications of influenza.[30]

Myocarditis

Viral infections are a common cause of myocarditis; the possible mechanism includes intensified cytokine release by pathological T cells and monocytes. Studies have shown that in several cases, fulminant myocarditis was a result of the complications of the SARS-CoV-2 infection, but none of them revealed viral particles in myocytes. Clinical manifestations in those cases included chest pain, dyspnea and fatigue.[58]

We have gained some information from the autopsies and endomyocardial biopsies of the patients infected with SARS-CoV-2. In a study on severely ill COVID-19 patients, cardiomyocyte hypertrophy, degeneration and necrosis were noted with mild interstitial hyperemia as well as edema with the infiltration of lymphocytes, monocytes and neutrophils.[59] In another study, low-grade interstitial and endocardial inflammation as well as viral particles were observed in the cytopathic, structurally damaged interstitial cells, which demonstrated the loss of the cytoplasmic membrane integrity, but, although the inflammatory cells and myocytes are closely adjacent, no viral particles were observed in myocytes.[60] The authors commented that cardiac myocytes showed non-specific damage, mainly characterized by focal myofibrillar lysis, but no cytopathic endothelial or small intramural vessel inflammation or thrombosis were noted; additionally, the authors claimed that more research studies were needed.[60] In yet another report, scattered individual myocyte necrosis was observed, with lymphocytes adjacent to, but not surrounding the necrotic myocytes, and degenerating myocytes were also present, possibly representing an early manifestation of viral myocarditis.[61] Tavazzi et al. suggested that myocardial injury in patients with the SARS-CoV-2 infection could be multifactorial, which was generally understood as numerous changes, such as atherosclerotic plaque rupture, coronary vasospasm, hypoxic injury to the vasculature, direct endothelial damage, or the formation of microthrombi.[60]

As previously mentioned, acute virus-negative lymphocytic myocarditis has been associated with the SARS-CoV-2 respiratory infection, and reports show an improvement in cardiac biomarkers after treatment with lopinavir/ritonavir and hydroxycholoroquine.[58,62] Aberrations in cardiac biomarkers and ECG changes occur in myocarditis, but they are not entirely specific to this cardiomyopathy. Laboratory findings, such as elevated lactate, abnormal values of erythrocyte sedimentation rate and inflammatory markers (e.g., CRP), could be helpful at early stages of myocarditis management.

It is still not clear whether SARS-CoV-2 exerts cardiotropism, as some authors suggest; at the same time others deny it. The final recognition is typically based on an endomyocardial biopsy, which is the gold standard for identifying myocarditis. It is possible that future studies that would include MRI of the heart in patients after COVID-19 could help us to better understand the complex pathologies in this matter.

Arrhythmias

It is known that the elevated cytokine levels and the systemic inflammatory response which accompany myocardial injury predispose patients to atrial and ventricular arrhythmias. Cardiac manifestations in some viral infections include atrial fibrillation (AF), supraventricular tachycardia (SVT) and ventricular tachycardia (VT). There are reports of rhythm disturbances in COVID-19 patients, ranging from sinus tachycardia to ventricular arrhythmias.

The potential mechanisms of AF in COVID-19 patients include the previously mentioned decrease in ACE2 receptor expression, cytokine storm, endothelial dysfunction, T cell exhaustion, and various kinds of electrolyte imbalance, like hypokalemia, which are common in COVID-19 patients and may be the trigger of AF induction.[63]

In a retrospective cohort study of 1,284 patients, 170 patients had elevated cardiac troponin I, and of that group, 44 patients had atrial tachycardia (AT) or AF (35 patients), ventricular arrhythmias (2 patients), or both atrial and ventricular arrhythmias (7 patients).[64] Only 4 out of 25 patients who developed AT/AF during infection had a prior history of AF, which suggests that it could be a result of the SARS-CoV-2 infection. Ventricular rhythm disturbances proved to be fatal in 6 cases.[64] Atrial fibrillation was also described in other studies; in a multi-center study of remdesivir therapy, among a group of 53 patients with a median age of 67 years whose data were analyzed, 34 patients were invasively ventilated and 2 patients had AF (6%).[65]

In another study of 138 hospitalized COVID-19 patients, arrhythmia was diagnosed in 16.7% of patients, with a higher incidence in ICU patients as compared to non-ICU patients (44.4% vs 6.9%; $p < 0.001$).[5] Transient

complete heart block was also reported in patients with critical COVID-19, who later died due to severe respiratory failure.[66]

At this moment, we cannot describe arrhythmias as primary COVID-19 complications per se, as it is difficult to discern if they are a result of the SARS-CoV-2 infection alone, general viral infection, or a side effect of treatment drugs. Drug interactions should also be considered and followed, as prolonged QTc, VT, and even lethal arrhythmias, like torsade de pointes, have been observed in patients taking hydroxychloroquine and azithromycin. Such interactions will certainly be described with time, as more and more studies on the complications and treatment of COVID-19 are conducted.

Venous thromboembolism

The laboratory data of COVID-19 patients confirm coagulation abnormalities. Reports include reduced platelet count, elevated D-dimer and fibrinogen levels, and prolonged prothrombin time, which are associated with a poorer prognosis.[25] The exaggerated production of procoagulants, severe hypoxia and inflammation lead to a hypercoagulable state, which promotes thrombus formation. In the previous studies of infection with other coronaviruses, pulmonary artery thrombosis was rarely reported, whereas with SARS-CoV-2, it is quite different.[67] In a recent study, pulmonary embolism (PE) was verified with pulmonary computed tomography (CT) angiograms in 32 of 106 patients.[68] Additionally, in a prospective cohort study, deep-vein thrombi were revealed in 7 of 12 cases in whom deep-vein thrombosis (DVT) was not suspected prior to death.[69] In 4 cases, thrombi from lower extremities induced PE, which was believed to be the direct cause of death.[69] Further studies showed changes in small pulmonary vessels as well, including microthrombi.[70,71]

An observation of 184 ICU patients with a mean age of 64 years demonstrated a strong correlation between COVID-19 and DVT and PE events.[72] Klok et al. found a 31% incidence of thrombotic complications in ICU patients with COVID-19, which is remarkably high, even though in all cases, standard doses of thromboprophylaxis were used, based mainly on nadroparin given subcutaneously.[72] The observed thrombotic complications included primarily PE (25 cases), with additional reports of proximal DVT of the leg (1 case), catheter-related upper extremity thrombosis (2 cases) and ischemic stroke (3 cases). The authors recommend the regular control of the D-dimer and fibrinogen levels, along with pharmacological thrombosis prophylaxis.[72]

In an article concerning coagulopathy, Iba et al. underlined that the clinical presentation of COVID-19-associated coagulopathy was primarily organ dysfunction, whereas hemorrhagic events were less frequent.[73] Moreover, they compared bacterial sepsis-associated coagulopathy/disseminated intravascular coagulation (DIC) with COVID-19 consequences and found that in COVID-19 cases, pathologies like the prolongation of prothrombin time, activated partial thromboplastin time and a decrease in antithrombin activity were less frequent, and thrombocytopenia was relatively uncommon. However, thrombocytopenia was described in some cases, which the authors suggested might be caused, at least in part, by treatment with heparin.[74]

The mechanism of coagulopathy in COVID-19 needs to be further examined, but for now we can say that it follows Virchow's triad, which consist of endothelial dysfunction, hypercoagulability and the stasis of the blood flow. Together, these effects contribute to a greater thromboembolic risk and lethal complications (e.g., DIC).

Treatment considerations

Generally, recommendations for the treatment of cardiovascular complications in patients with COVID-19 are not different from those from the pre-COVID-19 era. In the cited studies, mechanical ventilation was used when needed in severely ill patients with low blood saturation, vasopressor catecholamines were introduced to elevate decreased blood pressure in case of shock, and in many other clinical conditions, the use of drugs and specific procedures was similar.[47] However, some minor changes have been observed in ACS treatment in relation to the problem of handling the infected patient. The pandemic has created new challenges with regard to treating myocardial infarction, but the main management should not be changed. In case of STEMI, both SARS-CoV-2-negative and SARS-CoV-2-positive patients should be treated similarly, as any delay in obtaining test results can be harmful.[75] It has been recommended that, if a patient is referred to a non-COVID-19-trained lab or a non-PCI-capable hospital, and a transfer to a COVID-19-trained/PCI-capable facility can happen within 120 min, it should be initiated, yet if it cannot happen within 120 min, thrombolysis should be performed instead, with concomitant medical management with aspirin, clopidogrel, heparin, or enoxaparin, which generally meets the guidelines.[75] However, it should be noted that some patients may have contraindications to thrombolysis. Additionally, Zheng et al. suggests that drug-related heart damage during COVID-19 treatment is a concern, and that the use of antiviral drugs in particular should be monitored.[48] Such drugs are known to induce various cardiovascular disorders; cardiac insufficiency and arrhythmias, including sick sinus syndrome, have been observed after interferon and ribavirin. Thus, to avoid cardiac toxicity, antiviral dosing and side effects should be under control, particularly in patients with pre-existing CVD.[48,76]

As the pandemic continues, we will gain more knowledge and it may, with time, change some treatment regimens,

Table 1. Main cardiovascular complications in patients with COVID-19

References	Patients (*N*)	Severity of the disease (*n*)	Cardiac event (*n*)
Wang et al.[5]	138	ICU (36)	arrhythmia (16) acute cardiac injury (8)
		non-ICU (102)	arrhythmia (7) acute cardiac injury (2)
Si et al.[64]	1,284	severe COVID-19, hospitalized	arrhythmia (44)
Bangalore et al.[53]	18	hospitalized	myocardial infarction (8) non-coronary myocardial injury (10)
Meyer et al.[54]	1	hospitalized	Takotsubo syndrome (1)
Sala et al.[58]	1	hospitalized	myocarditis (1)
Tavazzi et al.[60]	1	hospitalized	cardiogenic shock (1)
Klok et al.[72]	184	severe COVID-19, hospitalized	thrombotic event (57)
Léonard-Lorant et al.[68]	106	COVID-19, hospitalized	PE (32)
Wichmann et al.[69]	12	COVID-19-positive deaths	deep-vein thrombi (7)

ICU – intensive care unit; COVID-19 – coronavirus disease; PE – pulmonary embolism.

which currently do not differ from the mainstream cardiovascular guidelines. One example is based on the finding that hypokalemia is a common metabolic abnormality in COVID-19 patients, which is probably secondary to the reduction of the albumin levels; thus, in this context, the antihypertensive medications known to increase the serum levels of potassium (including carvedilol and eplerenone) should be a first-line choice in COVID-19 patients with co-existing arterial hypertension.[77]

Conclusions

After nearly a year of the COVID-19 pandemic, we have gathered new knowledge on the symptoms, complications and pathophysiological mechanisms of this disease, and its impact on human health. We have learned not only how it affects the respiratory system, but also about other pathologies, including changes in blood and some alterations in the cardiovascular system (Table 1). Initial studies suggest an interaction with RAAS; however, we believe that new research is still needed.

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Is saliva a reliable biofluid for the detection of COVID-19?

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Abstract

This review aimed to assess the current evidence on the diagnostic potential of saliva regarding the detection of coronavirus disease 2019 (COVID-19). The literature published until May 24, 2020 was searched in the Web of Science, PubMed and Google Scholar databases with the keywords "COVID-19", "SARS-CoV-2", "2019-nCoV", "oral fluid", "saliva", and "diagnosis", individually and in combination, and 11 studies that explored the efficacy of saliva in the diagnosis of COVID-19 in different patient groups were found. Together, these studies suggest that saliva is a safe and reliable tool for the diagnosis of COVID-19. Further, saliva offers enhanced safety as well as logistical and economic benefits as compared to the current methods used to diagnose COVID-19. However, there is still limited evidence in the literature to make a definitive, clinically appropriate decision. The ideal specimen for the detection of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still an issue under investigation. Thus, new studies with large sample sets for the validation of easy, safe and reliable methods applicable for large-scale testing are immediately required.

Keywords: saliva, 2019-nCoV, SARS-CoV-2, COVID-19

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Introduction

In late December 2019, the outbreak of a disease of unknown biological origin occurred in Wuhan, China. The disease gave pneumonia-like symptoms and rapidly spread to nearly all continents.[1,2] The pathogen responsible for this epidemic was referred to as the 2019 novel coronavirus (2019-nCoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) and the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (ICTV), respectively. SARS-CoV-2 is a new type of coronavirus that can infect mammals and humans in a similar manner as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[1,3] As of March 11, 2020 WHO announced a global emergency and officially declared coronavirus disease 2019 (COVID-19) a pandemic.[4] Because of the novelty of 2019-nCoV, the information regarding the biological characteristics of the virus was largely unknown, and researchers are still trying to find innovative ways to prevent the spread of the infection. One of these preventative strategies is the development and implementation of large-scale rapid diagnosis protocols and technologies.[5]

In the last 2 decades, saliva has gained enormous attention in biomedical sciences. Furthermore, the development and improvement of highly sensitive diagnostic technologies have overcome the barriers preventing the broad implementation of saliva diagnostics.[6,7] Saliva research has advanced rapidly due to its use in metabolomics, genomics, proteomics, and bioinformatics approaches for the evaluation of overall health and disease.[8–10] These data has shown that saliva is an ideal, non-invasive material for the diagnosis of several diseases as well as for use in pharmacokinetic studies and therapeutic drug monitoring.[10,11]

The fast testing and isolation of the infected individuals, particularly the asymptomatic cases, which account for approx. 79% of the spread of COVID-19, are considered as the key issues in controlling the pandemic.[12,13] Currently, respiratory tract specimens are used for detecting the virus; however, the acquisition of such specimens has numerous shortcomings in terms of collection, exposure of the healthcare workers (HCW), patient discomfort, problems related to self-collection, shortage of testing materials, and equipment.[13–15] To overcome these shortcomings, new efficient methods that can be easily rolled out for large-scale virus scanning are required. From this point of view, the use of saliva seems a reliable alternative for the diagnosis of the 2019-nCoV presence, as the collection of saliva is minimally invasive, does not cause discomfort, can be is easily performed by the patient, prevents the contamination of the healthcare staff, and decreases the use of swabs and personal protective equipment (PPE).[3,10,16,17] Moreover, saliva has been reported to exhibit sensitivity comparable to respiratory tract swabs in the detection of other respiratory pathogens.[15,18,19]

This review aimed to present a concise update on the diagnostic role of saliva and to discuss the recent data regarding its diagnostic potential for COVID-19. To achieve this goal, we performed a literature search in the Web of Science, PubMed and Google Scholar databases with the keywords "COVID-19", "SARS-CoV-2", "2019-nCoV", "oral fluid", "saliva", and "diagnosis", individually and in combination, taking into consideration the research published until May 24, 2020. Clinical studies that used saliva as a diagnostic fluid for the detection of COVID-19 were included in this review, while case reports without enough clinical data and in vitro studies were excluded.

What is the entrance mechanism and transmission route of 2019-nCoV?

2019-nCoV is a novel enveloped, single-stranded, zoonotic, RNA virus that belongs to the β-coronavirus genus. It is reported to share a 96% identity with bat coronavirus, 91% with pangolin coronavirus and 79% with SARS-CoV.[20–24] The 2019-nCoV virion has 4 structural proteins.[20,24,25] Among them, the spike protein (S) facilitates the entrance of the virion into the host cell and determines the transmission ability of the virus.[22–24] To date, the exact entry mechanism of 2019-nCoV into human cell has not been completely elucidated. However, like in the case of the SARS-CoV infection, it is hypothesized that 2019-nCoV infects humans by binding to the angiotensin-converting enzyme 2 (ACE2) receptor of the host cell. Thus, the in vivo infection dynamics of 2019-nCoV is associated with the number and distribution of ACE2 receptors.[2,20,26–30] The expression of ACE2 has been identified in different parts of the body, i.e., the lungs, myocardial cells, esophagus, ileum, colon, kidneys, oral mucosa, and salivary glands.[1,26,31–34] Xu et al. reported that ACE2 could be expressed and highly enriched in the epithelial cells of the oral cavity.[32] Additionally, the salivary glands have been reported to express the ACE2 receptor, highlighting its potential as a target for the COVID-19 infection.[33–35]

The transmission of 2019-nCoV takes place via the spread of the infected aerosol droplets, which may be expelled during sneezing, coughing, speaking, or singing, or via contact with the mucous membranes of the nose and eyes, and saliva. It has been reported that the incubation period during the COVID-19 infection ranges from 1 to 14 days.[36–39] Furthermore, it has been observed that the clinical symptoms of COVID-19 differ among the infected patients and are affected by age as well as by the existing comorbidities. While some patients are asymptomatic, others present with a cough, fever and fatigue. Transmission can occur in the early period, before symptoms manifest themselves; thus, asymptomatic or mildly symptomatic patients can potentially transmit the virus

for longer periods, before they are diagnosed with the disease.[24,40–42] It is estimated that 1 infected person can transmit the virus to nearly 3 people.[24,43] The ability to quickly diagnose COVID-19 plays an essential role in controlling the spread of the virus through its accurate detection and the isolation of the infected persons.[24,36]

Physiology and functions of saliva

The salivary glands in the oral mucosa are responsible for the production and secretion of saliva.[11] Saliva is a biofluid that is important for mastication and oral cavity homeostasis.[11] It is composed of water (99.5%), organic (0.3%) and inorganic (0.2%) substances.[9,44,45] The amount of saliva produced daily by a healthy individual is approx. 1–1.5 L. Beside the standard components of saliva, whole saliva includes other substances, such as fluids from the gingival fold, desquamated epithelial cells, blood cells, mucus from the nasal cavity and pharynx, oral bacteria, and traces of medications.[45] Saliva has several functions in terms of maintaining the homeostasis of the oral cavity, namely it has a protective function for the teeth and oral mucosa, it has a buffering effect, and participates in clearing the oral cavity of residual food and deleterious bacteria. Additionally, saliva participates in digestion and taste perception. Furthermore, with a variety of components, such as lysozyme, lactoferrin, mucins, immunoglobulins, and histatins, saliva has also been shown to exhibit antimicrobial activity.[11,44,46]

The collection of stimulated and unstimulated saliva can be performed by means of different methods, such as draining/spitting or chewing an absorbent material. Additionally, with the use of special devices or aspiration, pure glandular saliva can be collected. However, since saliva shows great variations, the standarization of saliva collection is important.[9,11]

Saliva as a diagnostic material

Oral fluid is referred to as the "mirror of the body", enabling the evaluation of both health and disease progression within an individual. A better understanding of the molecular profiles found within saliva and their relation to disease has raised interest in the diagnostic potential of saliva.[7,47] Furthermore, saliva is a cost-effective and non-invasive diagnostic tool, with many advantages in terms of collection, procurement of sufficient and repeated samples, manipulation, processing, safety, longitudinal monitoring, applicability to large populations, and transportation.[7,8,11] Notably, saliva does not coagulate like blood and is stable for 24 h at room temperature and 1 week at 4°C. These factors make saliva samples easy to transport, store and manipulate for diagnostic purposes.[11] Recently, lab-on-a-chip technologies/point-of-care devices are increasingly leading to portable "labs" and real-time analyses of a variety of diseases by using saliva.[7,47,48]

Nowadays, the general health status of the body or the presence of several diseases can be diagnosed through the detection of biomarkers in saliva. Nearly all disease markers that are found in blood can also be detected in saliva. Moreover, human saliva has been reported to be successfully used for the diagnosis of many systemic diseases, such as cancer, autoimmune diseases, infections, endocrinological diseases, psychiatric diseases, cardiovascular diseases, and gastrointestinal tract diseases.[48–51]

Viruses frequently infect human through the mouth and eyes. Thus, the oral cavity is important in the transmission of certain viruses.[52] Viral DNA, RNA, antigen, and antibodies are used to detect 2019-nCoV in saliva.[50] Human immunodeficiency virus, hepatitis viruses, rotavirus, norovirus, Zika virus, human papilloma virus, herpes simplex viruses, Ebola virus, SARS-CoV, Epstein–Barr virus, and influenza viruses are all common examples of viruses that can be detected in saliva.[51,52] These viruses serve as an important precedent for the potential detection of 2019-nCoV in saliva.

