Review Article

Cannabis Associated Mental Health Effects: A Review

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ABSTRACT

According to the latest drift in Western countries, many lawmakers are trying to formulate policy to legalize the usage of *Cannabis* in the case of mentally vulnerable populations such as those suffering from depression, paranoia, and excessive anxiety. This particular trend has been due to short term success in the case of mood upliftment. *Cannabis* derivatives produce effects on both mood and cognitive function, which can be a double-edged sword if not followed with proper dosage. Beneficial effects, however, are limited and studies documenting those and even more meagre. Detrimental effects, especially those suffering from various hallucinating and delusional states, have been reported extensively in the literature. Here in the review article, we have tried to study and summarize various effects of *Cannabis* as well as *Cannabis* -derived products in the case of people who have various mental conditions. We have also tried to consider addiction to these substances and hence develop a framework for proper utilization of *Cannabis* in mentally ill people. Many clinicians are also in a dilemma when prescribing a *Cannabis* -based product to treat psychotic and mood-based disorders. Hence, a better understanding of the process of *Cannabis* -based treatment for the vulnerable population is necessary.

KEYWORDS: *Addiction, anxiety disorders, Cannabis, mood disorders, schizophrenia, therapeutics*

INTRODUCTION

Cannabis is a wholesome term to denote various species such as *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. These plants provide various psychoactive substances.[1] The resin can be obtained from the *Cannabis* plant and can be used in a crude and purified manner. This also includes >400 compounds which comprise cannabinoids, terpenoids, and flavonoids. The main compound which is responsible for causing the psychoactive effect is D-9-Tetrahydrocannabinol (THC). *Cannabis* and its derived chemical products such as cannabinoids act on cannabinoid receptors whihc are neurotransmitter released from the brain. *Cannabis* usually differs in bioavailability as well as pharmacokinetics and pharmacodynamics during the metabolism as compared to cannabinoids. Usually, these are of three different types-phytocannabinoids, endocannabinoids, and synthetically produced cannabinoids.[2] Various clinical manifestations are produced with the usage of *Cannabis*, including a feeling of being relaxed, alteration of various cognitive functions, disorientation of time and place, decrease or increase of emotional response. There can be harmful effects such as mania, delusions, worsening of depression, and panic attacks in larger doses and extremely vulnerable people. If given intravenously, then the prime active component of *Cannabis*, which is THC, produces symptoms resembling schizophrenia such as memory loss, hallucination, and excessive anxiety.[3] Amygdala as well hippocampus regions of the brain are responsible for causing depressive as well as psychotic symptoms in case of people who consume *Cannabis* on a chronic basis.[4] In case of *Cannabis* misuse or *Cannabis* use disorder (CUD) cases, the

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individuals have been reported to be already suffering from some kind of mental conditions such as depression, schizophrenia, and bipolar disorder (BD).[4-8] They usually see cannabinoids as having a therapeutic benefit for them.[9,10] This association has been widely studied, with mentally unstable people being often diagnosed with suffering from CUD as well. Most of the studies have indicated that *Cannabis* has detrimental effects on one's health rather than medicinal effects on people. However to study both sides of these effects, further research is needed in a much wider population and in cases of various mental illnesses.[11.12] In our review, we have tried to summarize the effects of *Cannabis* on a plethora of mental conditions, which can help a clinician to determine the usage of *Cannabis*.

Anxiety

Anxiety which is also acute has been one of the most common side effects of *Cannabis* usage. However, many users during initial usage of this product experience a reduced amount of anxiety. Hence, it is a paradoxical situation, but the variation is usually dose-dependent where deleterious effects occur due to a stronger dosage of cannabinoids. It has been reported that in rodents, anxiolytic effects were reported with a low dosage of *Cannabis* and higher doses induced anxiety by affecting the hypothalamic-pituitary-adrenocortical pathway. The central amygdala is triggered by D9-THC induces anxiogenic crisis of individuals.[13]

Depression

Cannabis and cannabinoids have been reported to be directly associated with major depressive disorders (MDDs) and worsening the depression crisis.[14,15] Many studies have reported the harmful effects. However, few studies dismiss this connection in lieu of not considering many other additional variables such as excessive drug usage, poor education and upbringing issues.[16-18] Most studies had reported the association of depression as a secondary manifestation when other chronic diseases were considered. Hence, there is a need to study a direct associative original research in this context.

Psychosis

When individuals are vulnerable to developing a psychotic illness, they use *Cannabis* under CUD due to extreme environmental influence. One in four individuals is dealing with this substance abuse in developed countries. Mostly chronic usage symptoms resemble the signs of schizophrenia. THC has been reported to cause increased psychosis when a higher dose is given, leading them to be in an near the edge situation mentally. A study carried out among 50,000 male patients described that young people who smoked *Cannabis* ended up twice as common with diagnosing mental illnesses such as schizophrenia.[19]

Paranoia

This type of mental state causes an individual to have unnecessary fears that they might be under attack.[20] The number of symptoms varies among patients as well. Many causes have been highlighted for the development of paranoia such as suicidal tendency, youth issues, physically being unwell, and cannabinoid usage.[21,22] Abnormal salience theory,[23,24] tries to explain the effects of *Cannabis* triggering paranoia in individuals, which in turn is caused due to the presence of THC. Along with producing paranoia, THC also induces anxiety amongst *Cannabis* users by affecting the cannabinoid receptors in the brain. This particular chemical generates fears by facilitating negative emotions as well as producing disorientation.[25,26]

Hallucinations

Individuals under *Cannabis* usage experienced visual hallucinations and altered perceptions when D-9-THC causes changes in the brain's occipital lobe, as reported in many studies compared to certain placebo groups. There was a marked reduction in smooth functioning and decreased sensory cortex activation of visual receptors resulting in hallucination. The same was also observed through the help of EEG and MRI reports.[27,28]

Disorientation

Navigational skills of an individual also come under a scanner when due to chronic usage of cannabinoids, which causes a deleterious effect on hippocampal regions of the brain and leads to shifting of this function to extrahippocampal regions. Hence, additional regions of the brain take over the function of cognitive realignment so that the neural elements in these individuals achieve some sort of spatial recognition.[29]

Bipolar Disorder

In one study, where over 40,000 people were recruited, the ones who were using *Cannabis* or derived materials had a greater chance of developing BD. With increasing dosage, leading to harmful effects in case of those people often leading to suicidal tendencies. Many users also complained of altering mood states, delayed recovery to normal situation. However, few studies have highlighted that the symptoms vary based on the type of *Cannabis* and the gender as well.[30]

Delusion

Dopamine transmission is affected in the case of chronic *Cannabis* users by acting through two pathways, either through cannabinoid receptors or through the glutaminergic system. Various genes are known to play a role in this, such as COMT, DAT-1, and AKT-1. A specific condition called delusional zoopathy has been associated with excessive cannabinoid usage.[31]

Suicidal Ideation

A study conducted by Christchurch Health and Development revealed that suicidal behaviours and concurrent usage of *Cannabis* were very strongly associated in individuals as young as 15 years of age. Apart from family issues, heterogeneity of other environmental factors can lead to this kind of behavior development, irrespective of the gender of an individual. Hence, in the case of suicidal ideation endogenous model, frequent consumption of cannabinoids with increased dose leads to increased suicidal thoughts.[32]