Is saliva a reliable tool for the diagnosis of COVID-19?

To control the spread of the disease, the rapid and large-scale detection of 2019-nCoV is crucial. So far, respiratory tract specimens, such as throat swabs, nasal swabs, nasopharyngeal swabs, sputum, and bronchoalveolar lavage, have been used for 2019-nCoV diagnostic testing.[36,37,53,54] However, the harvesting of oropharyngeal and/or nasopharyngeal specimens puts the healthcare staff at a high risk of accidental transmission, as obtaining these samples requires close contact with the infected patients and involves potential exposure to the virus through the patient's sneezing, gag reflex or cough.[36,53,55] Additionally, the collection procedures cause discomfort and may result in bleeding, particularly in patients with thrombocytopenia.[5,36] Thus, they are not suitable for the broad-scale repeated monitoring of the viral load.[37,53] Sputum, on the other hand, is a non-invasive specimen, but not all patients with 2019-nCoV can produce sputum for diagnostic evaluation.[5,18,36,53] However, the use of saliva has numerous advantages, such as non-invasiveness, easy self-collection, a reduced need for specific equipment and also PPE, and limited transmission to the healthcare staff. Importantly, saliva collection also facilitates taking samples from a single patient multiple times and allows for the use of point-of-care testing.[13,48] It is understood that saliva is the meeting point of respiratory tract secretions, blood, which can access the mouth via the gingival crevicular fluid, and the secretions of the major and minor salivary glands. Thus, saliva could reflect the viral

load of the COVID-19 infection within the salivary glands and the respiratory tract.[5,54] The findings of Liu et al. suggest that the epithelial cells of the salivary glands can be infected by the virus.[34] These findings imply that the salivary glands could function as an important reservoir for the virus, particularly in the early phase of the infection. This may also explain the transmission of the infection between asymptomatic cases, when the virus has not progressed to the respiratory tract.[41]

In the literature, we found 11 studies that explore the efficacy of saliva in the diagnosis of COVID-19 (Table 1 and Table 2). To et al. reported that the salivary viral load peaked in the 1st week after the onset of symptoms, and noted that 2019-nCoV could be easily spread by means of saliva when symptoms were mild.[54] They also reported the prolonged detection (>20 days) of 2019-nCoV in saliva and emphasized that despite the clinical recovery, the virus might be detected in saliva at low levels. Furthermore, they suggested using posterior oropharyngeal saliva, as it consists of secretions that originate from the salivary glands, the posterior nasopharynx and the tracheobronchial tree.[54] In another study by the same research group, 2019-nCoV was detected in saliva specimens from 11 of 12 patients (91.7%).[53] The authors reported that at least 11 days after hospitalization, 1 patient had detectable viral shedding in saliva. Based on these observations, the authors emphasized the possibility of the transmission of 2019-nCoV via saliva and recommended the use of surgical masks when dealing with potential cases.[53] Azzi et al. reported that saliva was a reliable material in the diagnosis of COVID-19, and that it could provide clinical information, useful for the monitoring of the disease.[16] Those authors also detected 2 patients who tested positive when using salivary samples, while pharyngeal or bronchoalveolar swabs were negative. Based on these data, the authors hypothesized that the infected individuals could transmit the virus even though their pharyngeal swabs were negative. To combat this, the authors suggested that the assessment of the salivary viral load be mandatory before the patient can be discharged from hospital.[16] In agreement with these findings, Wyllie et al. detected 2019-nCoV in saliva samples, while the matched nasopharyngeal specimens of 2 asymptomatic healthcare staff members were negative.[15] Those authors noted that for the determination of mild or subclinical infections, saliva might be a viable option.[15] In another study, Zheng et al. found that the viral detection rates for sputum and saliva were significantly higher relative to those observed for throat and nasal swabs.[18] Williams et al. found that 33 out of the 39 patients whose nasopharyngeal swabs were positive, also had a positive result for 2019-nCoV in saliva.[56] In another study conducted on non-hospitalized patients, Kojima et al. reported

Table 1. Characteristics of the selected studies

Study	Country	Patients (*N*)	Sample	Analysis	Conclusions
Zheng et al.[18]	China	65 CP	– TS – NS – S/SP	RT-PCR	– saliva sampling has high sensitivity and accuracy – it is more convenient in comparison with TS and NS
Wyllie et al.[15]	USA	44 CP 98 HCW	– S – NPS	RT-PCR	– saliva is a reliable alternative to NPS for identifying mild/subclinical infections – it is accurate in large-scale use
To et al.[54]	China	23 CP	– S – B – U – RS	RT-PCR	– saliva a non-invasive tool for diagnosis – its collection is highly acceptable by patients and the healthcare staff
To et al.[53]	China	12 CP	– S	RT-PCR	– saliva is useful for the diagnosis, monitoring and control of the infection
Pasomsub et al.[55]	Thailand	200 NP	– NP/TS – S	RT-PCR	– saliva can be used for the detection of COVID-19 – it is non-invasive and non-aerosol-generating – it can be used especially in low-resource settings
Jamal et al.[58]	Canada	53 CP	– NPS – S	RT-PCR	– saliva may substitute for NPS, especially when NPS is in short supply or patients cannot tolerate it
Chen et al.[4]	China	31 CP	– S – OPS	RT-PCR	– saliva is a useful diagnostic medium for critically ill patients – its collection is easy and non-invasive
Azzi et al.[16]	Italy	25 CP	– S	RT-PCR	– saliva is a reliable tool for detecting COVID-19 – it is useful for the clinical monitoring of the disease
McCormick-Baw et al.[59]	USA	156 CP/NP	– NPS – S	RT-PCR	– saliva is an acceptable alternative specimen for detecting COVID-19
Williams et al.[56]	Australia	622 NP	– NPS – S	RT-PCR	– saliva may be a suitable alternative for first-line screening in low-resource settings
Kojima et al.[57]	USA	45 CP/NP	– S – NS – NPS	RT-PCR	– supervised self-collected S and NS performed similarly to clinician-collected NS

CP – laboratory-confirmed patients; NP – non-confirmed patients; HCW – healthcare worker; TS – throat swab; NS – nasal swab; S – saliva; SP – sputum; NPS – nasopharyngeal swab; B – blood; U – urine; RS – rectal swab; OPS – oropharyngeal swab; RT-PCR – real-time polymerase chain reaction.

Table 2. Patient characteristics and saliva collection in the studies testing saliva as a diagnostic fluid for coronavirus disease 2019 (COVID-19)

Study	C– (*n*)	C+			Age [years]	Gender		Saliva collection
		AS (*n*)	mild (*n*)	severe or deceased (*n*)		F (*n*)	M (*n*)	
Zheng et al.[18]	–	–	23 – 19 – O_2 suppl	42 – 39 – O_2 suppl – 2 – MV – 10 – ICU admission	54 (39.5–62)	25	40	– a deep cough with a mask – 3–5 times through spitting
Wyllie et al.[15]	–	–	–	44 – 6 – ICU on admission – 19 – ICU during hospital stay – 10 – MV – 2 – deceased	61 (23–92)	21	23	– self-collected – every 3 days through spitting – throughout the clinical course
	98		–	–	36 (22–67)	82	16	– self-collected – every 3 days through spitting – for 2 weeks
To et al.[54]	–	–	13	10 – 10 – O_2 suppl – 5 – ICU (3 required EI) – 2 – deceased	62 (37–75)	13	10	– posterior oropharyngeal saliva with a deep cough – endotracheal aspirate for EI
To et al.[53]	–			12	62.5 (37–75)	5	7	– self-collected – saliva coughed out from the throat – collected at a median of 2 days after hospitalization
Pasomsub et al.[55]	181			19	36 (28–48)	131	69	– self-collected – without coughing
Jamal et al.[58]	–			53	63 (27–106)	21	32	– through spitting – on enrollment, then 3 times at 72-hour intervals
Chen et al.[4]	–	–	–	31 – 26 – heavy – 5 – critically ill	60.6 (18–86)	16	15	– from the salivary gland – collected with cotton swabs
Azzi et al.[16]	–	–	–	25	61.5 ±11.2	8	17	– drooling technique – with a pipette for EI and MV – the 2nd specimen after 4 days
McCormick-Baw et al.[59]			156		47.8	66	90	– saliva without sputum
Williams et al.[56]			622		NA	NA		– through spitting saliva after pooling it
Kojima et al.[57]	16			29	42 (31–52)	NA		– self-collected/supervised self-collected – a deep cough 3–5 times and rubbing the swab for 20 s

C–: COVID-19-negative; C+: COVID-19-positive; AS – asymptomatic; F – female; M – male; suppl – supplementation; MV – mechanical ventilation; ICU – intensive care unit; EI – endotracheal intubation; NA – not available.
Data concerning age presented as median (*Me*) (interquartile range (*IQR*)) or mean (*M*) ± standard deviation (*SD*) or *M*.

that they detected 6 cases of the 2019-nCoV infection by using saliva samples; again, 2019-nCoV was not detected in the clinician-collected nasopharyngeal swabs. Conversely, in 3 cases, they detected the 2019-nCoV infection with nasopharyngeal specimens, while it was not detected in saliva. Based on these results, the authors suggested that single-site testing might miss some cases of COVID-19.[57] Pasomsub et al. found that the detection of 2019-nCoV in saliva had a sensitivity of 84.2% and a specificity of 98.9%.[55] They also emphasized that the spectrum of the COVID-19 ranges from asymptomatic to severe. Thus, the detection of 2019-nCoV in specimens from different sample regions might also be possible.[55] Jamal et al. found that nasopharyngeal swabs were 10% more sensitive than saliva, and that the difference was more pronounced in the later stages of the disease.[58] According to their results, nasopharyngeal swabs may be preferred for 2019-nCoV diagnostics, particularly if the patient is in the late illness period. Moreover, the authors found that none of the nasopharyngeal or saliva samples was totally sensitive for the detection of COVID-19 alone.[58] Chen et al. found that out of 13 cases, 4 tested positive in saliva and 3 of those patients were critically ill.[4] They suggested that the salivary glands were destroyed during the infection due to a high viral load, and with the progression of the disease, the viral titer increased in saliva because of viral replication in critically ill patients with a weakened immune system.[4] Thus, the detection of the virus in saliva may be indicative of terminal-stage disease. Studies with much larger sample sizes relative to other studies indicated that saliva was an acceptable alternative specimen for the diagnosis of COVID-19, especially for first-line screening in low-resource settings.[15,55,56,59] However, conclusions from these studies are still contradictory.

Conclusions

The ideal medium for the detection of 2019-nCoV is still an issue under investigation. The validation of easy, safe and reliable methods that are easily applicable for large-scale testing for 2019-nCoV are immediately required. Saliva seems to be a reliable diagnostic tool for the diagnosis of COVID-19; however, there is limited evidence present in the literature to support this. Thus, new studies with large sample sizes are urgently required to accurately demonstrate the diagnostic validity of saliva in the detection of 2019-nCoV.

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Remote management of dental problems in children during and post the COVID-19 pandemic outbreak: A teledentistry approach

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Abstract

The recent pandemic outbreak of coronavirus disease 2019 (COVID-19) has created a helpless situation in healthcare systems worldwide. The disease can be transmitted in different ways, e.g., through contact, droplets, fomites, and aerosol-generating procedures. Subsequently, the World Health Organization (WHO) released recommendations regarding precautions to be taken by all healthcare workers, including dentists, in order to avoid the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 indeed has become a pandemic, and there is a need for an innovative method to continue providing dental care to children with a minimal risk of cross-infection.

The objective of this short communication was to draw special attention to the teledentistry model in pediatric dentistry and to guide the management of children with dental problems during the COVID-19 pandemic.

Teledentistry is a feasible method and its use can overcome challenges in the present situation. The teledentistry approach enables providing guidance, treatment plans and follow-up with remote-assistance dental care through the use of information technology instead of face-to-face contact with patients.

Keywords: dentists, coronavirus, COVID-19, SARS-CoV-2, practice management

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Introduction

Teledentistry is a form of telemedicine explicitly dedicated to dentistry. Teledentistry utilizes electronic dental records, information and communication technology (ICT), digital dental photography, and the Internet for consultation, supervision as well as continuing dental education. The usage of mobile phones in teledentistry has become an attractive innovation due to an increase in availability, and improved digital photography capabilities and data processing of smartphones, which allows users to multitask, having access to affordable and secure cloud storage. The smartphone camera can be useful in dental photography, in recording the baseline preoperative oral health status, and in facilitating diagnoses and appropriate treatment plans. Since smartphones can be easily carried and used at any time, they are useful in improving patient-centered care delivery as point-of-care testing (POCT) devices. The teledentistry model can facilitate screening, data collection and primary prevention.[1] With minimal training, parents, teachers or other caregivers can collect and share the required digital data from children at home or school, using user-friendly mobile technology for remote evaluation by a pediatric dentist.[2]

After the recent outbreak of the coronavirus disease 2019 (COVID-19) pandemic, the World Health Organization (WHO) released recommendations regarding precautions to be taken by all healthcare workers, including dentists, in order to avoid the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] These refer to different transmission modes, such as contact, droplets, fomites, and aerosol-generating procedures.[3,4] As dentistry is a profession that involves face-to-face contact with patients and attendants in a closed setting, as per the current information, there are high chances of contracting this disease.[5] Furthermore, almost all dental procedures involve aerosols in the dental operatory.[4] The WHO also makes it clear that, based on the available data and experience, the key is to limit close contact between the infected people and others in order to break the chain of COVID-19 transmission.[3] This risk is higher in pediatric dentistry, as the affected children are usually asymptomatic or have mild-to-moderate clinical symptoms of viral infection.[4] Hence, community-based COVID-19 transmission may involve children from different age groups. As there are no available universal guidelines for pediatric dental procedures during the COVID-19 pandemic, routine dental procedures should be deferred, and only acute dental emergencies should be treated. In acute emergencies, pediatric dentists should be aware of the recommended protocols for managing children's dental problems. It is essential to adopt these protocols to protect themselves as well as children and their parents, at the same time preventing viral transmission.[6] One of the best options to prevent viral transmission is teledentistry. It has been reported that there is high acceptance for teledentistry among patients and oral healthcare professionals.[1,7] Teledentistry saves time, and shortens the distance between the dental operatory and children and their parents. Teledentistry possibly allows dental teams to examine children in their most accustomed environments, and significantly diminishes dental anxiety and fear of children and their parents or caregivers.[7,8] This type of approach is very much required now to overcome the present COVID-19 pandemic crisis. Therefore, this narrative review was planned to outline the use of teledentistry in managing children's dental problems, both during and after the COVID-19 pandemic.

Literature search

An extensive search of the literature reported from December 2019 to December 2020 was conducted using the PubMed database. The keywords used in the search strategy were "COVID-19", "teledentistry", "children", "dental problems," and "management" in various combinations. In order to identify additional data published on the use of teledentistry to manage dental problems in children during COVID-19, a hand search was performed. The electronic search yielded 35 citations, and with regard to the details of the search words, the retrieved citations included: "COVID-19" AND "teledentistry" AND "children" – 1; "COVID-19" AND "teledentistry" – 30; and "teledentistry" AND "children" – 4. The hand search did not reveal any additional data. From the retrieved data, essential articles were utilized for this narrative review.

Discussion

Teledentistry for pediatric dental practice

During this COVID-19 pandemic, pediatric dentists may consider the use of teledentistry for the remote consultation, triage and delivery of dental care whenever possible and applicable. Teledentistry (virtual dental visits or dental care at a distance) enables pediatric dentists to meet various dental care requirements while avoiding close contact with their pediatric patients. However, teledentistry can only be practiced according to the respective national or state authorities'/associations' guidelines.[8] Teledentistry encompasses various components, such as consultation, diagnosis, triage, and monitoring. Teleconsultation is the most common form of teledentistry through which parents, caregivers or school teachers can seek advice for children who require a dental appointment. It may also help with the continuation of the treatment plan and follow-up advice during the quarantine or lockdown period. Teletriage consists in

the safe, correct and timely evaluation of the child's symptoms through remote consultation, using the pediatric dentist's smartphone or laptop computer. Similarly, parents can also use their smartphones to take pictures of their children's teeth and to provide information to the pediatric dentist. Triage involves distinguishing between emergency and non-emergency dental needs, and between those that require prioritization or deferment. In telediagnosis, the smartphone can be utilized to exchange information and photographs taken as directed by the pediatric dentist, thereby facilitating the diagnosis of emergencies related to early childhood caries (ECC), dental pain, traumatic dental injuries (TDI), and facial swelling. Telemonitoring (virtual visits) can substitute regular physical visits in routine monitoring of disease progression or treatment outcomes.[9]

Benefits and barriers related to pediatric teledentistry

The benefits include the ability to provide primary and specialized dental care, improved communication between the dental team and children/parents, and the effective triage of patients.[2] Thus, teledentistry reduces inappropriate referrals and waiting time, aids in timely diagnoses, treatment provision and follow-up, and lessens the costs related to travel and accommodation. Teledentistry might improve clinical outcomes and contribute to a reduction in pain and other comorbidities associated with delayed diagnosis and treatment. It supports monitoring a child's oral health and implementing preventive measures in such pandemic situations.[2] The possible barriers for teledentistry include the level of acceptance of its use by children, parents and pediatric dentists. The pediatric dentist may be concerned about making an inappropriate diagnosis and incurring additional expenses related to infrastructure, equipment and high-speed Internet. The issues related to poor Internet access, the lack of technical training and the lack of expertise can be causes for concern for the dental team and parents/caregivers. As teledentistry is new to the healthcare system, the concerns related to insufficient financial reimbursement, scanty guidelines, and the coordination between children, accompanying personnel and the dental team are other challenges.[10] The persons involved might have to depend on other people or government aid to utilize teledentistry in dental practice in communities without smartphones and Internet facilities.[2,9]

Teledentistry could aid the dental community by covering a broader geographical area, enabling more efficient functioning and helping many people in need while maintaining social distancing. The most recent systematic review confirms that teledentistry is a viable option for remote consultation, screening, diagnosis, treatment planning, and dentistry mentoring.[1] It also states that the rapidly developing ICT has greatly improved the cost-efficiency, precision and effectiveness of remote assistance for pediatric dentists.[1] There is high acceptance for teledentistry among clinicians and patients alike.[11,12] Parents have to be trained in video calling, taking the needed intraoral pictures and transferring them to the pediatric dentist by means of smartphones. Pediatric dentists have several possible approaches available for telecommunication with children and their parents, guardians and caregivers (Fig. 1). Through pediatric teledentistry, consultation with children and parents may be possible in 2 ways: real-time consultation (synchronous) or consultation through the stored records (asynchronous). Teleconsultation and teledentistry will impact the way the insurance company and the patient are billed. One may also want to consider accessing patient management software to review the patient's chart and radiographs. Such a review can be done via the virtual remote login applications using the software, private telenetworks or social media, including Skype, WhatsApp, Instagram, and Messenger.

A systematic review by a Brazilian research group suggested that teledentistry could improve the quality of care related to the diagnosis and management of oral lesions, and shorten distances for patients who need specialized diagnoses and specialists providing care.[13] Another systematic review from the USA concluded that teledentistry could be comparable to one-to-one dentistry for oral screening in remote areas, areas with limited access to care, long-term care facilities, and as part of school-based programs.[14] The authors also stated that teleconsultation was possible and valid in detecting oral health issues.[14] Consequently, Daniel et al. performed a systematic qualitative review and reported that the rapidly emerging communication technologies and information systems progressively revealed improvement in the cost-effeciency, precision and effectiveness of remote assistance for oral healthcare professionals.[15]

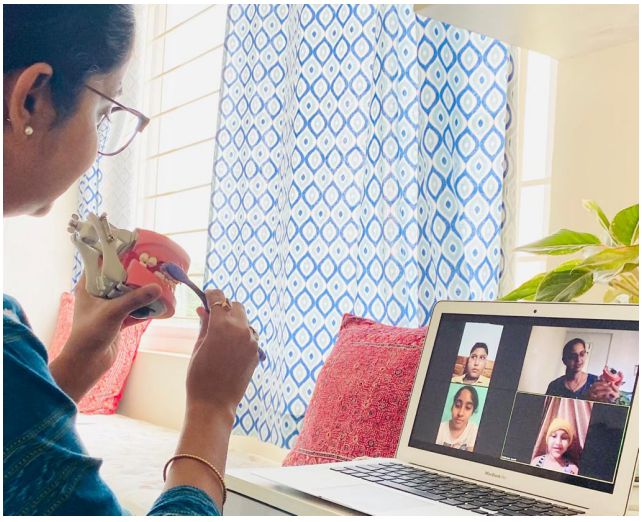

Fig. 1. Pediatric dentist providing remote oral hygiene instructions to children through teledentistry

Alabdullah et al. found that the exposure of pediatric dental students to the teledentistry model increased.[16] Regarding the records used in teledentistry, an Australian group reviewed photographic examinations and found that the image analysis provided accuracy comparable to visual inspection in diagnosing dental problems.[17] The authors concluded that the results were least comparable between photographic and visual inspection techniques in the case of enamel defects.[17] In the present COVID-19 pandemic situation, it is challenging to provide regular dental treatment to children. A Saudi Arabian cross-sectional survey was performed on undergraduate students and it was found that the study subjects knew very little about teledentistry.[18] The author suggested the inclusion of teledentistry as a continuing dental education topic.[18] Pereira et al. reported that teledentistry was an emerging tool to help maintain contact with the patient without any risk of the transmission of infections such as COVID-19.[19] A British study opined that healthcare professionals should consider adapting patient pathways and using telehealth as a consultation method to recover services and reduce the spread of COVID-19.[20] A cross-sectional survey by Surdu and Langelier found an increase in the utilization of oral health services for children, especially in rural areas.[21]

Furthermore, various authors worldwide preferred utilizing teledentistry in this pandemic period.[22–27] There is a shortage of specialists and a lack of holistic oral healthcare for children due to the closure of academic institutes and private practices. Hence, through the pediatric teledentistry approach, the number of dental consultations for children could be increased by enhancing specialists' accessibility to remote communities and otherwise inaccessible areas. The flowchart presented in Fig. 2 depicts a simple approach to teledentistry for children, including the use of various social media and communicators, decision-making for emergency vs non-emergency dental needs, triage, decisions on home care instructions, and mobile or portable dentistry at home vs treatment at the dental operatory/dental clinic based on the needs of the individual child.

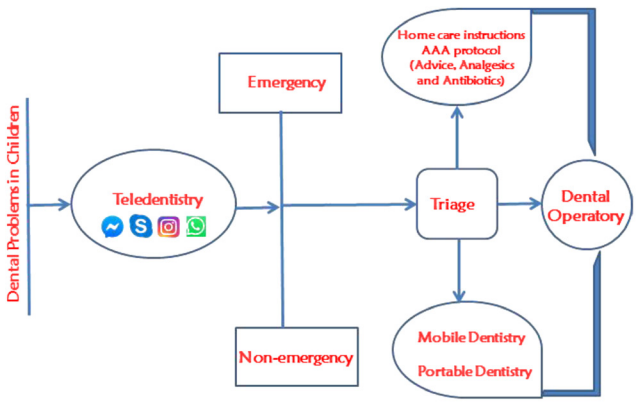

Fig. 2. Proposed teledentistry model to deal with dental problems in children during and post COVID-19 pandemic

Conclusions

Teledentistry for children could be considered as pediatric teledentistry. Pediatric dentists should train themselves and their teams also with regard to technical issues. Communication and the provision of treatment through teledentistry requires additional time and care to ensure proper advice to children and parents. Pediatric teledentistry could be a viable option for managing dental problems in children during pandemics.

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Handwashing revisited in dental practice during the COVID-19 outbreak

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Abstract

Healthcare-associated infections are well-studied in the literature, but remain a significant challenge for healthcare workers (HCWs) in dental practice. This type of infection is strongly correlated with the hand route of transmission of infectious agents. Thus, hand hygiene can be considered a crucial element in the prevention and control of infections.

The coronavirus disease 2019 (COVID-19) outbreak is an experience of a new human coronavirus infection that has been difficult for HCWs, such as dentists and dental assistants, to control. Handwashing (HW) is a keystone method for the prevention and control of spreading severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In healthcare settings, contrary to the general consideration of HW as a simple practice, HW is regarded as a specific procedure that should be clearly instructed to HCWs. Handwashing is based on using a correct method and the necessary equipment, and its role should be continually emphasized to reinforce compliance. Proper HW might contribute to avoiding possible cross-infection during healthcare activities, particularly in the pandemic situation.

The aim of this article was to report on different HW techniques in medical and dental practice, and appropriate HW equipment to perform this simple but important procedure to prevent cross-infection, particularly during the current COVID-19 outbreak.

Keywords: hand hygiene, handwashing, cross-infection, COVID-19 outbreak

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Introduction

Handwashing (HW) is an effective measure for the prevention of cross-infection in healthcare settings. While providing dental care, cross-infection may occur directly from person to person, or indirectly via soiled instruments, clothes or hands. Pittet et al. reported that the hands could be the principal route of transmission of microorganisms.[1]

Hand skin exhibits endogenous and exogenous microflora. The endogenous flora grows on the deeper layers of the skin and on hair follicles. It is residential, commensal and specific for each individual. It renews rapidly, and it is almost impossible to remove it completely; it may act as a biological barrier. By contrast, the exogenous flora is transient, colonizes the superficial skin layers and is mostly acquired via environmental routes. This flora mainly consists of saprophytes, commensal bacteria and fungi of the oropharyngeal sphere, and digestive microorganisms that are transferred from patients. The exogenous flora is harmful and pathogenic, but can be easily removed by means of clinical HW procedures.[2,3] In absence of correct hand hygiene, hand skin microflora, especially the exogenous flora, is frequently a source of the healthcare-related infections acquired while performing care activities.[2–4] Hence, it is crucial to emphasize the key role of this simple but important activity in preventing cross-infection, particularly during the ongoing coronavirus disease 2019 (COVID-19) pandemic. This emergent outbreak is the 6th public health emergency of international preoccupation, and the etiological agent – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – is the 3rd most pathogenic human coronavirus that occurred in the last 2 decades.[5,6] This new human betacoronavirus (βCoV) is an RNA virus belonging to the Coronaviridae virus family.[7] It has infectious potential through the respiratory droplets spread through coughing or sneezing by an infected individual, direct physical contact (e.g., shaking contaminated hands), or non-physical contact.[3,7–9] Distant contamination can be explained by the dynamic turbulent gas model, which has shown that pathogen-loaded droplets can circulate over a long distance.[10,11] This may happen even if a patient is not showing signs of the disease (coughing or sneezing).[6] According to previous studies, the moving turbulent gas can be transported over a distance of 23–27 feet, which corresponds to 7–8 m.[12–14]

The viability of SARS-CoV-2 depends on its capacity to be stable on surfaces. Chin et al. reported that in vitro, the viral stability was up to 3 h on paper, 2 days on wood and fabrics, 4 days on glass and banknotes, and 7 days on stainless steel and plastic.[15] Similarly, van Doremalen et al. reported that the viral stability of SARS-CoV-2 was higher on plastic and stainless steel than on copper and cardboard.[16] Santarpia et al. reported significant environmental contamination in rooms where patients positive for SARS-CoV-2 were taken care of.[17] Indeed, contamination was detected in all types of samples: air samples; personal items; room surfaces; and toilets. The presence of viral replication in the cell culture for some of the samples confirms the potential infectious nature of this virus.[17] Smither et al. suggested in an experimental study that when the virus was transmitted within small-particle aerosols, it might remain viable for at least 90 min.[18] However, it is worth mentioning that SARS-CoV-2 is sensitive to standard disinfection methods, even though it has high stability in favorable environment.[15]

Thus, proper measures are needed to prevent this deadly virus. Handwashing is considered one of the essential control measures for preventing the spread of this infection by healthcare workers (HCWs) until effective antiviral therapy and vaccination are discovered.[5,8,19]

The present review is a general overview of the importance of HW during the COVID-19 outbreak in dental practice. This review summarizes the mechanism of transmission of SARS-CoV-2, the HW procedure and the appropriate equipment needed to perform HW effectively in safe conditions. This work was designed as follows: the selection of databases was based on the principal electronic databases, i.e., MEDLINE/PubMed, Scopus (Elsevier), Science Direct Journals (Elsevier), and Google Scholar; the Medical Subject Headings (MeSH) terms used to search the articles were: "coronavirus", "coronavirus disease 2019", "COVID-19", "COVID-19 outbreak", "2019-nCoV", "SARS-CoV-2", "dental COVID-19", "dental COVID-19 outbreak", "dentistry COVID-19", "handwashing COVID-19", "hand hygiene", "cross-infection", and "healthcare workers", with the use of "AND" and "OR" between the MeSH terms. The retained articles were studies, reviews, and reports from international organizations focusing on HW during the COVID-19 outbreak in dental practice. Some earlier publications were included to understand the HW procedures and to overcome the lack of recent scientific studies regarding the issues.

Compliance with handwashing in medical practice

As cross-infection may occur in medical practice through HCWs' contaminated hands, HW is highly recommended. However, compliance with correct HW practice may vary among HCWs. Before the 1990s, it did not exceed 40% because of several factors.[20,21] Joshi et al. reported that differences in HW practice

among various medical staff members were due to such factors as workload, accessibility to soap dispensers, hand irritation, hand dryness due to chemical irritants, and the level of awareness regarding hand hygiene.[22] This study concluded that even though HCWs understood the importance of HW, they washed their hands selectively, depending on the situation. The majority of HCWs washed their hands after patient care rather than before.[22] This raises the need to emphasize the importance of HW in medical practice, particularly in dental practice, where HW compliance is relatively low and the risk of infection is high.[9] Thus, continuing education and training programs in medical settings could increase HCWs' HW compliance and the effectiveness of the procedures intended to prevent infectious diseases.[23–26]

During the outbreak of severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012, numerous studies recognized the impact of these occurrences on raising HW awareness and compliance in community settings in the affected regions. However, applicable procedures generally failed to be properly implemented.[23–25] Fung and Cairncross reported that a high fatality rate for SARS was a helpful factor to remind the individuals living in Hong Kong about the importance of HW, and that HW compliance increased and remained high for nearly 2 years after the outbreak.[25] Therefore, the preventative measures applied during those previous health emergencies may be used as a guide for HCWs during the current COVID-19 outbreak, but also after this situation to prevent possible cross-infection and to constantly review HCWs' attitudes regarding protection against infections.

On March 11, 2020, the World Health Organization (WHO) announced that the COVID-19 outbreak was a pandemic phenomenon, and outlined numerous recommendations and guidelines to face the situation.[27] The WHO's multimodal hand hygiene improvement strategy (MHHIS) in saving lives from COVID-19 global pandemic provides the evidence and the recommendations retained from the 2009 guidelines on hand hygiene in healthcare to support healthcare facilities. The following 5 key steps formed this approach[28–30]:

– a change in the system that consists in providing permanent access to hand hygiene products (alcohol-based hand rubs (ABHR), water supply, soap, and towels);
– regular training and education for HCWs;
– the evaluation of HW and feedback (monitoring practices and knowledge);
– reminders in the workplace; and
– the promotion of an institutional safety climate with the active participation of all HCWs.

Several studies reported that the implementation of MHHIS brought overall good results all over the world with regard to staff education.[16,17,31]

How and when to practice handwashing in dental practice?

'Hand hygiene' is a general term referring to any action of hand cleansing involving HW, antiseptic HW, antiseptic hand rubbing, or surgical hand antisepsis.[30,32,33] Handwashing is a "procedure of washing hands with plain or antimicrobial soap and water"; it can be performed by means of different methods, depending on the risk of infection from healthcare activities.[30,34] Three methods of HW can be practiced: routine HW; hygienic or antiseptic washing; and surgical washing (Table 1).

While HW can be considered a simple practice performed by everybody on an everyday basis, as a professional exercise, it needs to meet some specific requirements with respect to procedure and time (Fig. 1)[35,38]:

– the time required to achieve proper HW is 40–60 s;
– all jewelry or other accessories should be removed before HW;
– the hands should be held upward after rinsing;
– the hands should be dried carefully with a single-use towel; the last towel should be used to turn the faucet off, if no automatic source is available, before throwing it into a pedal bin;
– regarding surgical HW, the procedure is finished by brushing the fingernails and the subungual areas, where the concentrations of microorganisms are high, with a sterilized brush with or without antiseptic solution; the brush should be used only for the fingernails and not for the skin, as it could create micro-cuts or erosions, which might lead to the exposure of the underlying cutaneous layers to microorganisms and possibly enable infection.[2]

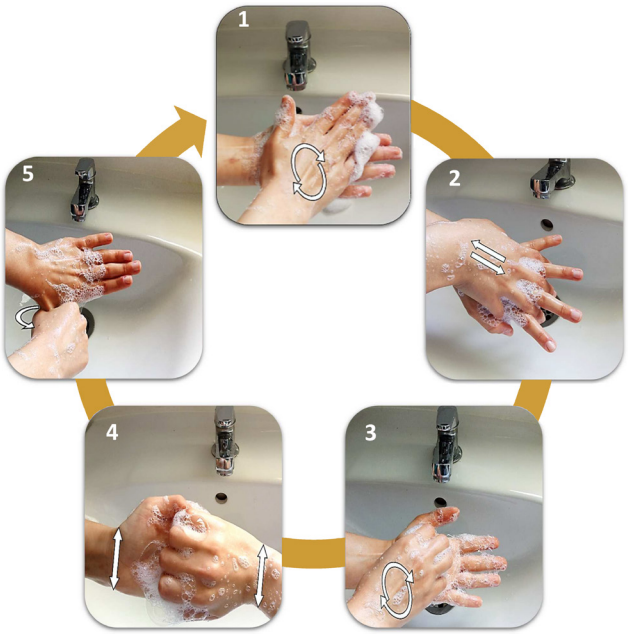

Fig. 1. Different steps of the professional handwashing (HW) procedure

Table 1. Different professional handwashing (HW) methods, depending on clinical situations in dental practice[2,3,32,35–37]

Method	Purpose	Indication	Agent	Technique
Routine HW	– to eliminate the transient flora	low risk of infection – when arriving to the clinical department and before leaving it – between 2 patients – between 2 activities – before and after non-invasive nursing care activities – before and after the activities of everyday life	– soft liquid soap and a dispenser – single-use paper towels – a faucet with non-manual control – a pedal bin	minimal duration: 30 s technique: – denude hands and elbows – wet hands and wrists – apply a soap dose – wash each hand while massaging, focusing on the interdigital spaces, the perimeter of nails, the pulp of fingers, and wrists – rinse thoroughly – dry hands by thoroughly wiping with single-use paper towels – turn off the faucet (if not automatic) with the last paper towel used – throw the paper towel into the bin without touching it with your hands
Hygienic or antiseptic HW	– to reduce the commensal flora – to eliminate the transient flora	medium risk of infection – invasive care – septic or aseptic isolation – aseptic care or techniques – after each care activity with medium contamination	– antiseptic foaming solution – single-use paper towels – a faucet with non-manual control – a pedal bin	It should be practiced before healthcare activities and at the nearest water point. longer duration: minimum 30 s the same technique as in routine HW, but: – use disinfectant soap – keep palms facing upward to avoid environmental contamination
Surgical HW	– to eliminate the transient flora – to reduce the commensal flora significantly (2–3 log 10)	high risk of infection – healthcare with a high risk of infection: • surgical activities (endodontic surgery, implant surgery, alveolectomy, etc.) • in operating rooms	– antiseptic foaming solution – a sterile single-use brush or a sterilized soft brush in a single bag – sterile paper towels – a faucet with non-manual control – a pedal bin	duration: a total of about 6 min it involves 3 stages: – 1st stage – prewash • wet hands, wrists and forearms • apply a dose of antiseptic soap and massage thoroughly from fingertips to elbows for 1 min • keep hands above elbows • rinse hands, wrists and forearms thoroughly – 2nd stage • repeat a dose of soap and lather by massaging, using the same technique • take a sterile brush and brush nails for 30 s per hand (a total of 1 min) • rinse hands, wrists and forearms thoroughly – 3rd stage • repeat a dose of soap, massage for 1 min (hands, wrists and forearms) and rinse • pat dry with a sterile paper towel

Independently of healthcare activities and procedures, HW is an imperative procedure for any person who comes into contact with patients, principally HCWs, such as dentists and dental assistants, who are at particularly high risk of the SARS-CoV-2 infection during the present COVID-19 pandemic.[39,40]

Handwashing is indicated once the hands get soiled or contaminated.[41–43] Peng et al. defined specific indications with regard to HW for oral health professionals during the COVID-19 pandemic as follows: before and after routine dental examinations or procedures; after touching non-disinfected surroundings and equipment; and after touching the oral mucosa, damaged skin or wounds, blood, body fluids, secretions, and excreta.[9] Ding et al. consider toilets as high-risk areas in hospitals with COVID-19 patients, and emphasize the strong need for hand and environmental hygiene as an intervention against the transmission of COVID-19.[44] Indeed, contaminated aerosols may come from 3 possible sources: the exhaled release from patients when using the bathroom; toilet-generated aerosols when the toilets are flushed of feces and urine; and the import of airborne particles from the stalls. This proves that the use of toilets in healthcare areas might result in vector transmission, especially hand transmission.[44,45]

During the COVID-19 pandemic, HW is a crucial procedure, especially given the persistence of SARS-CoV-2. Indeed, this virus can be present on surfaces for a few hours up to several days, which exposes HCWs to a high risk of infection. There is no sufficient data concerning the viral load of coronaviruses on inanimate surfaces or the hands, and its transmissibility from contaminated surfaces to the hands in healthcare settings in an outbreak situation.[46]

Therefore, surface disinfection, especially of the frequently touched surfaces with the highest viral load, is important for preventing hand contamination. To ensure environmental cleaning and disinfection, the WHO recommends the consistent, correct and thorough cleaning of environmental surfaces with water

and detergent as well as applying the commonly used hospital-level disinfectants, such as sodium hypochlorite, as effective and sufficient procedures.[46,47] Several studies investigated which disinfectant agents should be used for surfaces and the hands to protect against SARS-CoV-2. Many formulations were tested to assess their rapidity, spectrum of microbicidal activity, accessibility, and safety (Table 2). Furthermore, to limit the risk of airborne contamination, different air purifiers are relevant during this pandemic (Table 3).