Impaired Short-Term Memory, Attention Judgement

Cannabis causes memory loss in individuals with acute usage, just like alcohol with its intoxicated state of mind. However, more permanent damage is caused by chronic usage. There is a marked deficit in learning and then recalling things. Nevertheless, this has not been studied widely, especially at the chronic stage.[33]

Sleep Problems

Initial studies on *Cannabis* revealed that this product helps in treating long-standing insomnia in patients. In the short-term, THC definitely improves the amount of sleep-induced. However, with its addiction, it will impair the sleep pattern in the long-term future. Synthetic cannabinoids such as nabilone and dronabinol have a positive effect on sleep apnea by making changes in serotonin pathways. Daytime sleepiness can be treated acutely with the help of Cannabidiol (CBD), and anxiety due to Posttraumatic stress disorders (PTSD) can be decreased with the help of nabilone.[34]

Discussion

Therapeutic effects of CBD have been good in case of treatment-related to schizophrenia, but further clinical trials with a large number of population groups are required to address the uncertainties of side effects such as illicit recreational usage of *Cannabis*. Hence, a proper dose-dependent redressal needs to be done in understanding the pathophysiology of *Cannabis* on schizophrenia and various other types of paranoia.

Controlled clinical trials in the case of MDD patients need to be undertaken to understand the direct association of *Cannabis* with this disease process. It has been studied only as a secondary manifestation when *Cannabis* was used to treat other chronic pain disorders. The amount of risk in the acute usage of various types of cannabinoids has not been studied as yet related to a depressive state. *Cannabis* has long been tried in cases of anxiety to calm the patient. However, clinicians come under the scanner and dilemma such as situations considering the possibility of addiction and other delusional effects on its constant usage. More research is required to determine the ideal dose that clinicians can safely recommend to their patients without putting their lives in jeopardy. In cases of PTSD patients, mostly military patients have been studied. Hence, the research should include more groups of vulnerable populations of both genders and have age variations with larger sample size and having multicentric trials. Frequency, type of preparation, and when to use these compounds necessitates limited dose research in collaboration with clinicians and pharma companies. Addiction in people is common due to a variety of personal as well as societal factors. The people in the early stage are vulnerable, which later on with illicit reinforcement end up in chronic usage without a physician's consultation. This again turns into a risky situation when the individual is already suffering from deteriorating mental health conditions. Hence, they try to self-medicate themselves, common in the case of patients with schizophrenia. Hence, the recreational effects outweigh the therapeutic benefits, if at all present, which needs to be checked by law enforcement officials and clinicians so that many people do not end up in a harmful situation.

Conclusion

A paradox has been created between the detrimental physical and social implications and the consumers' self-proclaimed medicinal effects for the usage of *Cannabis* and its derivatives. Therefore, further documented research is necessary so that the general public who wish to use *Cannabis* can make their own choices with an informed background.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Autorotation of the Mandible as Sequelae to Maxillary Intrusion: A Systematic Review

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ABSTRACT

Background: Autorotation of the mandible is a normally anticipated phenomenon following a surgical superior repositioning of the maxilla in clinical situations where patients have an excessive gummy smile. Prediction of the surgical treatment outcome following a presurgical orthodontic treatment is a critical element in the surgical treatment planning. **Materials and Methods:** The relevant articles were selected by hand search and electronic media (Google Scholar, PubMed, Science Direct, Medline, Embase, and Cochrane) from 1982 to 2020. All the relevant articles were properly screened, and findings were extracted from the articles. **Results:** It was observed that, following maxillary intrusion, mandible would eventually autorotate to take a new occlusion. Mandibular autorotation as a result of maxillary intrusion would lead to minimal shortening of the lower lip in the vertical plane. It was observed that the amount of mandibular autorotation correlates with the extent of maxillary impaction. Studies have shown that there is a passive soft-tissue response which may be attributed to the fact that no muscular detachment had been affected in the lower lip and soft-tissue chin region during the maxillary surgery. **Conclusion:** It is observed that there is a definite influence on the mandibular and chin positions as a result of maxillary intrusion and autorotation of the mandible. Every 1 mm of maxillary superior impaction, the chin moved 0.6 mm vertically and 0.2 mm horizontally. There is an appreciable shortening of the lower lip length.

KEYWORDS: *Autorotation, gummy smile, maxillary intrusion, vertical maxillary excess*

INTRODUCTION

Facial esthetics is considered to be a critical factor in human interactions.[1] Vertical maxillary excess (VME) is a clinical scenario that results due to overgrowth of the maxilla. It manifests clinically with excess exposure of the upper incisors even at rest coupled with a gummy smile.[2] The vertical excess growth of the maxilla results in a consequent rotation of the mandible in a clockwise manner. This subsequently results in the mandible being positioned retrognathically.[2] The surgical correction of the VME is usually done by the superior repositioning of the maxilla

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through a LeFort 1 osteotomy. This subsequently results in the rotation of the mandible anteriorly and superiorly thereby enhancing the facial profile still further.[2]

Literature reveals that surgical impaction of the maxilla aids in the correction of long-face syndrome, anterior open bite, and in obtaining a competent lip seal in addition to the correction of VME.[3,4] The autorotation of the mandible associated with the maxillary impaction was initially advocated by Schendel *et al*., Bell *et al*., and Fish *et al*.[5-7] It is advocated that mandibular autorotation following a maxillary intrusion is associated with the projection of skeletal and soft tissues in the profile view and vertical shortening of the lower face in the frontal view.[3]

Materials and Methods

Literature search

The systematic literature search (displayed as a flow diagram in Figure 1) was initiated with Google Search the references of the DOI used in Sci-Hub. This service allowed the authors to use PubMed Central, ProQuest Dissertations and Theses, Science Citation Index Elsevier Science Direct Complete, Highwire Press, Springer Standard Collection, DOAJ Directory of Open Access Journals, Free E-Journals, Ovid Lippincott Williams and Wilkins Total Access Collection, Wiley Online Library Journals, and Cochrane Plus databases.

The heading sequence ([“Maxillary” OR “Le Fort I”] AND [“mandibular autorotation”] AND [“Advancement” OR “Retrusion” OR “Setback” OR “Impaction” OR “Intrusion” OR “Superior Repositioning” OR “Down grafting” OR “Inferior Repositioning” OR “Expansion” OR “Widening”]) was selected. Our initial search showed 2418 published articles. Since our inclusion criteria delegated only academic publications and the number of articles selected was decreased to 852. No articles were excluded by means of their language. Articles discussing nonhuman research were excluded, and 163 potential articles were found. Articles pertaining to syndromic cases, osteodistraction, or bimaxillary surgery were excluded such that only 51 articles remained. Among them, only 11 fulfilled inclusion criteria and exclusion criteria (see selection criteria). To finish the search, the authors also reviewed the references for each selected publication. Due to this, an additional 15 articles were found. However, only four of these could fulfill the inclusion and exclusion criteria. Eventually, this systematic review included a total of 15 articles.

Selection criteria

This study comprised the following inclusion criteria to hand-pick the probable articles from the existing literature. These include: (1) Only human patients; (2) a set of patients in whom only single jaw surgery was undertaken and that was maxillary intrusion; (3) the number of patients was mentioned; and (4) at least one parameter of soft-to-hard tissue ratio was measured from the data included in that paper. This study comprised the following inclusion criteria to hand-pick the probable articles from the existing literature. These include (1) nonsyndromic patients in the form of cleft lip and palate, Pierre Robin syndrome; (2) unrelated disease (i.e., oncologic or traumatic cases); (3) systematic reviews or meta-analyses; and (4) the use of distraction.

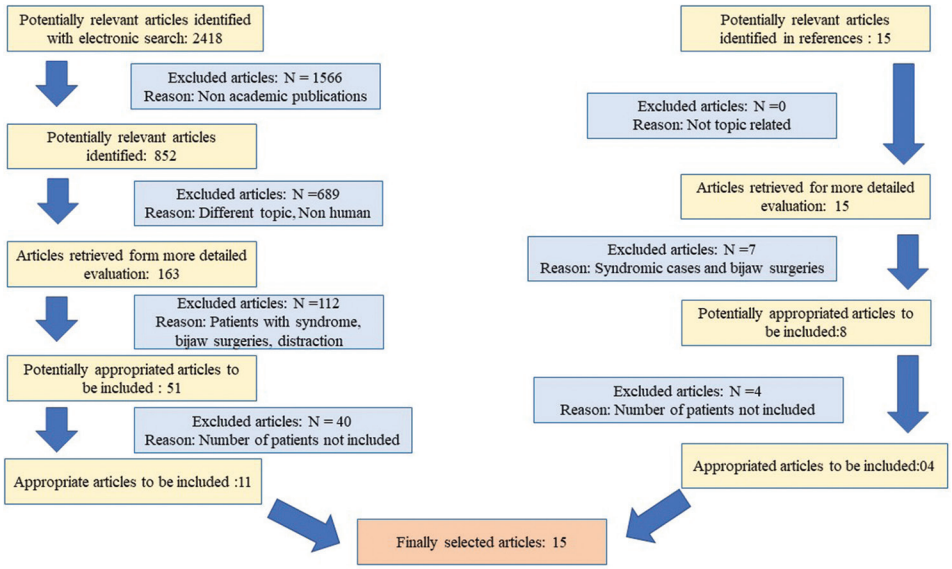

Figure 1: Search criteria

Data extraction

The following data were taken out from the full-text articles: (a) demographic data (i.e., the number of patients, age, gender, and race); (b) type of the study (i.e., follow-up period [months/years], course of analysis [prospective vs. retrospective], randomization, level of evidence, and method of analysis [i.e., lateral radiographs, cone beam]); and (c) type of surgical intervention (i.e., the type of surgery used for a certain bony movement, added orthognathic and/or facial procedures, use of bone graft, use of implants, amount of movement in mm [mm], removal of anterior nasal spine, use of an alar cinch suture, the use of VeY lip closure, subspinal osteotomy, and type of osteosynthesis).

Results

The results of the literature search reveal that maxillary intrusion which is generally known as maxillary impaction or superior repositioning of the maxilla was performed initially by Converse (1952) by posterior intrusion for the management of patients with open bite. However, it can also be performed anteriorly in clinical situations such as the long face syndrome with excessive prominence of the maxilla presenting with a gummy smile. All studies we found were mainly retrospective.

It was observed that, if an isolated maxillary intrusion was performed, the mandible would eventually autorotate to take a new occlusion. This ultimately would lead to the soft tissues to follow the hard tissues according to certain ratios. Previous studies have revealed that mandibular autorotation as a result of maxillary intrusion would lead to minimal shortening of the lower lip in the vertical plane.[8] However, few studies revealed that the lower lip actually lengthens following a mandibular autorotation as a result of maxillary intrusion.[9] Few studies have demonstrated that the amount of mandibular autorotation correlates with the extent of maxillary impaction.[10] Studies have shown that there is a passive soft-tissue response which may be attributed to the fact that no muscular detachment had been effected in the lower lip and soft-tissue chin region during the maxillary surgery [Table 1].

Discussion

Literature search reveals that a clinician evaluating the esthetics particularly on a profile photograph of an individual who underwent an orthognathic surgery emphasizes more on the lips and chin, followed by the nose.[11] This implies that an ideal anatomical positioning of lips and chin is of boundless importance.

Influence of maxillary intrusion on mandible

It is noteworthy that, in patients who have a mandibular deficiency in addition to a gummy smile, the sagittal advancement accomplished by the mandibular autorotation following a maxillary intrusion is more appreciable as it will eventually result in enhanced sagittal relationship of both the jaws.[12] A previous study revealed that an average of 5 mm maxillary impaction would lead to a 2 mm horizontal advancement and 1.2 mm vertical shortening of the chin in the postoperative phase when using the radiographic condylar center of the mandible as the

Table 1: Systematic review of published literature

Author (year)	Sample size	Follow-up period (months)	Course of analysis	Technique	Type of fixation	Magnitude of movement	Method for measurement
Schendel *et al*. (1976)	24	29	Retrospective	LeFort I impaction	Rigid internal fixation	6 mm	Cephalogram Computerized model
Radney and Jacobs (1981)	10	6	Retrospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Wessberg *et al*. (1982)	25	24	Prospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Mansour *et al*. (1983)	14	6	Retrospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Sakima and Sachdeva 1987	20	12	Retrospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Nattestad A and Vedtofte P 1992	10	5	Retrospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Nadjmi N *et al*. (1998)	20	Not clear	Retrospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Rosen 1988	23	9.8	Retrospective	LeFort I impaction	Rigid internal fixation	6 mm	Cephalogram
Rosenberg *et al*. (2002)	11	12	Retrospective	LeFort I impaction	Rigid internal fixation	6 mm	Cephalogram
Steinhauser *et al*. (2008)	42	Not clear	Retrospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Wang YC *et al*. (2008)	10	3	Prospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Ksiezycki Ostoya *et al*. (2009)	22	15	Retrospective	LeFort I impaction	Rigid internal fixation	6 mm	Cephalogram
Abhuzinada S *et al*. (2013)	10	Not clear	Prospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Jayakumar J *et al*. (2019)	45	3	Prospective	LeFort I impaction	Rigid internal fixation	Not clear	Cephalogram
Peleg O *et al*. (2019)	20	6	Prospective	LeFort I impaction	Rigid internal fixation	6 mm	Cephalogram

rotation center of mandibular autorotation in the presurgical predictions.[13]

It is a well-known fact that the vertical dimensions of the lower face would change when the maxilla is impacted and the mandible autorotates. There exist numerous reports in the literature on the degree of decrease in lower facial height following a maxillary impaction. Numerous researchers have dealt with the query of the impact of maxillary impaction on mandibular autorotation a long way back and suggested a replication of the esthetic outcome on the lateral cephalogram. They advocated a 1:1 ratio between lower-face shortening following maxillary impaction and mandibular autorotation.[13,14]

Maxillary impaction is generally performed to reduce the lower anterior facial height with concomitant advantages of mandibular autorotation to get the chin movement. A previous study found that the rotation center of the mandible revealed huge variations. The rotation center in this study was found lower than the radiographic condylar center.[15] It was concluded from the result of few studies that the mandible will eventually follow any changes in occlusion that arises as a result of maxillary impaction. It can be advocated that the esthetic changes in the mandibular and chin position would be little inconsistent and little predictable following maxillary intrusion.[16]

Influence of maxillary intrusion on temporomandibular joint

Literature reveals that clicks in the temporomandibular joint are more likely to be resolved following a prognathic reduction and maxillary impaction surgery than after mandibular advancement or combination maxillary and mandibular surgery.[12] It was observed that movements that would force the condylar head in a posterior or superior direction would eventually lead to an internal derangement of the joint. A previous study of condylar pathway tracing advocated a higher incidence of hypomobility following a mandibular advancement surgery but an enhanced function following a LeFort I osteotomy and mandibular reduction osteotomy.[17,18]

It was noted that the soft-tissue changes associated with a maxillary intrusion were prominent on the nasal tip with an increase in alar base width, shortening of lip length, and concurrent with horizontal movements of the maxilla.[8] Previous studies have revealed that autorotation of the mandible results in shortening of the elevator muscles. As a result of this, neither an active or passive distracting forces can be exerted on the intruded maxilla by the mandibular musculature. Hence, it is considered that superior repositioning of the maxilla with the aid of a LeFort osteotomy is perhaps the utmost stable orthognathic surgical intervention.[19] In addition to this, the biomechanics of the jaw can be changed due to the autorotation of the mandible.