During the COVID-19 pandemic, hand-rub products are widely used in healthcare settings as one of the infection control tools. In routine medical practice, the ABHR formulations (ethanol or isopropanol agents) are commonly applied, as recommended by the WHO.[30] However, their effectiveness appears to be limited and does not meet the European standards.[72,73] Thus, modified formulations have been suggested. Suchomel et al. proposed the following modified formulations:

– the WHO I formulation (Formula 1):

ethanol 96% v/v + glycerol 98%
+ H_2O_2 3% (6 mL in 60 s); (1)

– the modified WHO I formulation (Formula 2):

ethanol 80% w/w + glycerol 0.5% v/v
+ H_2O_2 0.125% v/v (3 mL in 30 s); (2)

– the WHO II formulation (Formula 3):

isopropanol (with a purity of 99.8%) + glycerol 98%
+ H_2O_2 3% (6 mL in 30 s); (3)

– and the modified WHO II formulation (Formula 4):

isopropanol 75% w/w + glycerol 0.5% v/v
+ H_2O_2 0.125% v/v (3 mL in 30 s).[74] (4)

In light of the ongoing circumstances, several reports from international organizations[40,75–78] recommend the use of medical gloves as part of the personal protective equipment (PPE) to strengthen protection against potentially infectious biologic secretions.[39] Ye et al. reported that gloves were the PPE most contaminated with SARS-CoV-2 at 15.4%.[79] Hence, wearing gloves should not be an alternative to HW in healthcare practice, mainly because of rapid bacterial proliferation due to the humidity of the hands under the surface of gloves and the deterioration of gloves.[4,80]

Additionally, HCWs should observe further precautions concerning the route of transmission of microorganisms by avoiding touching their face, eyes, mouth, and nose.[9] Macias et al. reported that during the influenza A (H1N1) pandemic, face touching behavior was commonly observed on average 3.3 times per hour in the community.[81] It was also reported that face touching behavior among medical students with their own hands was observed on average 23 times per hour, with contact mostly to the skin (56%), followed by mouth (36%), nose (31%), and eyes (31%).[82] These results cannot be generalized to all HCW categories because of several factors, such as the duration of the experiment and the degree of awareness. However, they illustrate the higher risk of infection HCWs face as compared to the rest of the community, which makes HW procedures an effective and inexpensive preventative method to break the colonization and transmission cycle from the autoinoculation route, and to minimize the spread of infection.[82] Furthermore, to avoid potential nosocomial infection, it is recommended to have short fingernails, no nail polish and no jewelry; otherwise, contamination can frequently occur even with proper HW.[83–87]

To summarize the timings of HW, the WHO recommends "My Five Moments for Hand Hygiene" approach as guidelines for dental practice as follows: before touching a patient; before clean/aseptic procedure; after body fluid exposure risk; after touching a patient; and after touching patient surroundings.[86]

Table 2. Effectiveness of different types of disinfectant agents at various concentrations [%] against severe acute respiratory syndrome coronavirus (SARS-CoV)

Disinfectant agent	Concentration for surface use and exposition time	Concentration for hand use and exposition time
Ethanol	70–90% / 30 s [48,49]	80% v/v, 85% v/v and 95% v/v UND / 30 s [48,55]
Isopropanol	70% and 75% / 30 s [50,51]	75% w/w D to 20% / 30 s [50,56]
Formaldehyde	0.5–3% / 2 min [49,51]	0.7–1% / 2 min [51,57]
Glutardialdehyde	0.5% / 2 min [49,51]	0.5% / 2 min [51,57]
Povidone-iodine	0.23–1% / 15 s [49,52]	0.5–10% / 15 s [52,57]
Sodium hypochlorite	0.5% (5,000 ppm) / 1 min [46,53]	<5% (0.05–0.21%) / <1 min [57]
Hydrogen peroxide	1–3% / 1 min [49,54]	0.125% v/v D to 40–80% / 30 s [50,56]
Triclosan/triclocarban	–	1–2% / <1 min [55,58]
Chlorhexidine	lower effectiveness against SARS-CoV is due to lower capacity to inactivate the enveloped human coronavirus, and also to some environmental factors (cold temperatures, external humidity and pH)[57,59]	
Benzalkonium chloride		

UND – undiluted concentration; D – diluted concentration.

Table 3. Air disinfection procedures against severe acute respiratory syndrome coronavirus (SARS-CoV)

Procedure types		Disinfection properties	Advantages	Disadvantages
UVGI[60,61–63]	– UVGI types: • UV-A WL: 315–380 nm • UV-B WL: 280–315 nm • UV-C WL: 100–280 nm – UVGI options: • UV-C flow germicidal lamps – contaminated air drawn through a filter • UV-C direct radiation tubes – direct disinfection of the whole room • dual-function UV-C flow germicidal lamps – combining the 2 above options	– bactericidal and virucidal activity – SARS-CoV-2 is highly susceptible to UV-C damage at a dose 0.377–0.590 J/m^2	– important role in reducing the risk of transmission of coronaviruses, such as SARS-CoV-1, MERS and SARS-CoV-2 – disinfection effectiveness is improved by the addition of UV-C radiation for 20–30 min after cleaning between 2 patients	– UV-C light disinfection may not always be effective due to a low penetration depth – access to rooms with UV-C direct radiation tubes should be denied to everyone – lower light effectiveness for the objects situated far away from the source of UV-C light
Air fogging[60,64,65]	– hydrogen peroxide processing forms: • vaporized hydrogen peroxide • aerosolized hydrogen peroxide – the gaseous form is more effective than the liquid form	– bactericidal, virucidal, fungicidal, and sporicidal activity	– hydrogen peroxide is the recommended agent for daily use in enclosed healthcare areas	– rooms should be evacuated and pre-cleaned of visible dirt – rooms cannot be immediately occupied after disinfection – physical irritation of the mucous membranes, the eyes, skin, and lungs is possible – users need to be trained
Photocatalytic disinfection[60,66,67]	– titanium dioxide filters stimulated by UV radiation	– effective against a wide range of Gram-negative and Gram-positive bacteria, fungi, protozoa, and viruses – effective against SARS-CoV-1, with a high probability of virucidal effect on SARS-CoV-2	– high potential for inactivating pathogens, increased by the use of silver and titanium dioxide filters	– disinfection effectiveness is influenced by the design of the device and the indoor air properties (relative humidity, temperature and the composition of contaminated air)
Plasma[60,68,69]	– non-thermal plasma adapted for biological applications	– biocidal effect on viruses, bacteria, spores or fungi, and prions, with little impact on the structural integrity of disinfected surfaces	– can be used in several devices to address air disinfection – safe and non-toxic for the environment – easy to handle – inexpensive	– new technique that is not largely used
Ozone generators[60,70,71]	– ozone gas	– bactericidal, virucidal and fungicidal activity – ozonation effectiveness against coronaviruses at 100 ppm/30 min	– easy penetration into all areas of the room and all objects	– rooms must be evacuated and enclosed – not the first choice as a disinfection method, since ozone is toxic – effective ventilation systems are required as well as the measures taken to check that residual ozone has been efficiently eradicated – corrosion risk for some materials

UVGI – ultraviolet germicidal irradiation; UV – ultraviolet; WL – wavelength.

Professional handwashing materials

In medical areas, a well-planned HW equipment set-up (washbasins, liquid soap dispensers, and hand wiping and drying systems) can protect HCWs from potential nosocomial infection and ensure correct HW. Indeed, Coleman et al. reported that contaminated washbasins and sink drain outlets were associated directly or indirectly with the hospital outbreaks of infection.[6] Ye et al. reported that hand sanitizer dispensers accounted for about 20.3% of contaminated objects.[79] Therefore, HW materials (washbasins, liquid soap dispensers, etc.) can be considered a possible source of microbial biofilm proliferation, and thus require good maintenance, regular cleaning and exclusive use for HW by HCWs.[6,79]

With regard to HW agents, it is recommended to apply those indicated for professional medical use.[87] These agents generally have the following features: are not perfumed; rarely induce allergic reactions; and are suitable for everyday use. Professional HW is based on the treatment of the hands with regular liquid soap or an antimicrobial product (soap, gel or solution), with the spectrum of activity targeted at micro-organisms that are part of the cutaneous flora to prevent their transmission.[76] Such products contain emollients, e.g., glycerine or aloe vera, that promote hand health and comfort.

These components have a softening effect that prevents the occurrence of dermatitis, which may result from frequent HW, and also helps to ensure HW compliance.[58] However, the specificity of the products indicated for antiseptic or surgical washing, as compared to simple wash products, consists in their net, rapid and persistent bactericidal and virucidal effect for several hours on the cutaneous flora of the hands.[88] The products commonly used in medical practice are based on chlorhexidine from 2% up to 4%, alcohols between 60% and 70%, or iodine-based compounds.[2,4,32] Regarding the soap form, bar soap should be avoided in hospitals to prevent creating a microbial niche that is consequently a source of contamination, unless it is intended for single use.[37] According to several studies, bar soap can be a reservoir of various microorganisms and using it in hospital practice can transform HW into a vehicle for spreading infections, such as gastrointestinal infection, respiratory infection or cutaneous infection, including the SARS-CoV-2 respiratory infection.[22,89,90] Thus, liquid soap is highly recommended instead of bar soap. Nevertheless, the risk related to the soap dispenser system must be controlled. The soap refill is screwed into the system and the liquid flows by gravity. To avoid contamination, the last drop should not be sucked into the cartridge, and the valves should be operated with the elbow to avoid direct contact with the soap dispenser.

In addition, the manual water faucets commonly installed in healthcare settings should be avoided because of the risk of infection and contamination. To avoid manual contact, the faucet should be controlled by a pedal or the elbow. Ideally, an automatic faucet (electro-sensitive) with a sufficiently large and deep washbasin to avoid splashing contamined water should be used for HW. Notably, the area reserved for HW should be independent of the instrument disinfection area.[37] For simple washing and antiseptic washing, warm water is more recommended than water of extreme temperature (hot or cold) to avoid cutaneous irritation and dryness.[58] Regarding surgical HW, using pure water is practiced; according to the microbiological quality control standards, 'clean water' is of level 1, which is obtained by the chlorination (0.1 mg/L) chemical treatment of the water supply.[91]

After HW, meticulous hand drying is the final and necessary step to prevent the transmission of microorganisms, which is caused more often by wet hands than by dry hands due to the nature of the clinical practice, frequently exposing HCWs' hands to wetness. In contrast, hand drying may decrease the number of microorganisms translocated through touch.[91,92] For wiping hands, single-use hand towels are recommended after simple and hygienic HW, and sterile hand towels after surgical HW. In general, the following characteristics of hand towels are recommended for safe hand drying: they should be absorbent; flexible to fit the hand's anatomy; and resistant to tearing. The hand drying system has an influence on the protection against cross-infection.

Apart from being slow and noisy, electric hand dryers are to be avoided in healthcare settings because, according to some studies, the waterborne microorganisms dispersed by hand dryers can become aerosols.[2] Kimmitt and Redway studied hand drying methods by comparing paper towels, a warm air dryer and a jet air dryer for their potential to disperse viruses and contaminate the immediate environment during use.[93] They found that the use of a jet air dryer led to a significantly greater and further dispersal of microorganisms from artificially contaminated hands as compared to paper towels and a warm air dryer.[93] Hence, it is necessary to make a careful choice of the hand drying system in healthcare settings, where the risk of cross-infection is high, especially during critical situations like the present outbreak, to safeguard patients and HCWs.[92,93] It is worth noting that before wearing gloves, HCWs should dry their hands completely after hand disinfection, as residual humidity, such as that from ABHR, may increase the risk of glove perforation during daily dental care.[94] Lastly, for collecting used hand towels, a pedal bin installation is required near the HW set-up to avoid touching the bin, and thus to limit the risk of contamination of HCWs' hands.

Conclusions

In medical practice, HW is a basic measure for preventing the transmission of germs and the spread of infection related to healthcare activities. The occurrence of more or less serious nosocomial infection is a real risk in dental practice, and prevention concerns are paramount. Hence, HW is a very important and simple – but indispensable – procedure to prevent the manual transmission of germs.

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Do fluoroquinolone agents produce therapeutic benefits or harmful effects in patients with periodontitis? A systematic review and meta-analysis

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Abstract

The adjunctive use of fluoroquinolone (FQ) agents in patients with periodontitis produces contradictory results. There has been no meta-analysis performed based on the evaluations of FQ use that would enable making appropriate clinical decisions. Our study aimed to evaluate, via a systematic review and meta-analysis conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines, the clinical benefits, antimicrobial effects and safety profiles of the FQ agents administered to periodontitis patients under a conventional treatment regime. Relevant databases were searched for studies published up to May 2020, with the quality and risk of bias evaluations performed on the selected studies, and meta-analyses, funnel plots and heterogeneity tests carried out based on the obtained data. Any finding of *p*-value less than 0.05 was considered statistically significant. Quality and the risk of bias ranged from high to low. With acceptable heterogeneity and no reporting bias, the meta-analyses showed that local or systemic FQ use produced the following results: a reduced probing depth change (ΔPD) ($p < 0.00001$ at ≤3 months); reduced bleeding on probing (BOP) ($p < 0.00001$ at 3–6 months); reduced subgingival detection of Aggregatibacter actinomycetemcomitans for up to 12 months (*p*-values from <0.00001 to 0.001); and an insignificant number of adverse events ($p \geq 0.05$) in patients subjected to a conventional therapy as compared to those subjected to an antibiotic-free therapy. Our study found evidence to show that FQ administration provides clinical benefits and ensures antibacterial effects in periodontitis patients subjected to a conventional therapy regime.

Keywords: periodontitis, meta-analysis, fluoroquinolone, adjunctive therapy

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Introduction

It is well-known that dental plaque can initiate gingival inflammation (gingivitis), which, in many cases, can progress, leading to the destruction of the underlying connective tissue and the alveolar bone (periodontitis), resulting in the loss of the affected tooth.[1] Periodontitis is one of the most predominant oral diseases; it affects the majority of the global population.[2] Variability in the individual host's response to local factors plays a crucial role in this condition, and the loss of balance between the host's response and the oral microbiome leads to development and progression of the disease.[1] *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) and members of the red complex (e.g., *Porphyromonas gingivalis* – *P. gingivalis*, *Tannerella forsythia* – *T. forsythia* and *Treponema denticola* – *T. denticola*) are the most significant species associated with periodontitis.[3] During the course of this disease, the foregoing bacteria penetrate the tissues and the periodontium, triggering the host's immune response to the invading bacteria.[4] Periodontitis also has been associated with the presence of various systemic disorders, such as coronary heart disease, diabetes, cerebrovascular disease, and pancreatic cancer.[5,6]

The conventional treatment of periodontitis involves an oral hygiene program administered at home, and professional management (e.g., scaling) conducted via surgical or nonsurgical access to the affected sites. This kind of treatment is effective for the majority of patients and is followed by a recall program, which provides periodontal care every 3–4 months and helps to prevent the progression of the disease to a chronic state. However, the use of adjunctive treatment is necessary in the case of patients for whom the recall program has been unsuccessful. Adjunctive therapies comprise the local or systemic administration of antimicrobials,[7] of which fluoroquinolone (FQ) agents are one of the most important antibiotics prescribed by oral healthcare professionals.[8,9] Fluoroquinolone agents, a family of broad-spectrum antibacterial agents acting against a wide range of aerobic gram-positive and gram-negative organisms,[10] act by binding to an intracellular target in the cytosol of bacteria, where they inhibit the activity of DNA gyrase, with a high selectivity for prokaryotic enzymes.[11,12]

While numerous studies have evaluated the clinical and microbiological efficacy as well as the safety profiles of FQ agents in patients with periodontitis,[3,13–26] the results are often contradictory. A precise clinical evaluation requires the use of statistical methods, such as meta-analysis, to combine the results obtained through independent studies. Meta-analysis provides a more exact estimate of the health effects of treatment than those derived from individual studies.[27] To date, there have been no review and meta-analysis carried out to evaluate the efficacy and safety profiles of the FQ agents used as adjuncts to the conventional treatment of periodontitis patients. Therefore, the aim of our study was to evaluate, using the systematic review and meta-analysis methodology, the clinical, antimicrobial and harmful effects of the FQ agents administered in combination with a conventional treatment for periodontitis.

Methods

Search strategy

The present study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[28,29] In addition, the protocol for the systematic review portion of the present study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) of the United Kingdom's National Institute for Health Research (NIHR).

The PubMed, MEDLINE, Cochrane, LILACS, and Imbiomed databases were searched from their earliest records to May 31, 2020 to identify interventional studies that employed FQ agents for the adjunctive treatment of periodontitis. The following search terms were used for the PubMed, MEDLINE, Cochrane, and LILACS databases: "chronic periodontitis" AND "fluoroquinolone"; "chronic periodontitis" AND "levofloxacin"; "chronic periodontitis" AND "moxifloxacin"; "chronic periodontitis" AND "ciprofloxacin"; "chronic periodontitis" AND "ofloxacin"; "chronic periodontitis" AND "sitafloxacin"; "chronic periodontitis" AND "sparfloxacin"; "aggressive periodontitis" AND "fluoroquinolone"; "aggressive periodontitis" AND "levofloxacin"; "aggressive periodontitis" AND "moxifloxacin"; "aggressive periodontitis" AND "ciprofloxacin"; "aggressive periodontitis" AND "ofloxacin"; "aggressive periodontitis" AND "sitafloxacin"; "aggressive periodontitis" AND "sparfloxacin"; "periodontitis" AND "fluoroquinolone"; "periodontitis" AND "levofloxacin"; "periodontitis" AND "moxifloxacin"; "periodontitis" AND "ciprofloxacin"; "periodontitis" AND "ofloxacin"; "periodontitis" AND "sitafloxacin"; and "periodontitis" AND "sparfloxacin". In this manner, 21 combinations of 2 different terms were used for each database. Due to the nature of the platform, the following single search terms were used for the Imbiomed database: levofloxacin (LVX); moxifloxacin (MOX); ciprofloxacin (CPX); ofloxacin (OFX); sitafloxacin (STX); sparfloxacin (SPX); fluoroquinolone; chronic periodontitis; aggressive periodontitis; and periodontitis.

Eligibility criteria

Research papers were selected based on the following inclusion criteria: a randomized or non-randomized controlled clinical trial that employed a parallel or split-mouth design to systemically treat healthy patients diagnosed with chronic, adult or aggressive periodontitis; at least 1 test group received an FQ agent; the report had been published in English or Spanish. The exclusions criteria were as follows: an FQ agent was not administered as an adjunctive therapy; an antibiotic-free group was not included in the study; the study participants had been prescribed an anti-inflammatory medication; the patients had taken an antibiotic in the previous 3 months; all the data used in the study had been taken from another study by the same author. This last criterion did not include duplicates, as those studies were not the exact copies of each other.

Data extraction

First, 2 researchers independently screened the titles and abstracts of the articles found, and then reviewed full-text papers. Once the initial evaluation was complete, a third researcher reviewed the work. Any discrepancy between the evaluations was resolved by consensus with the input of another experienced researcher. The following characteristics were extracted from each study: first author; year of publication; the participants' age; study design; confirmed diagnosis of the disease; number of patients; intervention characteristics (active principle, concentration, dose interval, and route of administration); periodontal parameters; adverse effects; and the number of patients in whom periodontitis-related microorganisms had been identified via subgingival detection. The periodontal parameters used were probing depth (PD), clinical attachment level (CAL), PD change (ΔPD), gain of CAL (ΔCAL), percentage of sites with bleeding on probing (%BOP), plaque index (PI), and gingival index (GI). When a study featured more than 1 group treated with the same FQ agent, but at a different concentration, the information was harvested solely from the test group which received the dose with the most beneficial effects. The extracted information was grouped into the following periods of time: ≤3 months post-intervention; >3 and ≤6 months post-intervention; and >6 and ≤12 months post-intervention. When a study involved 2 or more examinations in an established timeframe, the information was collected solely from the examination with the longest timeframe.

Assessment of quality and the risk of bias

The quality of the selected studies was assessed using the Oxford Quality Scale,[30] as described previously.[31–33] Clinical trials with scores ≥3 were classified as high-quality studies, while those with scores <3 were considered low-quality studies. The internal validity of the selected studies was evaluated using the Cochrane Collaboration's risk of bias (RoB) tool.[34] This tool uses the following criteria to assess the risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. According to the procedure described by Higgins et al., each criterion was categorized as a low, unclear or high risk of bias,[35] with a risk of bias graph used to show the proportion of the selected studies falling into each category. Each quality and risk of bias assessment was reviewed by an additional researcher, with any discrepancies resolved as described above.