There exists a controversy pertaining to the site for center of rotation of the mandible, following superior repositioning of the maxilla. Few authors advocated the condyle to be the center for the autorotation of the mandible, while few authors advocated that mastoid process as the center of rotation.[5,13] Wang *et al*. demonstrated that this center is located 2.5 mm behind and 19.6 mm below the radiographic condylar center of the mandible.[15] Another study proposed that the mandibular autorotation occurs at a point following maxillary intrusion that was similar to that occurred at preoperative mouth opening.[20]

A recent study observed that the occlusal plane angle in the mandibular autorotation group was steeper when compared to the nonautorotation group.[2] Another study advocated that the movement of maxilla in the superior direction has an effect on the repositioning of the chin in the anterior and cranial directions.[21]

Conclusion

The results of this study reveal that there is a definite influence on the mandibular and chin positions as a result of maxillary intrusion and autorotation of the mandible. It is noteworthy that every 1 mm of maxillary superior impaction, the chin moved 0.6 mm vertically and 0.2 mm horizontally. There is an appreciable shortening of the lower lip length.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Functional Role of Inorganic Trace Elements on Enamel and Dentin Formation: A Review

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ABSTRACT

Calcium and phosphate are the major components of hydroxyapatite crystals that form the inorganic portion of the teeth. Apart from these, certain elements are present in little amounts in enamel and dentin of the human teeth. Although they are required in minute quantities, their absence may alter healthy development of enamel and dentin and may result in developmental tooth defects as well as dental caries. Furthermore, excessive intake of some trace elements may inversely affect tooth development and health. The exact of effects that trace elements have on teeth and oral health is still an unexplored territory. The present paper reviews the presence of trace elements in teeth and their role in tooth health and development.

KEYWORDS: *Amelogenesis, dentinogenesis, trace elements*

INTRODUCTION

The human body's various functions depend substantially on various nutritional elements.[1] There are two types of nutritional elements required by the human body, namely macronutrients and micronutrients. Macronutrients include carbohydrates, fats, and proteins whereas micronutrients comprise vitamins and minerals. Macronutrients are required in larger amounts in the body as compared to micronutrients. The mineral component of the micronutrients is composed of macrominerals and microminerals.[2] The macrominerals required in smooth physiological functioning of the body include sodium, potassium, calcium, phosphorus chloride, and sulfur.[3] In a healthy adult, >100 mg/day of macrominerals is required. According to Frieden, microminerals include iron, copper, zinc, magnesium, cobalt, nickel, iodine, fluorine, vanadium, selenium, chromium, molybdenum, tin, and silicon.[3,4] These microminerals can be further subdivided into trace elements and ultratrace elements. Both trace and ultratrace elements are required in small amounts in the body. Trace elements are needed up to 1 mg/kg body weight while ultratrace elements are needed <1 mg/kg body weight in a healthy human adult. Even though trace elements are required in small amounts by the body, their deficiency can have serious implications.[1,5]

Trace elements in enamel

The hardest tissue in the entire human body is the enamel of our teeth. Dental enamel is greatly mineralized

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in its composition with approximately 92%–96% of inorganic matter, 1%–2% organic matter, and 3%–4% of water, weight/weight (w/w). Such high percentage of inorganic matter is what makes the dental enamel brittle and nonvital. The smaller organic part of dental enamel comprises mostly proteins which include amelogenins, tuftelins, and aminoglycans.[6] The larger inorganic part of dental enamel is mostly composed of hydroxyapatite crystals. These hydroxyapatite crystals are arranged as prisms and interprisms of 70 nm width and 30 nm thickness.[7,8] Hydroxyapatite crystals also contain numerous trace elements. These trace elements are mostly incorporated within the dental enamel during tooth mineralization and maturation.[9,10] Shashikiran *et al*.[11] have enumerated the presence of eighteen trace elements in dental enamel by atomic absorption spectrometry. They found the presence of fluorine (F), strontium (Sr), potassium (K), aluminum (Al), silicon (Si), nickel (Ni), boron (B), iron (Fe), copper (Cu), chromium (Cr), zinc (Zn), manganese (Mn), cobalt (Co), selenium (Se), lead (Pb), molybdenum (Mo) and vanadium (V) in sound human dental enamel samples. They also found differences in the concentrations of certain trace elements in primary and permanent teeth. They discovered that K, F, and Sr concentrations were higher in the enamel of permanent teeth as compared to primary teeth. On the other hand, concentrations of Cu, Al, and Si were more in dental enamel of primary teeth as against the dental enamel of permanent teeth.[11] Ghadimi *et al*.[12] in their study postulated that trace elements may have a significant effect on the size of hydroxyapatite crystals which constitute a major part of dental enamel. Some trace elements in the form of ions such as iron in ferrous (Fe^{2+}) and ferric (Fe^{3+}) form, strontium (Sr^{2+}), and zinc (Zn^{2+}) (with molar fraction >10%) ions can expand the crystal lattice of hydroxyapatite crystals along the a-axis, whereas carbonate (CO_3^{2-}), silicate (SiO_4^{4-}), magnesium (Mg^{2+}), titanium (Ti^{4+}) and zinc (Zn^{2+}) (with molar fraction <10%) ions have the potential to shrink the lattice along the a-axis. Along the c-axis, silicate (SiO_4^{4-}), carbonate (CO_3^{2-}), ferrous (Fe^{2+}), ferric (Fe^{3+}), zinc (Zn^{2+}), and strontium (Sr^{2+}) ions can expand the hydroxyapatite crystal lattice and magnesium (Mg^{2+}), chromic (Cr^{3+}), titanium (Ti^{4+}), nickelous (Ni^{2+}), and cobaltous (Co^{2+}) shrink the hydroxyapatite crystal lattice. Therefore, trace elements can affect the average size of the inorganic component of the dental enamel, i.e., the hydroxyapatite crystals.

Trace elements in dentin

In a healthy human tooth dentin is sealed from the environment since it is encased by enamel and cementum.[13] Another major difference from enamel is that physiological exchange of elements occurs in tooth dentin even after mineralization unlike dental enamel.[14] After the metabolism of elements in dentin formation completes it becomes inactive, which leads to accumulation of these elements.[15,16] Kumagai *et al*.[17] postulated that the concentrations of trace elements in human tooth dentin increase with age. They reported increased concentrations of ten trace elements, i.e., B, Co, Cr, Mn, Zn, Sr, Mo, Cd (cadmium), Rb (rubidium), and Pb (lead).[17] It may be due to abundance of collagen fibers in dentin. It is believed that certain elements have a propensity to accumulate in the collagen fibers present in the tooth. Therefore, such elements increase in concentrations over in the collagen-rich tooth dentin.[18] Fernández-Escudero *et al*.[18] investigated the concentration of trace elements in human coronal dentin with age using inductively coupled plasma-mass spectrometry. They found that 12 elements, namely Sr, Mg, S (sulfur), K, Zn, Ba (barium), B, Co, V, Li (lithium), Sn (tin), and Pb, had a significant correlation with age. Out of these 12 elements, Li, Sn, and Pb have been considered potentially toxic to the body. They also suggested that the increase in concentration of Pb with age may be due to its tendency to be attracted to collagen fibers.[18] Skalnaya *et al*. have reported that Li and Sn concentrations increase with age in human hair also.[19] Li, though used in the treatment of mood disorders, has been found to increase the risk of hypothyroidism, hyperparathyroidism, reduced urinary concentration, and weight gain. Sn intoxication has been seen to affect the metabolism of other elements in human tissues like Fe, Cu, and Zn in human tissues. In addition, Pb has been considered an environmental pollutant and increase in its concentration may also inversely affect the concentrations of Fe, Cu, and Zn in dentin. Mg has been regarded as a calcium antagonist and regulates many cell functions. Its deficiency may result in several pathological conditions.[20] Previous studies indicate a positive correlation between decreased levels of Mg, periodontitis, and heart disease.[21] Boron (B) has been actively derived from food and water contaminated with borate-containing fertilizers. It has been reported to have favorable effects in thyroid and lipid metabolism and in obesity.[22] Cariostatic effects of boron have also been reported in the literature.[23] Strontium is known to accumulate in bones and result in hypocalcemia.[15] It has been reported to have anticariogenic effects by substitution of calcium in the hydroxyapatite crystals.[24] Strontium is considered as an essential trace element.[24] Strontium accumulates in the bones and its excessive deposition can result in disturbances in metabolism and mineralization of bones which in turn results in loss of calcium from bones resulting in hypocalcemia.[15] It is also believed to possess anticariogenic properties.[25] It

can be derived from plants and animals and is stored in human bones and teeth.[26] Recent studies have reported that strontium is essential for bone and teeth health and that its deficiency leads to defective mineralization of bones and teeth. Furthermore, a supplement of strontium, strontium ranelate, has been shown to be effective in osteoporosis among women by decreasing bone resorption and increasing osteoblastic activity.[27] Boron deposits in teeth in the form of calcium borate instead of calcium phosphate and helps in making them caries resistant.[26] It can be derived from food and water esp. contaminated with borate-containing fertilizers.[22] It improves lipid metabolism and is helpful in obesity and thyroid metabolism.[23] Barium reportedly replaces calcium in dentin hydroxyapatite, but its excessive consumption may lead to acute intoxication.[15] Barium accumulates largely in bone, but small amounts may also be found in skin, fat, and muscular tissues.[26] Furthermore, its accumulation in bones and teeth increases with age and is also found to have some caries-reducing properties.[18,26,28]

Anticariogenic effect of trace elements

Fluoride

The anticariogenic potential of fluoride has been well known in dentistry for many decades. The milestone shoe leather survey by Petersen *et al.* in the early 1970s paved the way for further studies on the effect of fluoride on teeth. The caries preventive effects of fluoride have been so well-documented that most toothpaste today come with fluoride incorporated in them and so much so that the World Health Organization recommends community water fluoridation in areas with high caries prevalence.[29] Fluorine in the form of fluoride (F^-) possesses the potential to replace the hydroxyl ion (OH^-) in the hydroxyapatite crystals of dental enamel. The newly formed fluorohydroxyapatite is less soluble than hydroxyapatite and also more acid resistant. Thus, fluorohydroxyapatite has superior caries and dental erosion resistance than hydroxyapatite. It has been speculated that this substitution of OH^- with F^- stabilizes the crystal structure of the hydroxyapatite.[30,31] It is also believed that fluoride hastens post-eruptive maturation and helps in the remineralizing incipient carious lesions.[32]

Molybdenum

Molybdenum has been reported to have a cariostatic effect. Adler and Straub[33] in their study reported decreased prevalence of dental caries in Hungarian children residing in areas with molybdenum content in drinking water as compared to those living in areas without the presence of any molybdenum in water.[34] Hewat and Eastcott[34] also reported a lower prevalence of dental caries in children that consumed vegetables derived from areas with soil containing molybdenum as opposed to children living in a nearby area which did not have any molybdenum content in its soil.[34]

Strontium

Increased strontium ion (Sr^{2+}) concentrations in dental enamel have also been reported to have an anticariogenic effect. Its affinity to exchange calcium makes teeth somewhat caries protected by replacing the calcium in hydroxyapatite crystals.[25] Deficiency of strontium may lead to defective mineralization of bones and teeth.[27] Qamar *et al*. reported that the strontium content in teeth decreases with age.[1]

Lithium

Lithium has been reported to have anticariogenic effect on teeth. It is also used in treatment of bipolar mental disorder.[1,35]

Trace elements promoting dental caries

Selenium

Selenium has been found to increase the incidence of caries in humans. Previous studies have found an increased incidence of dental caries in children with selenium present in their urine.[1,32] It is believed that selenium induces structural changes in the dentin of teeth.[36]

Copper

Copper is considered to be a caries promoting trace element.[37,38] Increased occurrence of caries has been found to be associated with the presence of copper in food and water.[39]

Cadmium

Cadmium has been linked to increased prevalence of dental caries in teeth.[38] Despite that, some studies claim that cadmium when incorporated in teeth postdevelopment does not have caries promoting activity but while not excluding previous fluoride exposure.[40]

Lead

It is believed that lead ions substitute calcium and calcium and phosphorus in the crystals of bone minerals causing hypercalcemia and hyperphosphatemia.[41] It is considered as a caries promoting element. A direct relationship has been found between enamel hypoplasia and lead exposure in children.[42] Needleman *et al*. in their study found an increased incidence in deciduous teeth of American suburban children exposed to lead.[43] Furthermore, a direct link has been found between development of early childhood caries in children and lead exposure.[44]

Conclusion

Many trace elements are required for proper development of the body and our teeth. They may play a vital role in the development of teeth, including that in amelogenesis as well as dentinogenesis. Further studies should be done in this field to accurately determine the role of various trace elements on enamel and dentin formation.

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Review Article

Drug Repurposing for Tooth Regeneration: The Promising Premises

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Abstract

Drug repurposing which identifies new therapeutic use(s) for drugs currently in use is a brand-new avenue of research interest worldwide. It circumvents the high-end monetary and time investment usually associated with contemporary drug discoveries. In the field of dentistry, recent studies in drug repurposing focuses in attaining dentin repair or reduction of bone resorption associated with apical periodontitis. Metformin, an anti-diabetic drug has shown pro-osteogenic properties. Aspirin a known anti-inflammatory agent with anticoagulant action is found to modulate the differentiation of dental pulp cells. The significant role of glycogen synthase kinase-3 inhibitors in activating the Wnt/-beta cat signaling pathway of mesenchymal pulp stem cells may pave the way to the pharmacological treatment of dental caries in near future. It is to be noted here that further preclinical and clinical studies are warranted for the regular therapeutic use of these potential drugs in clinical dentistry.