Data analysis

The meta-analyses were performed based on the data obtained from studies of periodontitis patients treated with an adjunctive control or FQ intervention, administered either locally or systemically. For continuous data, each meta-analysis was carried out with the use of the inverse variance (IV) method. The mean differences (or standardized mean differences) and their 95% confidence intervals (*CI*s) were analyzed with the fixed effects model, using the Review Manager 5.3 software.[34] For dichotomous data, the meta-analysis was performed with the Mantel–Haenszel (MH) method. The odds ratios (*OR*s) (or risk differences) and their 95% *CI*s were analyzed with the fixed effects model, using the software mentioned above, and statistic Z, statistic I^2 and p-values were used to evaluate the overall effect, heterogeneity and probability, respectively. Statistic I^2 ranging from 0 to 40%, from 40 to 70%, or from 70 to 100% was considered as absent, acceptable or considerable heterogeneity, respectively, with probability of less than 0.05 accepted as significant. With a funnel plot used to detect reporting bias in each conducted meta-analysis conducted, the presence of any reporting bias produced an asymmetrical funnel.[36]

Results

Characteristics and evaluation of the studies

Thirty-one studies were identified as complying with the selection criteria of using an adjunctive FQ agent to treat patients with periodontitis (Fig. 1). Of these studies, nineteen were excluded: 1 did not employ an FQ insert as an adjunctive therapy,[25] 14 did not include a comparator group without an antibiotic,[9,21,37–48]

3 studies used the data extracted from a study by the same author that had already been considered in the present study,[13,15,49] and 1 other study used ibuprofen together with MOX.[50] Thecharacteristics and outcomes of the studies selected for analysis are summarized in Table 1 and Table 2. A dose of 0.4% MOX was selected for our review, as Flemmig et al. claimed that this dose produced better results than other doses.[19] The studies conducted by Ardila et al.,[14] Pradeep et al.,[3] Pradeep et al.,[17] Flemmig et al.,[19] Khan et al.,[16] Nakajima et al.,[18] Guentsch et al.,[20] Kimura et al.,[26] Tezel et al.,[51] Kleinfelder et al.,[23] Parthasarathy et al.,[22] and Nagaraju et al.[24] received quality scores of 5, 5, 5, 5, 3, 3, 3, 3, 2, 2, 1, and 1, respectively.

Our quantitative analyses did not include the studies of Parthasarathy et al.[22] and Kimura et al.,[26] as the former used incomplete data (means without standard deviations) and the latter solely reported undetectable subgingival levels of *A. actinomycetemcomitans* in their patients during the entire course of the therapeutic intervention. Furthermore, some of the information from the studies included in the present review could not be extracted, as it was presented solely in the graphic form (e.g., the PD, CAL, %BOP, and GI values presented by Khan et al.[16]). Since 2 studies by the same author,[3,17] which were included in the present study, were conducted in the same place and period of time, the data extraction procedure was performed in such a way as to avoid redundancy. Figure 2 shows the risk of bias for the 10 studies subjected to the quantitative analysis presented below.

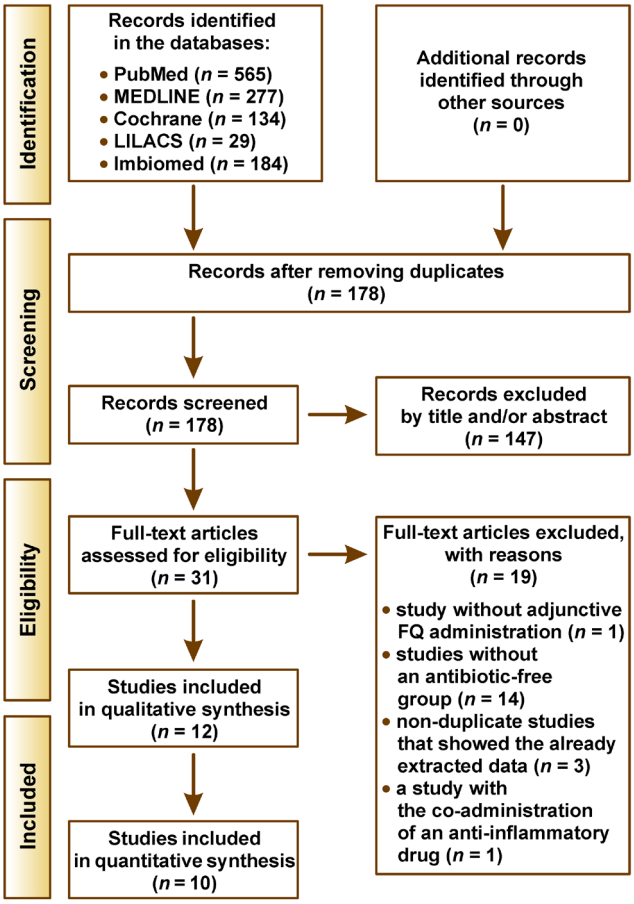

Fig. 1. Search strategy – PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram

FQ – fluoroquinolone.

Table 1. Characteristics of the included studies

First author, year of publication	Study design, diagnosis of disease	Groups (sample size) and the participants' age	Intervention characteristics	Clinical and/or bacteriological measurements
Kimura et al. 1991[26]	– design: randomized, placebo-controlled, split-mouth clinical study – disease: chronic periodontitis	– groups: • test group: SRP + OFX (*n* = 27) • control group: SRP + placebo (*n* = 27) – mean age of the participants: 43.9 years	– Each insert was 1 mm wide and 0.4 mm thick. The test insert contained OFX 10% w/w (40 µg/mm of the film length). – The patients received instructions for appropriate oral hygiene. – Before the baseline visit, STC was carried out and inserts were placed into pockets on a weekly basis for 2 weeks. The test and control inserts were applied in different pockets of the same patient. – During the baseline visit, the SRP intervention and the application of inserts were carried out. – After the baseline visit, the test and placebo inserts were applied on a weekly basis for 3 weeks.	– 2 weeks before the baseline visit – during the baseline visit – 1 and 4 weeks after the baseline visit
Nagaraju et al. 1999[24]	– design: placebo-controlled, split-mouth clinical study – disease: chronic periodontitis	– groups: • test group: STC + CPX implant (*n* = 10) • control group: STC + placebo implant (*n* = 10) – age of the participants: not provided	– Each drug implant contained 1 mg CPX and was cut to a 0.5 cm × 0.5 cm size. – The patients received instructions for appropriate oral hygiene. – After the removal of supragingival surface deposits, the test and placebo implants were placed in different pockets of the same patient without sutures or dressing.	– before the implant application – 10, 20, 30, and 40 days after the implant application
Kleinfelder et al. 2000[23]	– design: controlled, single-blinded, parallel-arm clinical trial – disease: *Aa*-associated adult periodontitis	– groups: • test group: flap surgery + STC and OFX (*n* = 22; mean age: 47.7 years) • control group: flap surgery + STC (*n* = 10; mean age: 46 years)	– Before the surgical therapy, the patients received an STC intervention and instructions for appropriate oral hygiene. – An open flap debridement was conducted on the pockets of patients with PD ≥ 5 mm. Full-mouth surgery was performed within 3 or 4 appointments, and was completed after 2 or 3 weeks. In addition, the patients belonging to the test group received the systemic application of 400 mg OFX once a day for 5 days, starting from the 1st day of flap surgery. – After the surgical therapy, the patients received STC every 3 months.	– before the surgical therapy – 3 and 12 months after the flap surgery

First author, year of publication	Study design, diagnosis of disease	Groups (sample size) and the participants' age	Intervention characteristics	Clinical and/or bacteriological measurements
Parthasarathy et al. 2002[22]	– design: placebo-controlled, split-mouth clinical study – disease: severe chronic periodontitis	– groups: • test group: STC + SPX chip (n = 10) • control group: STC + placebo chip (n = 10) – age of the participants: not provided	– Each chip was 10 mm long, 2 mm wide and 0.5 mm thick. The drug chip contained 2 mg SPX. – Before the implantation of chips, the patients underwent an STC session. – Both the test and placebo chips were inserted into different pockets of the same patient and kept in place with a periodontal dressing. – Twenty-one days post-implantation, each chip was removed from the periodontal pocket.	– before the implantation – 1, 7, 14, and 21 days after the implantation
Tezel et al. 2005[51]	– design: single-blinded, parallel-arm clinical study – disease: chronic periodontitis	– groups: • test group: SRP + CPX (n = 8) • control group: SRP alone (n = 8) – mean age of the participants: 39.2 years	– Before the intervention, the patients were instructed to apply solely manual toothbrushing and to use dental floss for the duration of the study. – The intervention comprised full-mouth SRP, with the patients belonging to the test group receiving systemic 500 mg CPX once a day for 7 days.	– before the intervention – 7, 21 and 90 days after the intervention
Guentsch et al. 2008[20]	– design: randomized, controlled, single-blinded, parallel-arm clinical trial – disease: severe chronic periodontitis	– groups: • test group: SRP + MOX (n = 35) • control group: SRP + placebo (n = 21) – mean age of the participants: 49.6 years	– Before the treatment, the patients received instructions for appropriate oral hygiene. – The treatment consisted of rinsing with chlorhexidine, one-stage full-mouth SRP, and the daily administration of the test or placebo tablet for 7 days. The drug tablet contained 400 mg MOX. Some patients belonging to the control group did not receive the placebo tablet.	– 1 week before the treatment – 3, 6 and 12 months after the treatment
Flemmig et al. 2011[19]	– design: randomized, placebo-controlled, double-blinded, parallel-arm clinical trial – disease: chronic periodontitis	– groups: • test group: SRP + MOX (n = 15; mean age: 47.7 years) • control group: SRP + placebo (n = 15; mean age: 46 years)	– Before the application of gel, full-mouth SRP was performed in the patients on 2 consecutive days. – A single dose of 0.4% MOX or placebo gel was placed in the periodontal pocket of the tooth. Gel was applied until the pocket overflowed with excess gel. – After the application of gel, the patients performed routine oral hygiene and used amine fluoride dentifrice.	– before SRP – 6 weeks and 3 months after the gel application
Nakajima et al. 2012[18]	– design: randomized, controlled, single-blinded, parallel-arm clinical trial – disease: chronic periodontitis	– groups: • test group: STC + STX (n = 20; mean age: 60.7 years) • control group: STC + SRP (n = 19; mean age: 63.4 years)	– During the baseline visit, the patients received an STC intervention and instructions for appropriate oral hygiene. In addition, the patients belonging to the test group were orally administered 50 mg STX twice a day for 5 days, whereas the patients belonging to the control group received an SRP intervention. – The patients received STC 1 and 3 months after the baseline visit.	– during the baseline visit – 1 and 3 months after the baseline visit
Pradeep et al. 2014[17]	– design: randomized, placebo-controlled, double-blinded, parallel-arm clinical trial – disease: *Aa*-associated chronic periodontitis	– groups: • test group: SRP + LVX (n = 34; mean age: 36.7 years) • control group: SRP + placebo (n = 32; mean age: 36.8 years)	– One week before the baseline visit, the patients received an STC intervention and chlorhexidine rinse, and instructions for appropriate oral hygiene. – During the baseline visit, the patients underwent an SRP session and the experimental therapy (500 mg LVX or the placebo tablet once a day for 10 days).	– during the baseline visit – 10 days, and 1, 3 and 6 months after the baseline visit
Pradeep et al. 2015[3]	– design: randomized, placebo-controlled, double-blinded, parallel-arm clinical trial – disease: chronic periodontitis	– groups: • test group: SRP + LVX (n = 33; mean age: 35.6 years) • control group: SRP + placebo (n = 32; mean age: 35.9 years)	The same intervention as described by Pradeep et al. 2014.17	– during the baseline visit – 10 days, and 1, 3 and 6 months after the baseline visit
Ardila et al. 2015[14]	– design: randomized, placebo-controlled, triple-blinded, parallel-arm clinical trial – disease: generalized aggressive periodontitis	– groups: • test group: SRP + MOX (n = 20; mean age: 28.4 years) • control group: SRP + placebo (n = 20; mean age: 26.4 years)	– The patients received oral hygiene and home dental care instructions during the course of the study. – On the day of the intervention, the patients received one-stage full-mouth SRP and the oral administration of the test (400 mg MOX) or placebo therapy. The capsule was taken once a day for 7 days.	– before SRP – 3 and 6 months after SRP
Khan et al. 2016[16]	– design: randomized, placebo-controlled, single-blinded, split-mouth clinical study – disease: chronic periodontitis	– groups: • test group: SRP + LVX (n = 10) • control group: SRP + placebo (n = 10) – age of the participants: 20–50 years	– Each film weighed 6.13 ±0.04 mg, with the drug film containing a total LVX content of 93.8 ±2.2%. – The patient's oral hygiene status was evaluated alongside the clinical measurements. – After a full-mouth SRP intervention, the test and placebo films were inserted into different pockets of the same patient and kept in place with a periodontal dressing, which was removed 1 week after the insertion of the film.	– before the intervention – 1, 2, 4, and 8 weeks after the intervention

Aa – *Aggregatibacter actinomycetemcomitans*; SRP – scaling and root planing; OFX – ofloxacin; STC – supragingival tooth cleaning; CPX – ciprofloxacin; SPX – sparfloxacin; MOX – moxifloxacin; STX – sitafloxacin; LVX – levofloxacin; PD – probing depth.

Table 2. Qualitative synthesis of the included studies

FQ agent	Was the periodontal parameter improved due to an FQ intervention in comparison with the control group?							Was the detection of the pathogen reduced due to an FQ intervention in comparison with the control data?					Were any adverse events reported in the groups?
	CAL	PD	ΔCAL	ΔPD	%BOP	GI	PI	*Aa*	*Pg*	*Tf*	*Td*	*Si*	
local administration													
CPX[24]	–	–	yes[a]	yes[a]	–	yes[a]	no[a]	–	–	–	–	–	–
LVX[16]	no[a]	yes[a]	–	–	yes[a,d]	yes[a]	–	–	–	–	–	–	none
MOX[19]	–	–	no[a]	yes[a]	–	–	no[a]	no[a]	no[a]	no[a]	no[a]	no[a]	yes (both groups)
SPX[22]	–	–	–	–	yes[a,d]	–	yes[a]	–	–	–	–	–	–
OFX[26]	–	–	–	–	–	–	–	ND[a]	–	–	–	–	–
systemic administration													
CPX[51]	yes[a]	–	–	–	–	no[a]	no[a]	–	–	–	–	–	–
LVX[3]	yes[a,b]	yes[a,b]	yes[a,b]	yes[a,b]	no[a,b]	no[a,b]	no[a,b]	yes[a,b]	no[a,b]	no[a,b]	–	–	yes (FQ group)
LVX[17]	yes[a,b]	yes[a,b]	–	–	no[a,b]	no[a,b]	no[a,b]	yes[a,b]	–	–	–	–	yes (FQ group)
MOX[14]	yes[a,b]	yes[a,b]	–	–	no[a,b]	–	no[a,b]	yes[a,b]	yes[a,b]	yes[a,b]	–	–	none
MOX[20]	no[a,b,c]	no[a,b,c]	yes[b,c]	yes[b,c]	no[a,b,c]	–	–	yes[b]	yes[b]	yes[a,c]	yes[a]	–	none
STX[18]	no[a]	no[a]	–	–	no[a]	–	–	yes[a]	no[a]	no[a]	no[a]	–	yes (FQ group)
OFX[23]	yes[a,c]	no[a,c]	–	–	no[a,c]	–	–	yes[a,c]	–	–	–	–	–

[a] assessment at ≤3 months post-intervention; [b] assessment at >3 and ≤6 months post-intervention; [c] assessment at >6 and ≤12 months post-intervention; [d] measurement performed as an index; CAL – clinical attachment level, ΔCAL – gain of CAL; ΔPD – PD change; %BOP – percentage of sites with bleeding on probing; GI – gingival index: PI – plaque index; *Pg – Porphyromonas gingivalis*; *Tf – Tanerella forsythia*; *Td – Treponema denticola; Si – Streptococcus intermedius*; ND – not detected in either group.

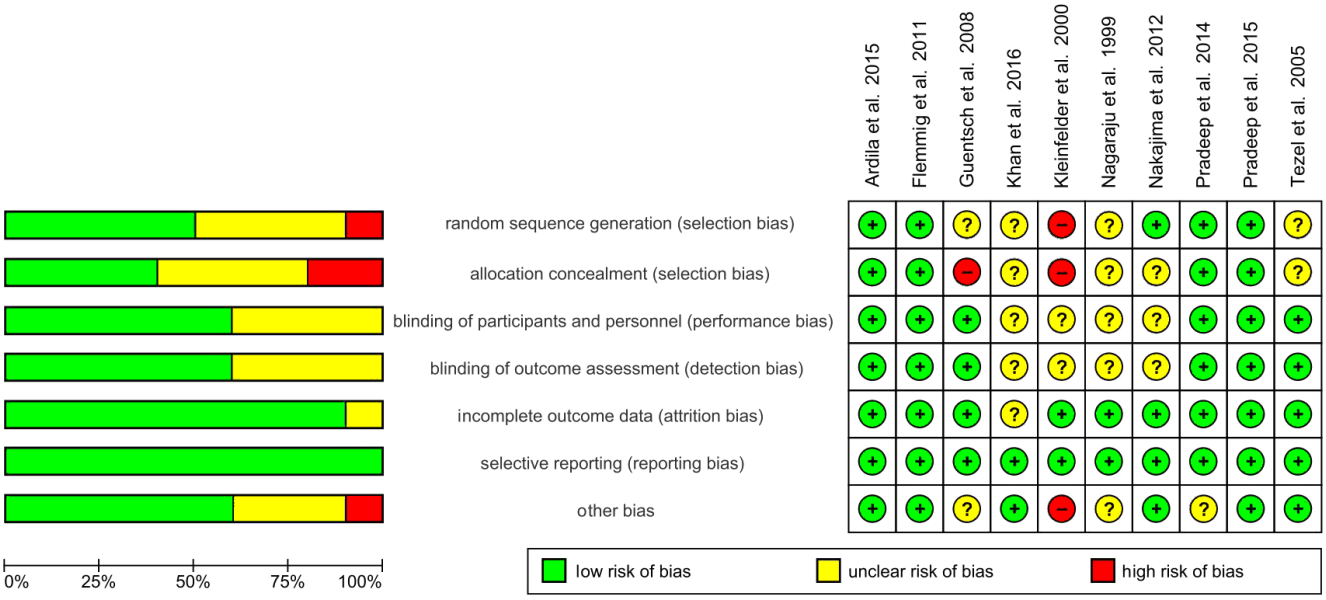

Fig. 2. Graph illustrating the risk of bias of the studies used for the meta-analyses

Periodontal, bacteriological and safety examinations

At ≤3 months post-intervention, the 95% *CI*, *Z*- values and *p*-values obtained in the meta-analyses showed a reduction in ΔPD and the number of patients with *A. actinomycetemcomitans* due to the adjunctive use of FQ, a finding that contrasted with the control data (Fig. 3). On the contrary, the PI values as well as the subgingival levels of *P. gingivalis* and *T. forsythia* were not significantly modified by FQ use (Fig. 3). Each of the above-mentioned analyses exhibited acceptable heterogeneity and reporting bias (Fig. 3 and Fig. 4). While the meta-analyses conducted for ΔCAL, CAL, PD, %BOP, and GI showed significant changes in their *Z*-values, significant heterogeneity and reporting bias were observed (Table 3).