Keywords: *Aspirin, dentine regeneration, drug repurposing, metformin, tideglusib*

Introduction

Drug repurposing can also be termed as drug repositioning. It is concerned with the recognition of new pharmacological indications of existing/failed/old/investigational/already marketed/Food and Drug Administration approved drugs and their utilization in the treatment of diseases other than the drug's proposed therapeutic use. Drug repositioning mitigates the exponential cost and high failure risk and long duration of development in traditional drug discovery.[1-3] The two main strategies of drug repositioning are on-target and off-target. In on-target strategy, for a new therapeutic indication an established pharmacological action of a drug is applied. Here, the biological target is the same, whereas diseases are different. Whereas in the off-target profile, both targets and indications are novel.[4] There are two main methods for drug repositioning. One is an experimental method, and the other a computer simulation method. An experiment-based approach involves the screening of original drugs through experimental analysis. Computer simulation involves virtual screening of public databases using computational biology and bioinformatics/cheminformatics tools, and is based on molecular interactions between drug molecules and protein targets.[5-7] Since the discovery of new drugs is usually associated with high risk, high level of financial and time investment, drugs currently in the market when repurposed for dental applications also becomes an interesting arena.

Metformin

Metformin (N, N-dimethyl l-biguanide) is the first-line drug for type 2 diabetes treatment.[8] It has an anti-inflammatory activity besides its hypoglycemic effect.[9] It was evident from clinical trials that, topical metformin is a potential ancillary in periodontal therapy.[10] Increased infiltration of monocytes/macrophages has been observed in the progression of apical periodontitis. The significant chemokine responsible for monocyte recruitment is found to be the monocyte chemoattractant protein-1 otherwise known as C-C motif chemokine ligand-2 (CCL-2). Repressing CCL-2 expression and thereby chemotaxis of macrophages/monocytes can dampen the disease

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progression.[11] Enhanced activity of inducible nitric oxide synthase (NOS) is another factor in developmental apical periodontitis. Accelerated inflammation by activated macrophages results due to generation of nitric oxide by (NOS).[12-14] Metformin pharmacologically modulates the iNOS/NO pathway[15] thereby attenuating the progression of apical periodontitis.[13] Metformin additionally suppresses iNOS expression induced by Lipopolysaccharide (LPS). LPS being a major virulence factor of endodontic pathogens influences the pathogenesis of apical periodontitis. Proinflammatory cytokines such as tumor necrosis factor and interleukin-1a (IL-1a) are released by the induction of macrophages by LPS. Consequently, breakdown of the extracellular matrix is triggered leading to bone resorption associated with apical periodontitis.[16] Metformin in addition mediates suppression of' LPS-induced inflammatory signaling and resultant production of inflammatory mediators through AMPK dependent and independent pathways.[17] Thus, the regulation of iNOS expression, NO production, and suppression of LPS-induced inflammatory signaling leading to suppression of monocyte recruitment, etc., makes metformin a potential agent as root canal medicament with positive effects on both monocytes and osteoblasts thus contributing toward host response modulation.

Aspirin

Multipotent stem cells in dental pulp are of prime importance in the regenerative capacity of pulp-dentine complex, especially in trauma or caries induced dental tissue loss.[18] Osteogenic effects when brought about by employing biomolecules, helped in achieving odontogenic differentiation of dental pulp cells (DPCs).[19] Wnt/beta-catenin signaling pathway was targeted through pharmacological approach to bring about dentine repair and *in vivo* dentine formation.[20] Gene expression connectivity mapping (CMap) which identifies the regulation of gene expression by small molecules,[21] specifies aspirin as a molecule which induces odontogenic differentiation. Aspirin, an anti-inflammatory agent and antiplatelet agent are a linchpin candidate for drug repurposing owing to its thoroughly represented human safety profile.[22] Aspirin induces stem cell differentiation[23] and many recent studies demonstrate its ability to regulate osteogenic differentiation of DPCs.[24] Improved osteogenic differentiation of' SHEDS and the regulation of (TERT)/ Wnt/beta-catenin pathway in both *in vitro* and *in vivo* studies was demonstrated by Aspirin, even at low concentrations.[25] Reduction in levels of inflammatory cytokines IL-6 and matrix metalloproteinase-9 and induced odontogenic differentiation was brought about by Aspirin even at a concentration of 0.05 Mm evidences its regulation of odontogenic genes DMP-1 and DSPP.[26] The anti-inflammatory potential along with induction of odontogenic differentiation in DPCs, thus make Aspirin a promising agent in vital pulp therapies. Future works thus have to target on efficient delivery methods of this drug for *in vivo* scenarios.

Glycogen Synthase Kinase-3 Inhibitors

Glycogen synthase kinase-3 (GSK3) is a protein kinase. It is concerned with the production of a vast variety of proteins in numerous pathways.[27] Targeted GSK-3 inhibition has evidenced therapeutic benefits since the pathogenesis and progression of various ailments including diabetes, obesity, cancer[28] and Alzheimer's disease are influenced by this Kinase.[28,29] The activation of the Wnt pathway, retention of Rex-1, Oct-3/4, Nanog and pluripotent state-specific transcription factors and preservation of undifferentiated embryonic stem cells phenotypes are all made possible by attaining GSK-3 inhibition through 6-bromoindirubin-3'-oxime.[30] Tideglusib a GSK-3 antagonist demonstrates a tooth repair potential based on this inhibitory effect as reported recently by Neves *et al*.

Mode of action is thought to be activation of Wnt/§-cat signaling pathway of' pulpal mesenchymal stem cells. If reproducible in *in-vivo* studies, this holds a possibility of pharmacological treatment for loss of dental tissue.[20] The potential of tideglusib (or other GSK-3 molecules) in achieving regeneration of the teeth are in initial trial phases. Tivantinib is another GSK3 inhibitor which is an antiproliferative agent, currently in phase III trials for the treatment of the lung and hepatocellular carcinomas.[31] *In vivo* investigations aimed at delivering tivantinib adsorbed on collagen sponges into exposed pulpal lesions are being carried out currently.

Conclusion

Drug repurposing with a long-recorded history through serendipitous observations provides a new boulevard in developing new therapeutic approaches based upon existing/approved drugs. This drug repositioning strategy, in an era of precision and integrated medicine, thus gains significance in the field of dentistry too. To attain beneficial results through drug repositioning in dentistry, a meticulous understanding of the nuances coupled with a comprehensive approach is called for. Novel researches in drug repurposing can thus revamp the existing chemotherapeutics in dentistry and are to be emphasized both from a prognostic and economical perspective.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Comparative Evaluation of Genotoxicity in Tobacco Users versus Nontobacco Users

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ABSTRACT

Background: Many of the contents of cigarette smoke are genotoxic in nature, and consequently, cytogenetic injury seems to be a trustworthy biomarker for deciding the influence of exposure to chromosome damaging agents in smoke. The cytokinesis-block micronucleus assay (CBMN assay) has been proven to be an effectual tool for the study of micronuclei (MN) that will help in estimating the genotoxicity in tobacco users alone which will further help in early cancer detection. **Objective:** The objective is to find out whether there is pronounced contrast in genotoxicity between tobacco users and nonusers by determining MN number in peripheral blood lymphocytes using CBMN assay. **Methodology:** MN frequency in peripheral blood lymphocytes was estimated in 5 ml of fresh blood obtained from sixty individuals using tobacco either smoking, chewing, or combination of both and also from thirty individuals with no habit of tobacco use. All were in the age group of 20–40 years. **Results:** There was a significant increase in genotoxicity in tobacco users when compared to that of nontobacco users. A positive correlation was also obtained between smoking index and MN frequency in the study. **Conclusion:** Approximation of frequency of MN by CBMN assay can be used to evaluate the genotoxicity present in blood and helps in identifying tobacco users who are at a high risk for the presence of cancer even before the appearance of clinical changes.