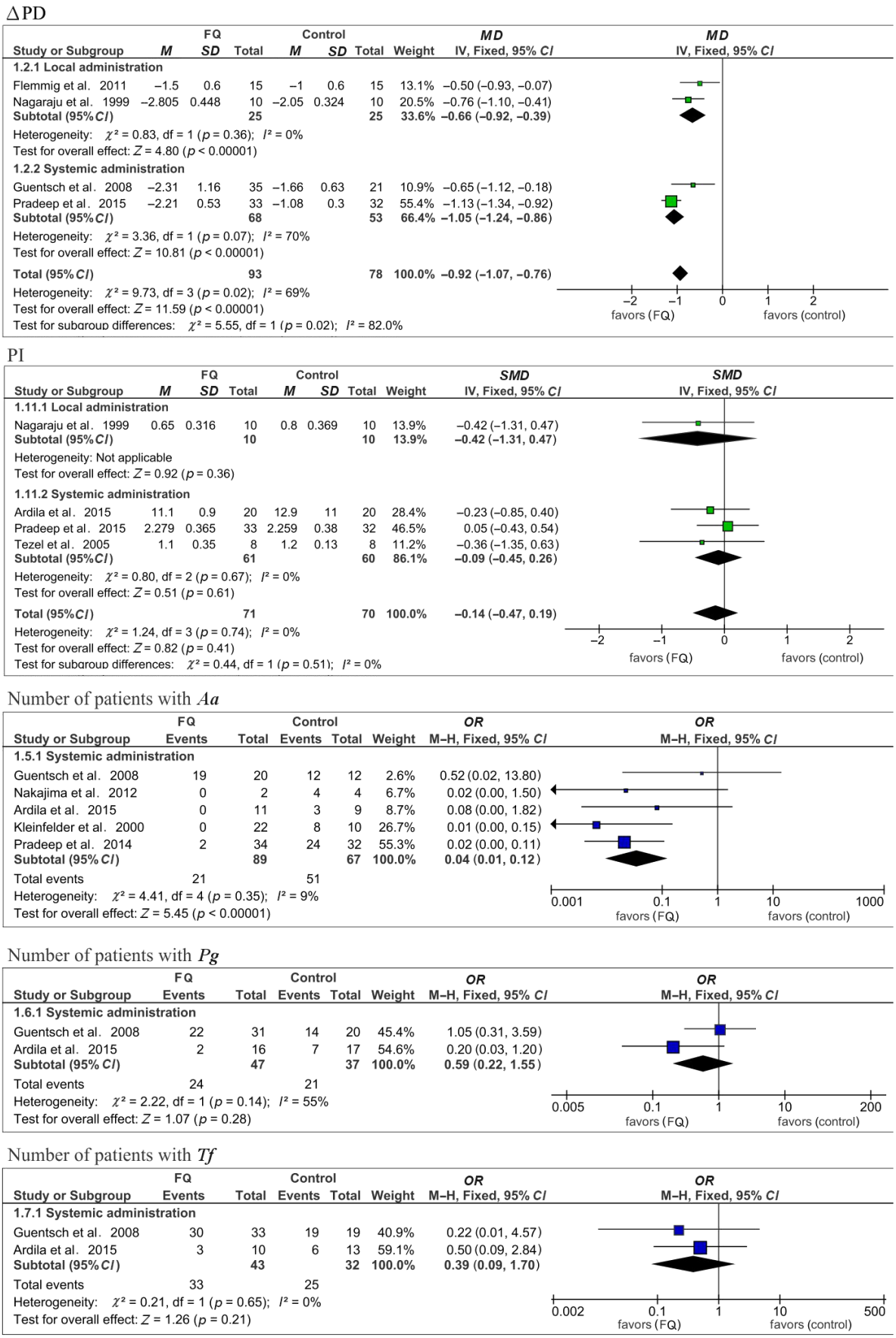

Fig. 3. Periodontal and bacteriological parameters obtained at ≤3 months after the fluoroquinolone (FQ) intervention in patients subjected to a conventional therapy

M – mean; *SD* – standard deviation; *MD* – mean difference; *SMD* – standardized mean difference; *CI* – confidence interval; df – degrees of freedom; *OR* – odds ratio; M–H – Mantel–Haenszel method.

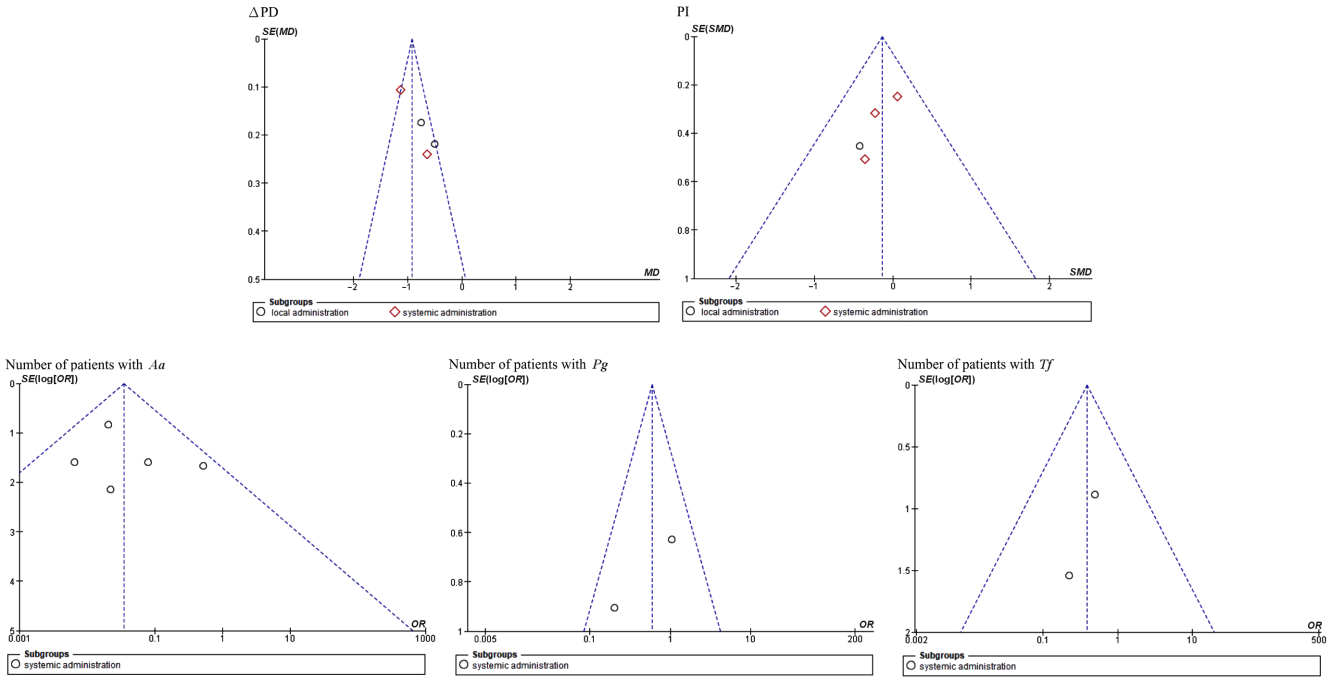

Fig. 4. Funnel plots of meta-analyses at ≤3 months after the adjunctive fluoroquinolone (FQ) use in patients subjected to a conventional therapy
SE – standard error

Table 3. Additional meta-analyses of the periodontal and microbiological parameters obtained with the adjunctive fluoroquinolone (FQ) use

Time [months]	Parameter	Number of studies	Total 95% *CI*	Total *Z*-value (*p*-value)	Action in favor of FQ or control group	Total I^2 statistic [%] (*p*-value)	Symmetrical funnel plot
≤3	ΔCAL	$2^L + 2^S$	−0.94, −0.74	16.35 (<0.00001)	FQ	91 (<0.00001)	no
	CAL	6^S	−0.71, −0.41	7.21 (<0.00001)	FQ	68 (0.008)	no
	PD	5^S	−0.66, −0.32	5.75 (<0.00001)	FQ	84 (<0.00001)	no
	%BOP	4^S	−3.67, −3.04	21.04 (<0.00001)	FQ	71 (0.02)	no
	GI	$1^L + 2^S$	0.12, 0.32	4.47 (<0.00001)	control	91 (<0.00001)	no
>3 and ≤6	%BOP	3^S	−1.12, −0.49	5.02 (<0.00001)	FQ	0 (0.97)	yes
	PI	2^S	−0.46, 0.31	0.38 (0.70)	none	32 (0.22)	yes
	Aa#	3^S	0.01, 0.12	5.38 (<0.00001)	FQ	18 (0.30)	yes
	Pg#	2^S	0.19, 1.36	1.34 (0.18)	none	18 (0.27)	yes
	Tf#	2^S	0.05, 0.98	1.98 (0.05)	none	0 (0.41)	yes
	ΔCAL	2^S	−1.12, −0.70	8.55 (<0.00001)	FQ	92 (0.0003)	no
	CAL	3^S	−0.91, −0.05	6.77 (<0.00001)	FQ	89 (<0.00001)	no
	ΔPD	2^S	−1.39, −0.98	11.19 (<0.00001)	FQ	82 (0.02)	no
	PD	3^S	−0.64, −0.33	6.22 (<0.00001)	FQ	93 (<0.00001)	no
>6 and ≤12	*Aa*#	2^S	0.00, 0.22	3.29 (0.001)	FQ	0 (0.33)	yes
	%BOP	2^S	0.38, 7.78	2.16 (0.03)	control	33 (0.22)	yes
	CAL	2^S	−0.37, 0.21	0.52 (0.60)	none	44 (0.18)	yes
	PD	2^S	−0.34, 0.10	1.05 (0.29)	none	0 (0.74)	yes

^{L} FQ agents administered locally; ^{S} FQ agents administered systemically; # number of patients with a pathogen.

At >3 and ≤6 months post-intervention, the 95% *CI*, *Z*-values and *p*-values obtained in the meta-analyses showed a reduction in the %BOP and the number of patients with *A. actinomycetemcomitans* due to the adjunctive use of FQ, a finding that contrasted with the control group (Table 3). On the other hand, the PI values and the number of subjects with *P. gingivalis* and *T. forsythia* were not modified by the FQ agents (Table 3). All the foregoing analyses found the absence of heterogeneity and reporting bias (Table 3). While the meta-analyses of ΔCAL, CAL, ΔPD, and PD showed statistical changes in their *Z*-values, these results presented with considerable heterogeneity and reporting bias (Table 3).

At >6 and ≤12 months post-intervention, the 95% *CI*, *Z*-values and *p*-values obtained in the meta-analyses showed a reduction in the number of patients with detectable *A. actinomycetemcomitans* due to the use of FQ agents as adjuncts to a conventional therapy, a finding that contrasted with the control group (Table 3). During this period, the control group exhibited reduced %BOP, in contrast with the test group, while the meta-analyses conducted for CAL and PD did not show beneficial changes due to the adjunctive use of FQ. Acceptable heterogeneity and reporting bias were found in these analyses (Table 3).

For the safety evaluation, the overall analysis (95% *CI*, *Z*-values and *p*-values) did not show a significant presence of drug-related adverse events due to the use of FQ in patients with periodontitis, in contrast to the control data. The absence of heterogeneity and reporting bias was observed for this analysis (Fig. 5).

Discussion

To our knowledge, this is the first systematic review and meta-analysis that has evaluated the beneficial and harmful effects of the use of FQ agents as adjuncts to a conventional therapy for patients with periodontitis. The present study included patients diagnosed with chronic, adult or aggressive periodontitis (Table 1). It should be noted that the term 'adult periodontitis' was replaced with 'chronic periodontitis' in 1999 to avoid a diagnostic dilemma for clinicians.[52] Previously, authors either classified periodontal disease in accordance with the American Academy of Periodontology's 1999 classification system[3,14,17,19,51] or reported the diagnosis of the disease without any description of the classification system used.[16,18,20,22–24,26] While we confirmed the classification of periodontal disease used in each study selected for the present paper,[1,52] we cannot support the diagnosis of the disease in 3 studies due to the limited information presented on the classification used.[16,22,24] The review presented here analyzed aggressive and chronic periodontitis together, given that the updated guidance on the management of periodontitis proposes that they be combined as a single entity, despite having different phenotypes.[1] The meta-analysis included only 1 study conducted on patients with aggressive periodontitis.[14]

All of the studies included in the meta-analyses examined either locally or systemically administered CPX, LVX, MOX, SPX, STX, or OFX in combination with conventional treatment for periodontitis (Table 1). Our literature search found 2 previous reviews and meta-analyses in this area, including more than 25 studies.[53,54] Both these works compared the efficacy of systemic antibiotics combined with scaling and root planing (SRP) with the use of SRP alone. Each meta-analysis included only 1 study that had tested the use of MOX,[20] while the remainder of the analyzed studies used doxycycline, amoxicillin/metronidazole, metronidazole, azithromycin, clarithromycin, tetracyclines, amoxicillin plus clavulanic acid, ornidazole, or spiramycin in their test groups.[53,54] The combined use of CPX with metronidazole was mentioned in a previous extensive review that evaluated the effects of adjunctive antimicrobial therapies on *A. actinomycetemcomitans*-associated periodontitis.[55] The remaining reviews and meta-analyses evaluating the effects of antibiotics in patients with periodontitis did not include studies that used FQ in their test groups.[56–60] Our study focused on FQ agents, since other types of antibiotics have already been extensively analyzed, as mentioned above. Moreover, the subgroup or independent analysis should be performed separately for each class of antibiotics in order to correctly evaluate the data from the application of meta-analysis methodologies.[61]

As *P. gingivalis*, *T. forsythia* and other bacteria compose the subgingival plaque biofilm, their microbial communities can negatively affect host immunity in the oral cavity.[62] *Porphyromonas gingivalis* is known to be the key pathogen underlying the pathogenesis of chronic periodontitis,[63] while *A. actinomycetemcomitans* plays a crucial role in the etiology of aggressive periodontitis, and is also associated with the etiology of chronic periodontitis.[17,64] Furthermore, very few clinical cases of aggressive periodontitis have been associated with the presence of *P. gingivalis*.[65] The present study found that systemic FQ use as an adjunct to a conventional therapy reduced the number of patients with positive *A. actinomycetemcomitans* detection in the subgingival plaque for up to 12 months post-intervention (Table 2, Table 3 and Fig. 3). This microbiological benefit of the use of FQ agents results from their greater distribution in the gingival crevicular fluid as compared to other antibiotics, their strong antibacterial activity against *A. actinomycetemcomitans*, and their robust inhibitory effect on the early and mature phases of biofilm formation of *A. actinomycetemcomitans*.[3,9,14,66] The present study did not find evidence of a reduction in the number of patients with subgingival detection of *P. gingivalis* and *T. forsythia* for up to 6 months after a systemic FQ intervention (Table 3 and Fig. 3). A previous study conducted on patients with chronic periodontitis showed that *P. gingivalis* isolates possessed low susceptibility to CPX as compared to other antibiotics, such as doxycycline, amoxicillin/clavulanic acid

and azithromycin.[67] However, a study conducted on patients with generalized aggressive periodontitis showed that *P. gingivalis* and *T. forsythia* isolates were greatly susceptible to MOX.[68] The above-mentioned in vitro susceptibility tests do not accurately reflect the clinical efficacy of antibiotics, and the strains can present different resistance profiles in different geographical areas, depending on the local use and abuse of antimicrobials.[68] While resistance against MOX in the isolates of periodontal bacteria from patients is yet to be reported, eventually, MOX may be found to be ineffective due to its structural similarity to CPX.[11] The present study quantitatively analyzed the information pertaining to *A. actinomycetemcomitans*, *P. gingivalis* and *T. forsythia*, as these periodontopathogens are strongly associated with the clinical parameters of periodontal disease. Moreover, these bacteria

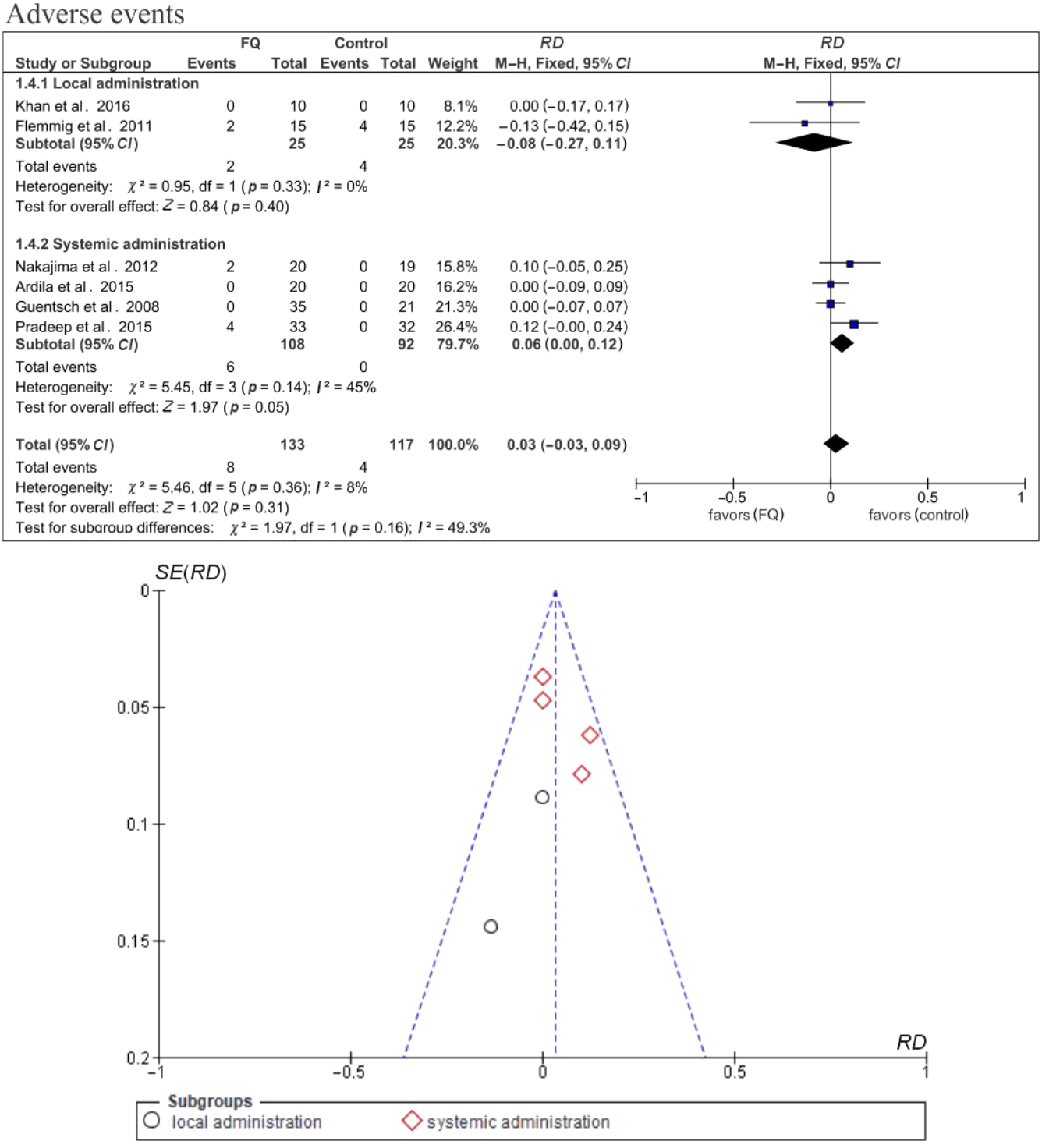

Fig. 5. Meta-analysis and funnel plot of the adverse events caused by the adjunctive use of fluoroquinolone (FQ) agents in patients with periodontitis
RD – risk difference.

are predictors for the treatment outcome[14] and sufficient data was extracted to enable the corresponding analyses.