Keywords: *Genotoxicity, micronuclei, tobacco*

Introduction

Cancer is one of the main reasons for morbidity and mortality of our times. Oral cancer is the sixth most prevalent cancer, of which 95% are oral squamous cell carcinoma.[1] It is estimated that around 43% of cancer deaths occurred due to tobacco use, insalubrious diets, alcohol intake, and inactive lifestyle.[2] In recent years, aggravating number of these malignancies are accounted among younger adults.[3]

Tobacco intake is the world's most avertible risk factor of cancer as 80% of oral cancers are associated with its use.[4] The risk appears to increase with increase in duration and intensity of tobacco smoking.[5]

On intake of carcinogenic content in tobacco smoke, there is the development of covalent bonds among carcinogens and DNA creating DNA adducts which result in ineffaceable mutations in critical genes of somatic cells.[6] Therefore, cytogenetic injury seems to be a superior biomarker for finding the influence of exposure to chromosome harming agents in smoke.[7]

Cytogenetic damage can be quantitatively measured by cytogenetic biomarkers such as chromosomal aberrations, sister chromatid exchanges, and micronuclei (MN) in PBLs.[8] Cytokinesis-block micronucleus (CBMN) assay is one of the benchmark cytogenetic tests for measuring chromosomal damage in PBLs because of its simplicity, good duplicability, and dependability.[9]

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We did not come across any study which estimated the level of MN in peripheral blood of tobacco users alone. Thus, the present study was conducted to find out whether there is pronounced contrast in genotoxicity in tobacco users and nonusers by CBMN assay in human peripheral blood lymphocytes by evaluating the average number of MN.

Methodology

Study setting

This study was conducted in the outpatient department, PMS College of Dental Sciences and Research, Trivandrum, and laboratory procedures were carried out in "Genitika" (an ISO certified laboratory), Pettah, Thiruvananthapuram, over a duration of 1½ years.

Study subjects

All the patients were briefly informed about the test procedure before sample collection, and informed consent was obtained. Study group consisted of sixty individuals using tobacco either smoking, chewing, or combination of both. The criteria for deciding the tobacco smokers were based on the definitions given by the US Centre for Disease Control and Prevention.[10]

- Never smokers
- Former smokers
- Nonsmokers
- Current smokers.

The classification of tobacco chewers[11]

- Current tobacco chewers
- Tobacco chewing quitters
- Ever tobacco chewers
- Never-Tobacco-Chewers.

Control group consisted of thirty individuals with no habit of tobacco use (smoking or chewing) and normal oral mucosa.

The study was reviewed and approved by the institutional ethical committee of the institution.

Inclusion criteria

- Patients with a habit of tobacco use and having clinically normal mucosa
- Patients aged 20–40 years
- Patients with no other reported systemic illness.

Exclusion criteria

- Patients with clinically detectable changes in the oral mucosa
- Patients below 20 years and above 40 years
- Patients with confirmed systemic illness
- Exposure to cytotoxic drugs, chemicals, or radiation therapy.

Sample size

Sample size was calculated based on the equation:

$$n = \frac{2\sigma^2 \left(Z_\alpha + Z_\beta\right)^2}{\delta^2}$$

where, n – Sample size, σ – Standard deviation, δ – Difference in mean, and α and β are Type I and Type II errors.

Armamentarium

- Disposable gloves
- Mouth mask
- Tourniquet
- Spirit
- Sterile gauze pieces
- Syringe and needle
- Mouth mirror
- Probe
- Tweezer
- Cotton rolls.

Reagents

- Lymphoprep, sterile 500 ml
- Hank's balanced salt solution, sterile, with calcium and magnesium, without phenol red
- Roswell Park Memorial Institute 1640 medium, without L-glutamine
- Fetal bovine serum, heat-inactivated
- L-Glutamine solution
- Sodium pyruvate solution
- Cytocalasin-B
- Dimethyl sulfoxide
- Phytohemagglutinin
- Isoton II
- Zapoglobin
- Depex
- 1% (w/v) hypochlorite solution
- Diff-Quik staining set
- Methanol
- Isotonic saline
- 4.25 g sodium chloride
- 500 ml Milli-Q water
- Acetic acid.

Sample collection

All participants completed a questionnaire which gave their demographic data, medical status, smoking and drinking habits, prior or current exposure to medication, or environmental agents affecting MN frequency.

Five milliliter of fresh peripheral blood was drawn from all volunteers by venepuncture. Two milliliters sent for routine blood examination to rule out systemic changes, remaining 3 ml was transferred into heparinized

vacutainers and sent to the laboratory within a few hours after collection of samples.

CBMN assay procedure was then carried out.

Evaluation

Each of the slides was coded before scoring and examined at ×100 magnification. The number of MN with no <1000 binucleated cells was scored, and the distribution of MN among binucleated cells was recorded.

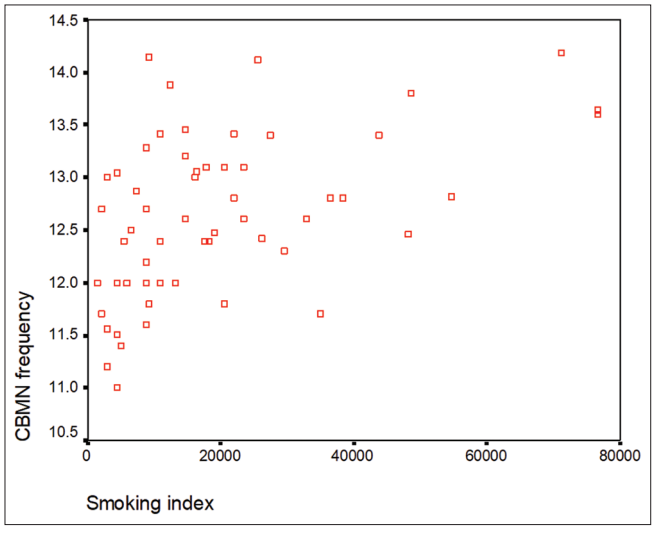
The MN frequency between tobacco users and nontobacco users were then compared.

Statistical analysis

Data were analyzed using the computer software, Statistical Package for the Social Sciences (SPSS), Version 16, manufactured by (International Business Machines Corporation company, United States of America) for Windows Operating System.