It is well-known that PD is a useful overall indicator of the state of periodontal pockets, while %BOP reflects the current status of periodontal inflammation and CAL reflects the accumulative periodontal damage.[69] The present study showed that the levels of ΔPD and %BOP improved at ≤3 months and at >3 and ≤6 months after local/systemic or systemic FQ use, respectively (Table 3 and Fig. 3). However, the %BOP, CAL and PD results did not show beneficial changes for patients after 6 months of a systemic FQ intervention (Table 3). The improvement observed in the periodontal parameters was a consequence of 2 mechanisms exerted by FQ agents. Firstly, the antibacterial activity of FQ reduced the inflammatory response of the host due to a reduction in the level of periodontopathogens observed in pockets.[4] Secondly, the direct modulation by FQ of the toll-like receptor 4-myeloid differentiation protein-2/nuclear factor-κB signaling reduced the synthesis and release of pro-inflammatory cytokines in immune cells.[8,70] It should be noted that Table 3 shows that a control therapy had a more beneficial effect on %BOP at >6 months than an FQ intervention. This estimate was produced based on the data extracted from a study by Kleinfelder et al., whose baseline examination presented a higher level of %BOP in the test group than in the control group.[23] Therefore, a control intervention was more effective, despite a similar level of change in the baseline %BOP for both groups.[23]

The PI values were recorded in 7 out of the 12 selected studies (Table 2), as dental plaque plays an important role in the development and progression of gingival inflammation.[71] The present study found that the adjunctive administration of FQ agents did not change supragingival plaque levels for up to 6 months (Table 3 and Fig. 3). This was observed despite the antibacterial effect of FQ agents against bacteria that colonize the supragingival plaque biofilm, such as *Streptococcus mitis* (*S. mitis*), *Streptococcus oralis* (*S. oralis*) and *Streptococcus mutans* (*S. mutans*), their inhibitory action against the biofilm formation of *S. mutans*,[62,72,73] and their extensive penetration into saliva after their systemic administration.[74] It should be noted that adequate oral hygiene routine, the use of mouth rinse and supragingival teeth cleaning (STC), which can contribute to disrupting supragingival plaque, were used in both the test and control groups in some of the studies analyzed in the present paper.[71,75–77]

The present study also found that the adjunctive use of FQ agents exhibited an acceptable safety profile in patients with periodontitis, as these antibiotics did not produce a significant change in the number of adverse events as compared to the control group (Fig. 5). Dizziness, diarrhea and light-headedness were reported in patients receiving a systemic FQ intervention in 3 out of the selected studies,[3,17,18] while gastrointestinal system disorders and resistance mechanism disorders were observed in both the local FQ and placebo therapy groups in 1 study analyzed here.[19] On the other hand, 3 studies reported the absence of adverse events in patients subjected to both local or systemic drug delivery (Table 2).[14,16,20] As the widespread use of antibiotics should not be promoted in dental practice,[60] dental care professionals must balance the clinical benefits against the adverse effects of FQ use, and consider the potential development of both microbial resistance to antibiotics and gut dysbiosis in patients. This latter condition can produce dysbiosis-related systemic diseases, such as increased susceptibility to infectious diseases, altered immune homeostasis, allergic diseases, and metabolic syndrome.[78,79] As resistance to FQ agents is mediated by a reduction in the number of porins and reduced accumulation of the drug in the bacteria,[80] the induction of resistant bacterial mutants is rapidly promoted by exposure to low FQ concentrations. The spontaneous mutation rate also contributes to drug resistance via the strain- and quinolone-dependent mechanism. The mechanism of resistance to FQ agents comprises a single amino acid mutation, which leads to a Ser83→Phe substitution in DNA gyrase.[11] In addition, the administration of FQ agents exposes the subject to a high risk of developing gut dysbiosis.[78] Since the protection of the gut microbiome during antibiotic therapies should be a priority for the dental care professional, the use of probiotics, such as *Saccharomyces boulardii* or *Lactobacillus rhamnosus* GG, can help to prevent gut dysbiosis. These probiotics compete with bacterial pathogens for attachment sites on intestinal cells, and then may exert their biological effects, including the modulation of the content of the gut microbiota and the immune response.[78] Due to the beneficial health effects of probiotics, treatment with probiotics should be started as soon as possible after the commencement of FQ treatment.

We found 66.7% and 33.3% of the studies selected for the present study to be classified as high- and low-quality research, respectively, and acceptable levels of heterogeneity and reporting bias were found. All of the analyzed studies were categorized with a low (65.7%), unclear (28.6%) or high (5.7%) risk of bias (Table 3, Fig. 2, Fig. 3, and Fig. 4). All said, the analyses found evidence that FQ can be used safely to improve clinical and microbiological parameters in periodontitis patients receiving a conventional therapy. The outcomes reported in the present study are similar to the beneficial health effects produced by the systemic or local application of other antibiotics (amoxicillin, clavulanic acid, metronidazole, azithromycin, clarithromycin, doxycycline, tetracycline, or chlorhexidine) in diabetic patients with periodontitis, smokers with chronic periodontitis or subjects with aggressive periodontitis.[57–60] Additionally, our results are in agreement with a recent consensus report on the use of adjunctive antibiotics with SRP in patients diagnosed with periodontitis.[56] Given the previous absence of a review and meta-analysis of data taken from studies that used FQ combined with

a conventional therapy, the report recommended the sensible and restricted administration of a combination of amoxicillin and metronidazole, metronidazole alone or azithromycin in patients with periodontitis.[56]

The remainder of our analyses mostly showed that for up to 6 months post-intervention, FQ agents exerted more beneficial effects on the periodontal parameters as compared to controls (Table 3). However, as the meta-analyses conducted in the present study showed high levels of heterogeneity and reporting bias, these results should not be taken into consideration.[81] Our study shows that there is an urgent need for further high-quality studies with a low risk of bias to add to the currently available evidence in this clinical context. The main limitation of our study was the small number of studies included in some of the meta-analyses undertaken, which may impact the interpretation of the results. Nevertheless, the use of the available data for appropriate statistical analyses is essential to support the growing demand for effective dental, medical and public health decisions.[32]

Conclusions

Despite its limitations, the present study showed that the local or systemic administration of FQ agents produces positive effects on some clinical and microbiological parameters of periodontitis in patients receiving a conventional therapy. These positive effects, which include an improvement in ΔPD at ≤3 months, reduced %BOP at >3 and ≤6 months and a low prevalence of patients with *A. actinomycetemcomitans* for up to 12 months, are not observed following an antibiotic-free conventional therapy. All of the beneficial effects of FQ agents were observed with an insignificant presence of mild adverse events. The adjunctive use of FQ should be considered only when the expected benefits are greater than the potential adverse clinical consequences, including bacterial resistance, dysbiosis and dysbiosis-related diseases.

Ethical approval

This study was not performed on human participants or animals.

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Drug-related cancers: Analyses of head and neck cases reported in the literature

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Abstract

Background. Recent advances have attributed carcinogenic potential to pharmacotherapy. Cancers of the head and neck region are no exception.

Objectives. This descriptive investigation aimed to identify studies reporting on drugs that have contributed to cancer development in the head and neck region.

Material and methods. Online databases were searched for relevant articles and their data were summarized, including age, gender, main drug classification and name, additional drugs, primary disorders, drug-related cancers, and the site of each drug-related cancer.

Results. The mean age of the patients included in this analysis was 52.9 years. However, drug-related head and neck cancers (DR HNCs) were most prevalent in persons over 60 years of age. Overall, these cancers were more prevalent in females than in males (1.33/1). The HNC-related drugs could mainly be categorized into 3 groups, namely, immunomodulatory/immunosuppressive, chemotherapeutic and chemoprotective drugs, while the most frequently used additional drugs across the studies were corticosteroids. The 5 most prevalent primary conditions for which the patients had received pharmacotherapy were organ transplantations, lymphoproliferative disorders (LPD), rheumatoid arthritis (RA), Epstein–Barr virus (EBV) infection, and bone sarcoma. The most prevalent HNCs were squamous cell carcinoma (SCCs), thyroid cancers (including papillary and follicular thyroid carcinomas), LPD, and mucoepidermoid/acinic cell carcinomas, which occurred mostly in the oral cavity, neck, salivary glands, pharynx/larynx, and head/face.

Conclusions. This study was the first of its kind to analyze and discuss the aforementioned findings regarding the head and neck region in depth. Clinicians should familiarize themselves with DR HNC cases to effectively screen suspected patients.

Keywords: drugs, malignancy, pharmacotherapy, carcinogenesis, head and neck cancer

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Introduction

Carcinogenesis is defined as the transformation of normal cells into cancer cells, and can be attributed to a number of factors, including pharmacotherapy.[1–3] The therapeutic use of drugs may cause long-term toxicities[4] or immunosuppression,[5,6] which can facilitate cancer development. The subsequent malignancies may present as ulceration,[7,8] hyperplasia[9,10] or lymphoproliferative disorders.[5,11] Although drugs are tested in various ways to ensure their safety, they may not be safe for human use if carcinogenesis is taken into account.[12] This is because of the relatively non-specific nature of the tests which are used for determining drug toxicity.[13,14] Head and neck cancers (HNC) are no exception to drug-related (DR) cancers of the human body.[2,15]

Head and neck cancers are defined as cancers occurring within the mouth, pharynx, larynx, nose, paranasal sinuses, thyroid, parathyroid, salivary glands, and cervical esophagus; malignancies related to the skin in this region are also counted as HNCs.[16] Head and neck cancers are the 9th most prevalent malignancies, with over 650,000 cases worldwide each year.[17] Although risk factors for HNC, such as smoking,[18,19] alcohol consumption,[18,19] and human papillomavirus (HPV)[18,19] and Epstein–Barr virus (EBV)[19] infection have been recognized, the incidence of HNC has not decreased significantly in the USA,[20] Asia,[21,22] Europe,[23] or Australia[24] in recent years. Also, various kinds of treatment for these cancers are yet to be considered effective at eradicating the malignancies in case of late diagnosis.[25,26] Regarding the incidence and mortality rate, the importance of prompt diagnosis cannot be overemphasized; still, a timely diagnosis of HNCs with the use of the current measures is yet to be achieved.[27] Therefore, attention should be given to developing more efficient screening techniques and to their evaluation by the clinicians treating diseases of the head and neck region.[28] However, the lack of a holistic account of DR HNCs precludes success in this matter.

Objectives

The recognition of the drugs which have been reported to cause HNCs and their documented presentations may help clinicians identify patients at risk so that the subsequent screening procedures and management of these patients may be accomplished without troublesome complications. We considered an analysis of publications about drugs that can potentially induce HNCs helpful; thus, the current descriptive study was undertaken to answer the following question: "Which drugs have been reported to induce cancers in the head and neck region or increase their risk?" by analyzing publications about DR HNCs.

Material and methods

Online databases, namely, PubMed, Embase, Cochrane Library, and Web of Science, were searched for relevant articles without any past date restrictions published until March 2020. The following keywords were used in the search queries: "head", "neck", "cancer", "malignancy", "drug", "medication", "medicine", and "medicament". Thesaurus terms, such as "therapy-related cancer", "cancer of head and neck" and "head and neck neoplasms", were also used, according to the requirements of each database. In addition, journals with scope encompassing head and neck or oral oncology as well as the reference lists of relevant articles were also manually searched. Finally, complementary exploration was conducted in Google Scholar for articles related to the topic and those which cited studies relevant to drug-induced cancers. The obtained papers were screened by their titles and abstracts as well as by full texts in a stepwise manner. Eligible studies were determined as English-language case reports, case series, case–control studies, cohorts, randomized or non-randomized controlled studies, and longitudinal studies describing at least 1 drug which had resulted in HNC or had increased the risk of its development. Any studies with incomplete information, i.e., not mentioning the site of the newly developed cancer, the drug name or the type of cancer, were excluded. To exclude the outdated pharmacotherapeutic treatment protocols, we did not take into account studies published before January 2000. Finally, after a thorough search and screening process, 35 articles were included in this study. They comprised 30 case reports and case series, 3 longitudinal studies, 1 case–control study, and 1 cohort study. Table 1 presents a summary of the included studies sorted by the year of publication. Additionally, Fig. 1 depicts the flowchart of study selection and screening in detail.

The following data were extracted from the studies, where possible: author(s), year of publication, patients' age and gender, drug name and dosage, the primary disease for which the drug(s) were prescribed, type of cancer, cancer site, description of cases and control groups, odds ratios (*OR*s), and the significance of findings. To provide a better insight into the clinical characteristics of DR HNCs, we combined the data from all the included studies and analyzed them according to the assessed outcome, whenever possible. The assessed outcomes were age, gender, drug classification, drug name(s), additional drug(s), primary disorder(s), DR cancer, and its site. In case of absence of data in any of the studies regarding these outcomes, such study was excluded from the analysis. Table 2 presents the results of the combination of the data from all studies according to the aforementioned outcomes.

Table 1. Reported cases of drug-related head and neck cancers (DR HNCs) in the literature from January 2000 onward

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Sandoval and Jayabose[29]	2001	3	male	chemotherapeutic drug	cyclophosphamide	1,200 mg/m^2, 1 dose	daunomycin, vincristine, asparaginase, prednisone, cytarabine, MTX	ALL	MEC	parotid gland
Preciado, et al.[35]	2002	mean age: 53	–	immunosuppressant	prednisone (n = 23) and azathioprine (n = 22)	prednisone (7.22 mg/day) azathioprine (66.67 mg/day) (for those who survived >2 years)	–	solid organ transplantation	SCC (n = 23)	parotid gland (n = 8), oral cavity (n = 7), hypopharynx (n = 2), larynx (n = 2), neck (n = 2), lip (n = 1), nasal cavity (n = 1)
Kalantzis, et al.[77]	2005	72	female	immunosuppressant	MTX	–	–	RA, EBV+	polyclonal B cell lesion	upper jaw gingiva
Savelli, et al.[66]	2005	14	female	chemotherapeutic drug	cyclophosphamide	–	vincristine, daunomycin, prednisone, MTX, cytarabine	lymphoma of scalp	MEC	parotid gland
Savelli, et al.[66]	2005	14	female	chemotherapeutic drug	vincristine, prednisone, L-asparaginase, daunomycin, MTX	6 cycles as maintenance therapy	–	ALL	MEC	parotid gland
Acero, et al.[78]	2006	79	female	immunosuppressant	MTX	7.5 mg/week for 15 years	sulfasalazine	RA, EBV+	DLBCL	upper jaw gingiva
Becker, et al.[9]	2006	56	female	immunosuppressant	tacrolimus	0.1% ointment	–	lichen planus	SCC	tongue
Kojima, et al.[79]	2006	73	female	immunosuppressant	MTX	for several years	steroid therapy	RA, EBV+	PSLLPI	oral cavity
Muirhead and Ritchie[80]	2007	63	male	immunosuppressant	azathioprine	–	cyclosporine	liver transplantation	Merkel cell carcinoma	neck
Tebbi, et al.[4]	2007	–	–	chemoprotective drug (topoisomerase II inhibitor)	dexrazoxane	300 mg/m^2 intravenously	ABVE (doxorubicin, bleomycin, vincristine, and etoposide)	Hodgkin's disease	PTC	thyroid gland
Tanaka, et al.[81]	2008	44	male	immunosuppressant	MTX	10 mg/week	betamethasone	RA, EBV+	DLBCL	upper jaw gingiva
Uneda, et al.[82]	2008	70	male	immunosuppressant	MTX	2 mg/week for 6 years	prednisolone	RA, EBV+	DLBCL	upper jaw gingiva

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Hasserjian, et al.[83]	2009	72	female	immunosuppressant	adalimumab	for 7 years	MTX	RA	extranodal B cell lymphoma	right inferior orbital rim
Hasserjian, et al.[83]	2009	63	female	immunosuppressant	infliximab	for 5 months	MTX	Crohn's disease, arthritis	Hodgkin lymphoma	neck
Dojcinov, et al.[84]	2010	80	male	immunosuppressant	MTX	–	–	RA, EBV+	LPD	tongue
Dojcinov, et al.[84]	2010	60	female	immunosuppressant	MTX	–	–	RA, EBV+	LPD	lip
Kikuchi, et al.[85]	2010	69	female	immunosuppressant	MTX	6 mg/week for several years	–	RA, EBV+	LPD	upper jaw gingiva
Mattsson, et al.[86]	2010	46	male	immunosuppressant	tacrolimus (topical)	total 3 tubes of 30 mg each	acetonide triamcinolone	lichen planus	SCC	buccal mucosa
Cannon, et al.[69]	2011	76 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	SCC	tongue
Cannon, et al.[69]	2011	67 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	high-grade squamous dysplasia	sublingual
Cannon, et al.[69]	2011	71 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	SCC	tongue
Cannon, et al.[69]	2011	52 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	multifocal SCC	left retromolar trigone, hard palate, right buccal mucosa
Ben-David, et al.[68]	2013	59	female	chemotherapeutic drug	doxorubicin	total dose: 60 mg every 6–8 weeks	–	ovarian cancer	SCC	maxilla
Ben-David, et al.[68]	2013	59	female	chemotherapeutic drug	doxorubicin	standard ovarian cancer treatment protocol	–	Kaposi's sarcoma	SCC	maxilla
Güngör, et al.[87]	2013	50	male	immunosuppressant	pimecrolimus	cream	topical steroid	lichen planus	SCC	lip
Hanakawa, et al.[7]	2013	67	male	immunosuppressant	MTX	6 mg/week for 20 years	prednisolone – sodium aurothiomalate – diclofenac sodium	RA	LPD	oropharynx

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Ishida, et al.[88]	2013	76	female	immunosuppressant	MTX	for 10 years	infliximab, prednisolone	RA, EBV+	LPD	gingiva
Wimmer, et al.[36]	2013	–	–	immunosuppressant	cyclosporine ($n = 3$) and tacrolimus ($n = 3$)	cyclosporine (100–150 ng/mL) for 11 years tacrolimus (8–10 ng/mL) for 11 years	–	liver transplantation	oropharyngeal cancer ($n = 6$)	oropharynx ($n = 6$)
Orouji, et al.[30]	2014	84	female	chemotherapeutic drug	vismodegib	150 mg/day for 16 weeks	–	BCC, actinic keratosis	SCC	lower lip
Tokuyama, et al.[90]	2014	67	female	immunosuppressant	MTX	5–12.5 mg/week for 9 years	prednisolone, alendronate sodium hydrate	RA, EBV+	DLBCL	hard palate
Fabiano, et al.[10]	2015	74	female	kinase inhibitor	ruxolitinib	–	–	myelofibrosis	SCC	forehead, mandible
Hashimoto, et al.[91]	2015	74	female	immunosuppressant	MTX	total dose: 260 mg for 40 weeks	prednisolone	RA, EBV+	LPD	tongue
Hashimoto, et al.[91]	2015	74	female	immunosuppressant	MTX	total dose: 1,936 mg for 248 weeks	prednisolone, tacrolimus	RA, EBV+	LPD	tongue
Horie, et al.[89]	2015	60	male	immunosuppressant	MTX	8 mg/week for 12 years	prednisolone, folic acid, bucillamine	RA, EBV+	DLBCL	upper jaw gingiva
Longhi, et al.[70]	2015	13	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	13	male	chemotherapeutic drug	vincristine, doxorubicin, ifosfamide, cyclophosphamide, etoposide, dactinomycin	–	–	Ewing's sarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	10	female	chemotherapeutic drug	vincristine, doxorubicin, ifosfamide, cyclophosphamide, etoposide, actinomycin-D	–	–	Ewing's sarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	27	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	17	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	acinic cell carcinoma	submandibular gland

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Longhi, et al.[70]	2015	11	female	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	9	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	submandibular gland
Miyashita, et al.[92]	2015	82	male	immunosuppressant	MTX	5 mg/week for 8 years	–	RA, EBV+	LPD	tongue
Saintes, et al.[67]	2015	76	male	chemotherapeutic drug	vismodegib	150 mg/day	–	BCC	SCC	left frontal
Saintes, et al.[67]	2015	82	female	chemotherapeutic drug	vismodegib	150 mg/day	–	BCC	SCC	left frontal
Saintes, et al.[67]	2015	49	female	chemotherapeutic drug	vismodegib	150 mg/day	cetuximab	sclerodermiform BCC	SCC	nasal pyramid
Xu, et al.[93]	2015	59	male	chemotherapeutic drug	lenalidomide	25 mg orally q.d. d1–21	bortezomib, doxorubicin, dexamethasone	multiple myeloma	NPC	nasopharynx
Spiliopoulou, et al.[71]	2016	42	male	chemotherapeutic drug	bleomycin, cisplatin	3 cycles	etoposide	malignant undifferentiated teratoma	papillary carcinoma	thyroid gland
Spiliopoulou, et al.[71]	2016	27	male	chemotherapeutic drug	bleomycin, cisplatin	2 cycles	etoposide	malignant undifferentiated teratoma	papillary carcinoma	thyroid gland
Spiliopoulou, et al.[71]	2016	36	male	chemotherapeutic drug	bleomycin, cisplatin	2 cycles	etoposide	mixed germ cell tumor	papillary carcinoma	thyroid gland
Tao, et al.[6]	2017	–	–	immunosuppressant	rituximab	–	chemo- and radiation therapy	DLBCL	thyroid cancer ($n = 23$)	thyroid gland ($n = 23$)
Chambon, et al.[94]	2018	6	female	immunosuppressant	nivolumab	3 mg/kg injection every 2 weeks	2 courses of chemotherapy (5-fluorouracile 100 g/m^2 per day for 5 days and cisplatin 100 mg/m^2 per day for 1 day)	xeroderma pigmentosum	sarcomatoid carcinoma (SCC)	scalp
Lavacchi, et al.[95]	2018	82	male	immunosuppressant	nivolumab	3 mg/kg as 2nd line treatment for 7 cycles	vinorelbine	lung adenocarcinoma	Merkel cell carcinoma	upper eyelid
Niimi, et al.[5]	2019	63	female	immunosuppressant	MTX	8 mg/week	–	RA	LPD	palate

MTX – methotrexate; q.d. – quaque die (every day); ALL – acute lymphoblastic leukemia; RA – rheumatoid arthritis; EBV+ – Epstein–Barr virus-positive; BCC – basal cell carcinoma; DLBCL – diffuse large B cell lymphoma; MEC – mucoepidermoid carcinoma; SCC – squamous cell carcinoma; PSLLPI – polymorphous small lymphocytic lymphoplasmacytic infiltrate; PTC – papillary thyroid carcinoma; LPD – lymphoproliferative disorders; NPC – nasopharyngeal carcinoma.

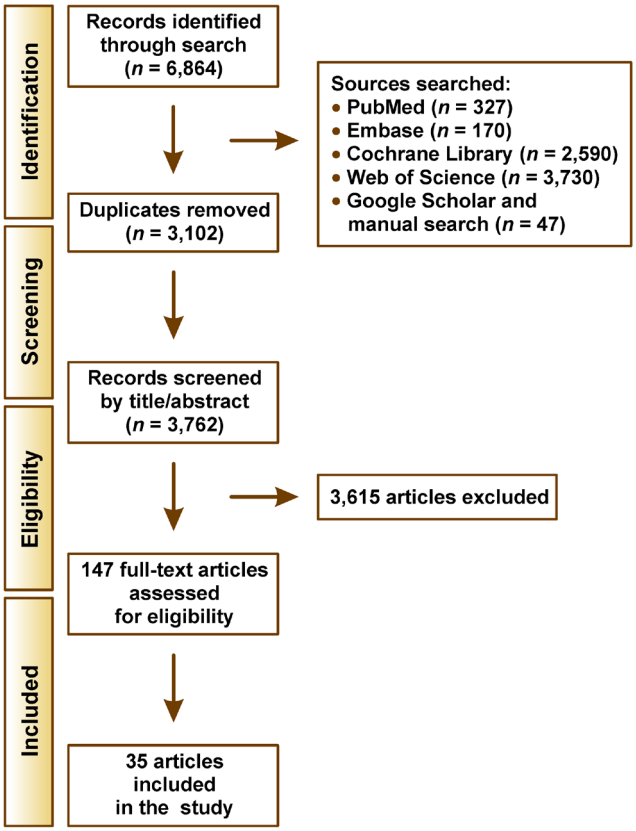

Fig. 1. Search flowchart

Results and discussion

We hereby discuss the most significant findings with regard to each outcome presented in Table 2.

Age

The lowest reported age for DR HNCs was 3 years,[29] while the highest reported age was 84 years.[30] Similar cancer incidences were found in the 1st (<40 years) and 2nd (40–60 years) age groups. However, the relative frequency of cancer incidence in the 3rd group (>60 years) was nearly twice as high as in other groups. This finding is in agreement with the latest statistics of the Surveillance, Epidemiology, and End Results (SEER) program, which also reports higher cancer rates in the older population.[31] However, the relative frequencies of HNCs in the first 2 age groups in this program were much higher than those reported in the present survey. This possibly reflects the nature of DR cancers; drugs damage the genes related to the cancer-associated pathways, as opposed to the chronic accumulation of aberrant genetic and epigenetic changes, which are related to the pathogenesis of ordinary cancers.[32,33] A potential implication of this finding, despite the limitations imposed by the type and number of studies, is that screening for DR HNCs should be implemented in a variety of age groups, conversely to the conventional screening procedures, which mainly screen the older-adult population.[34] The mean age of patients at the time of diagnosis of DR HNCs was 46 years for males and 58 years for females. However, the mean age for the total number of cases of DR HNCs was 52.9 years. The difference between the mean age values for males, females and all cases in total could be explained by different total numbers of cases in each of these groups (21, 28 and 72, respectively). This difference between the numbers of the reported cases arose from the data inadequacy of some studies regarding the gender specifications of the HNC patients.[4,6,35–37] The values of the reported mean age are lower than those reported for ordinary HNCs,[38] which might hint at the role of drugs in inducing HNCs.

Gender

Although we attempted to classify the reported outcomes by gender specifications, we could not achieve this, as most of the data regarding gender were incomplete or ambiguous. Thus, the only outcome which could be classified by gender was the patients' age.

Regarding the total relative frequencies, the female/male ratio of the diagnosed DR HNCs was 1.33/1, which is contrary to the ratios reported for ordinary cancers, which occur more frequently in males than in females.[38]

Table 2. Summary of the data combined from the included studies regarding specific outcomes

Specific outcome			Frequency (*n*)	Relative frequency* [%]
Age [years]	<40	male [29,70,71]	8	16.3
		female [66,70,94]	5	10.2
	40–60	male [71,81,86,87,89,93]	6	12.2
		female [9,67–69,84]	6	12.2
	>60	male [7,67,80,82,84,92,95]	7	14.3
		female [5,10,30,67,69,77–79,83,85,88,90,91]	17	34.7
	total		**49**	**100.0**
Gender	male		21	42.9
	female		28	57.1
	total		**49**	**100.0**

A closer look at the data reveals that DR HNCs occurred in females slightly more often in the 2nd than in the 1st age group, as can be expected by taking account of the statistics of human papillomavirus (HPV)-negative HNCs.[39] However, an interesting finding was that DR HNCs occurred approx. twice as often in females than males in the 3rd age group. This finding may partly be explained by the shorter life expectancy of males in comparison with females, which results in a higher number of surviving senile females.[40] Additionally, the most frequently used drug in this age group was methotrexate (MTX), which has been shown to incur higher acute toxicities in women than men,[41] suggesting that sex-specific differences can also be a factor in determining adverse outcomes. Moreover, higher clearance rates of drugs such as ruxolitinib,[42] doxorubicin[43] and adalimumab[44] have been reported in males than females, which may contribute to increased morbidity in females. These findings could indicate that females may have a higher propensity for developing DR HNCs in older age, yet data on this matter remains limited.

Main drugs (classification and names)

Cancer-related drugs in the included studies could mainly be classified into 3 groups, namely, immunomodulators/immunosuppressants, and chemotherapeutic and chemoprotective drugs. The 5 most prevalent drugs in the immunomodulator/immunosuppressant group were corticosteroids, azathioprine, rituximab, MTX, and tacrolimus. The 5 most prevalent cancer-related drug prescriptions in the chemotherapeutic group were doxorubicin, cisplatin, ifosfamide, MTX, and cyclophosphamide. Only 1 study, in which dexrazoxane was used, evaluated the effects of chemoprotective drugs on cancer development.[4]

Predictably, carcinogenic potential has been shown for most of the aforementioned drugs, namely, azathioprine,[45] cyclosporine,[46] doxorubicin,[47,48] cyclophosphamide,[49] cisplatin,[50] ifosfamide,[51] and dexrazoxane.[52] However, carcinogenicity was not the only modality by which these drugs could have contributed to the development of secondary cancers. It has been shown that

Specific outcome			Frequency (*n*)	Relative frequency* [%]
Main drug classification and names	immunosuppressant	corticosteroid [35,66]	24	15.4
		azathioprine [35,80]	23	14.7
		rituximab [6]	23	14.7
		methotrexate [5,7,77–79,81,82,84,85,88–92]	16	10.3
		tacrolimus [9,36,86]	5	3.2
		cyclosporine [36]	3	1.9
		nivolumab [94,95]	2	1.3
		pimecrolimus [87]	1	0.6
		total	**97**	**62.2**
	chemotherapeutic drug	doxorubicin [68–70]	13	8.3
		cisplatin [70,71]	8	5.1
		ifosfamide [70]	7	4.5
		methotrexate [66,70]	6	3.8
		cyclophosphamide [29,66,70]	4	2.6
		vismodegib [30,67]	4	2.6
		bleomycin [71]	3	1.9
		vincristine [66,70]	3	1.9
		etoposide [70]	2	1.3
		actinomycin-D [70]	1	0.6
		adalimumab [83]	1	0.6
		dactinomycin [70]	1	0.6
		daunomycin [66]	1	0.6
		infliximab [83]	1	0.6
		L-asparaginase [66]	1	0.6
		lenalidomide [93]	1	0.6
		ruxolitinib [10]	1	0.6
		total	**58**	**37.1**
	chemoprotective drug	dexrazoxane [4]	1	0.6
	total		**156**	**99.9**

corticosteroids[53] and rituximab[54,55] can inhibit the immune function, thus disrupting the normal immune system surveillance. Furthermore, it has been demonstrated that MTX, despite its immunosuppressive properties, is not associated with an increased cancer risk.[56,57] However, it was the 4th most frequently used drug in the immunodulator/immunosuppressant group. Furthermore, we found an additional controversy regarding the use of oral contraceptives. Although in a study by Grevers et al. the relationship between an increased thyroid cancer risk and the use of oral contraceptives was shown in the primary analysis, additional analyses proved that after adjusting for various other factors, their use was not associated with an increased thyroid cancer risk.[58] Additionally, studies have shown that while the use of oral contraceptives can increase the risk of various cancers,[59] their effects on thyroid cancer development are disputable.[60–62] Due to inconsistent results regarding the use of oral contraceptives, we chose to exclude this type of drugs from our study. Such controversial findings warrant further research, yet it may be hypothesized that the many confounding variables which were present across the studies, e.g., age, predisposing conditions and co-carcinogens, might have contributed to DR HNCs development. Future research should describe the pathways by which these drugs may cause cancers, especially HNCs.

Additional drugs

As could be expected, additional drugs were similar to the main drugs analyzed in the included studies. The most prevalent additional drugs used in the studies were corticosteroids. The role of additional drugs in cancer development may be described as either facilitating cancer growth, as can be seen with the use of corticosteroids, or exacerbating cancer development, as can be observed with the use of cytotoxic drugs. Additionally, drug interactions might have also occurred in these studies, which could further contribute to the problem.

Primary disorders

From a clinical perspective, recognizing the conditions which may predispose a patient to secondary cancers, either due to their inherent characteristics

	Specific outcome	Frequency (*n*)	Relative frequency* [%]
Additional drugs	corticosteroid [7,29,66,81,82,86–91,93]	14	28.6
	methotrexate [29,66,83]	4	8.2
	etoposide [4,71]	4	8.2
	vincristine [4,29,66]	3	6.1
	cytarabine [29,66]	2	4.1
	daunomycin [29,66]	2	4.1
	doxorubicin [4,93]	2	4.1
	acetonide [86]	1	2.0
	alendronate sodium [90]	1	2.0
	asparaginase [29]	1	2.0
	bleomycin [4]	1	2.0
	bortezomib [93]	1	2.0
	bucillamine [89]	1	2.0
	cetuximab [67]	1	2.0
	cisplatin [94]	1	2.0
	cyclosporine [80]	1	2.0
	diclofenac sodium [7]	1	2.0
	folic acid [89]	1	2.0
	5-fluorouracil [94]	1	2.0
	hydrate [90]	1	2.0
	infliximab [88]	1	2.0
	sodium aurothiomalate [7]	1	2.0
	sulfasalazine [78]	1	2.0
	tacrolimus [91]	1	2.0
	vinorelbine [95]	1	2.0
	total	**49**	**99.4**

	Specific outcome	Frequency (*n*)	Relative frequency* [%]
Primary disorders	organ transplantation [35,36,80]	30	25.4
	LPD** [4,6,66,93]	26	22.0
	rheumatoid arthritis [5,7,77–79,81–85,88,89,91,92]	17	14.4
	EBV+ [77–79,81,82,84,85,88–92]	14	11.9
	bone sarcoma [70]	7	5.9
	ovarian cancer [68,69]	5	4.2
	basal cell carcinoma [30,67]	4	3.4
	lichen planus [9,86,87]	3	2.5
	testicular cancer [71]	3	2.5
	leukemia [29,66]	2	1.7
	actinic keratosis [30]	1	0.8
	arthritis [83]	1	0.8
	Crohn's disease [83]	1	0.8
	lung adenocarcinoma [95]	1	0.8
	myelofibrosis [10]	1	0.8
	soft tissue sarcoma [68]	1	0.8
	xeroderma pigmentosum [94]	1	0.8
	total	**118**	**99.5**

or their pecific treatment, may be helpful when screening patients for DR HNCs. The 5 most prevalent conditions were organ transplantations, lymphoproliferative disorders (LPD), rheumatoid arthritis (RA), EBV infection, and bone sarcoma. As could be expected, these disorders were the predictors of the drug choices discussed in the previous sections. However, as the literature on DR HNCs is limited, clinicians should be aware of similar disorders when evaluating a patient. Additionally, screening by primary disorders may help with the diagnosis of more cases of HNC, as different therapeutic regimens may not include the drugs which are listed in this study as cancer inducers.

Drug-related cancers

Although previous studies have omitted thyroid cancers and LPD from their HNC categories,[63,64] we used the HNC definition provided by Holland et al.[16] in order to perform a more comprehensive analysis. The 4 most prevalent types of DR HNCs were squamous cell carcinoma (SCC), thyroid cancer, LPD, and mucoepidermoid carcinoma/acinic cell carcinoma. Similar to ordinary thyroid cancers,[65] the most prevalent cases of DR thyroid cancers were papillary carcinomas followed by follicular carcinomas. The relative frequencies of these DR cancers are in line with the results of previous studies, which reported higher prevalence for cancers of epithelial origin,[63] although these studies excluded thyroid cancers from their analyses.

While the direct cause-and-effect relationship between drug use and cancer incidence cannot be established at this time, some findings can lead us to reflect on the role of drug therapy in cancer incidence. It has been stated in the literature that radiotherapy can increase the risk of secondary cancer in the head and neck region.[66] While some patients in the included studies received radiotherapy in the head and neck

	Specific outcome	Frequency (*n*)	Relative frequency* [%]
DR cancers	squamous cell carcinoma [9,10,30,35,67–69,86,87,94]	38	36.9
	thyroid cancer [4,6,71]	27	26.2
	LPD** [5,7,77–79,81–85,88–92]	18	17.5
	mucoepidermoid carcinoma/acinic cell carcinoma [29,66,70]	10	9.7
	pharyngeal cancer [36,93]	7	6.8
	Merkel cell carcinoma [80,95]	2	1.9
	sarcomatoid carcinoma [94]	1	0.9
	total	**103**	**99.9**

region,[67–69] others did not receive it,[10,29,30,70–73] or reported that HNCs had developed regardless of receiving or not receiving radiotherapy.[6] While the genetic or acquired predisposition of individuals to secondary cancers through field cancerization,[74] immunosuppression,[75] or even infection with oncogenic viruses[76] cannot be ignored, the temporal relationship between drug use and cancer incidence, which was sometimes observed within months of its use,[30] may indeed indicate that drug use can have a significant impact on HNC development.

To explain the biological plausibility of this statement, the most prevalent drug classifications used in the included studies should be considered. The 2 most often mentioned cancer-related drug classes in these studies were immunomodulatory/immunosuppressive and chemotherapeutic drugs. These drugs may induce the double-strand breakage of the DNA structure, which may result in aberrant lesions.[77] Additionally, immunosuppression can impair immune surveillance,[75] as some chemotherapeutic drugs do.[66] However, the exact mechanisms through which drugs can cause HNCs is not yet clear.

Other, less prevalent DR HNCs reported in the literature were pharyngeal cancers, Merkel cell carcinoma and sarcomatoid carcinoma. Additional entities of DR HNCs may also be present, but they have not yet been discovered. Clinicians should be aware of the possibility of occurrence of these DR HNCs to diagnose them in a timely manner.

Site of drug-related cancers

The sites of DR HNCs closely correspond to the types of DR HNCs discussed in the previous section. These sites were the oral cavity, neck, salivary glands, including the parotid and submandibular glands, pharynx/larynx, and head/face. Clinicians should take note of the most prevalent sites of DR HNCs and implement appropriate diagnostic screening measures, such as the continuous surveillance of each site.

Limitations

Although we tried to find as many studies as possible about the subject matter, and analyze their data in a way that could be easily comprehended, this study was not without limitations. Most of the included studies about DR HNCs were case reports or cases series, which inevitably have a low level of evidence. Furthermore, some of the studies' data regarding the analyzed outcomes were incomplete. We hope that this descriptive study will help clinicians, including dentists and general practitioners, in diagnosing HNC patients. A detailed discussion on the possible intra- and extracellular pathways responsible for the development and promotion of DR cancers was well outside the scope of this study. Future research should not only be dedicated to DR HNCs, but also to DR cancers occurring within other parts of the human body.

Conclusions

In summary, drug therapy may induce secondary cancers in the head and neck region. These DR HNCs were more prevalent in older-adult populations, with no noticeable disparities between males and females after adjusting for sex-specific drugs. The most common DR HNCs were thyroid cancer, SCC, LPD, and mucoepidermoid carcinoma/acinic cell carcinoma, with the neck being the most commonly affected site. Drugs that can cause these types of cancers can be broadly classified into chemotherapeutic drugs, immunomodulatory/immunosuppressive drugs, oral contraceptives, and chemoprotective drugs. Although biologically plausible pathways may be hypothesized as the mechanisms of action of these drugs in inducing DR HNCs, the direct relationship between drug use and HNCs is yet to be established. Further research is necessary to understand the nature of DR HNCs.

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Specific outcome		Frequency (*n*)	Relative frequency* [%]
Sites of DR cancers***	oral cavity [5,9,30,69,77–79,81,82,84–92]	33	31.4
	neck [4,6,35,71,80,83]	31	29.5
	salivary glands [29,35,66,70]	18	17.1
	pharynx/larynx [7,35,36,93]	12	11.4
	head/face [10,35,67,68,83,94,95]	11	10.2
	total	105	99.6

* Note that the sum of the relative frequencies may not equal to 100% due to the rounding of numbers. ** LPD includes the following: Hodgkin and non-Hodgkin lymphomas; DLBCL; multiple myeloma; polyclonal B cell lesion; pseudolymphoma; and PSLLPI. *** Details of each site: oral cavity – lips, tongue, gingiva, palate, buccal mucosa, alveolar ridge, retromolar trigone, and sublingual; neck – thyroid gland, cervical lymph node and soft tissue; salivary glands – parotid and submandibular glands; pharynx/larynx – nasopharynx, oropharynx, hypopharynx, and larynx; head/face – scalp, frontal, zygoma, ethmoid sinus, orbital rim, maxilla, mandible, ear, eyelid, chin, nasal cavity, and pyramid.

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