Results

In our study, a novel attempt was made to correlate smoking index with MN frequency in PBLs. We noted a strong significant positive correlation between smoking index and MN frequency [Table 1]. Using linear regression analysis [Graph 1], we were able to deduce that 23.3% variability in MN frequency was attributed to smoking index [Table 2], and thus by making the use of this regression model, we were able to predict the MN frequency in PBLs from that of smoking index in tobacco users. The regression coefficient of smoking index (0.000021) indicates that, as smoking index increases by 10,000 units, the CBMN frequency increases by 0.2 units. The predicted model is significant ($P < 0.001$). Thus, it can be concluded that the average CBMN frequency increases by 0.2 units for every 10,000 units of smoking index (roughly three cigarettes/day for 10 years). R^2 of the regression analysis is 0.233. It means that 23.3% of variation in CBMN frequency is explained by smoking index. The implication of the result is that CBMN frequency is significantly influenced by smoking index [Table 2].



Graph 1: Scatter diagram of smoking index and cytokinesis-block micronucleus frequency

The MN frequency of both tobacco users and nontobacco users was statistically compared. The mean MN frequency in tobacco users was found to be 12.6 ± 0.8 and in nontobacco users was 10.7 ± 0.5 [Table 3]. Results revealed that there was a statistically significant increase ($t = 12.74$, $P < 0.01$) in number of MN among tobacco users when compared with nontobacco users.

Discussion

Results revealed that there was a statistically significant increase ($t = 12.74$, $P = 0.000$, $P < 0.01$) in number of MN among tobacco users when compared with nontobacco users, emphasizing the fact that a pronounced higher level of genetic injury and cytotoxicity exist among tobacco users. The above result obtained is in consensus with studies done by El-Zein *et al.*,[12] Zamani *et al*.[13] and Guttikonda *et al*.[14]

El-Zein *et al.* in their study analyzed MN in mononucleated cells along with other variables in lymphocytes of lung cancer patients to improve the

Table 1: Comparison of micronuclei frequency based on the smoking index

Smoking index	Mean±SD	*n*	*t*	*P*
≤10,000	12.2±0.8	24	3.96**	0.000
>10,000	12.9±0.6	36		

**Significant at 0.01 level. SD: Standard deviation

Table 2: Prediction of cytokinesis-block micronucleus frequency using smoking index (linear regression)

Variable	Constant	*B*	SE	*P*
Smoking index	12.22	0.000021	0.482	0.000

Predicted equation for CBMN frequency using regression analysis, CBMN frequency=smokingindex × 0.00002 + 12.22, CBMN frequency-dependent variable, smoking, index-independent variable. R^2=0.233. SE: Standard error, CBMN: Cytokinesis-block micronucleus

Table 3: Comparison of micronuclei frequency between tobacco users and nontobacco users

Group	Mean±SD	*n*	*t*	*P*
Tobacco users	12.6±0.8	60	12.74**	0.000
Nontobacco users	10.7±0.5	30		

**Significant. SD: Standard deviation

predictive value of CBMN assay. They showed that CBMN cytome assay is an exquisite and explicit predictor of lung cancer risk.[12]

Studies which showed a boost in MN frequency in different types of cancer patients were done by Jianlin *et al*.,[15] Venkatachalam *et al*.,[16] and Milosevic-Djordjevic *et al*.[17] Milosevic-Djordjevic also observed that gender, smoking, and cancer sites did not have any influence on MN frequency in untreated cancer patients.[17]

Guttikonda *et al*. evaluated DNA injury levels in PBLs of tobacco inveterate patients with clinically normal mucosa and patients with oral carcinoma using Single Cell Gel Electrophoresis (SCGE) and deduced that DNA damage in PBLs in both groups were statistically significant and that DNA damage in the former group was exhibited much before clinical alterations were evident. It was also found that, by this method, potential malignancy, predisposition, and cancer development may be predicted in susceptible individuals.[14]

Calderon-Ezquerro *et al*. study indicated a pronounced lesser number of MN in smoker group. A probable cause for the lesser MN frequency in smokers could be that severely injured cells might have waned to divide or died during their *ex vivo* culture, so it was not feasible for the induction of MN. In this study, values between the number of cigarettes/day and nicotine densities were less and trivial and this may be due to fake information provided by smokers, with a probability of being belittled in some cases and exaggerated in others.[18]

In our study, we also found that MN frequency increased with duration of tobacco use. Simi

lar result was obtained in the study done by Naderi *et al*.[19] However, the result obtained was statistically not significant. They proposed that chromosomal alterations caused by smoking are possibly not linked to the time of smoking as cigarette has the capacity to exhibit chromosomal modifications from the initial period itself. However, our results showed a statistically significant correlation ($F = 10.78$, $P = 0.000$, $P < 0.01$) between duration of tobacco use and MN frequency.

Conclusion

There was a statistically pronounced increase in the MN frequency in tobacco users when compared to nontobacco users. MN number also had a linear correlation with duration of tobacco use and smoking index.

The results deduced the fact that the genotoxicity in tobacco users was profoundly higher by comparison to that of nontobacco users. The results deduced the fact that we can predict the Micronuclei frequency in an individual by obtaining the duration and frequency of his/hertobacco usage. This in turn would allow us to evaluate the genotoxicity in tobacco users at an initial stage even before the clinical signs of cancer. This would further help in conducting tobacco cessation programs among high-risk individuals for cancer.

A higher sample size with longer duration follow-up is the need to further verify the correlation between the number of MN in peripheral blood lymphocytes and tobacco use and its use in cancer risk prediction in individuals.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

The Prevalence of Root Resorption after Orthodontic Treatment in Patients Attending a University Hospital Dental Clinic

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ABSTRACT

Introduction: After orthodontic treatment, some teeth undergo external root resorption due to different factors, such as the root shape, oral habits, biological and genetic factor, gender, and age. Furthermore, extraction cases, long treatment duration, and the amount of force applied during the treatment might be related to root resorption. **Materials and Methods:** Panoramic radiographs for 226 patients treated in the orthodontic department were screened. The lower first permanent molars, lower second premolars, and lower first premolars were measured in centimeters on a ruler using ImageJ System. Teeth were measured from the cusp tip to the cementoenamel junction (CEJ) and from the CEJ to the root apex, and then, the tooth was measured as a whole before and after the treatment. **Results:** Multiple analysis of variance showed that there were no interactions between the root lengths of all teeth tested and either gender, treatment type, or treatment duration ($P > 0.05$). **Conclusion:** Based on the results of this study, no statistically significance relationship between external apical root resorption and gender, type of treatment, and treatment duration was found.

Keywords: *Orthodontics, panoramic radiograph, root resorption, tooth movement*

Introduction

Root resorption is defined by Ne *et al*. "as a condition associated with either physiologic or pathologic process resulting in the loss of dentine, cementum, or bone."[1] Some teeth undergo external root resorption after the orthodontic treatment due to many factors, such as the root shape, oral habits, biological, genetic factors, gender, and age.[2-6] Further, root resorption has been linked to orthodontic cases with extraction, long treatment duration, and the amount of force applied during the orthodontic treatment.[7,8] Root resorption is considered the prominent hidden scars of orthodontic treatment. It constitutes a nightmare for almost all orthodontists.[9]

Brezniak and Wasserstein formulated the term "orthodontically induced inflammatory root resorption" to denote this kind of root resorption and differentiate it from others such as those caused by periodontal lesions or trauma.[10] Abbas and Hartsfield found an incidence of about one in every 20 orthodontically treated subjects having at least 5 mm of root resorption. This information considers root resorption as the second most common unfavorable consequence of orthodontic treatment after white spot lesions of the enamel.[11] The focus of this research is to study the prevalence of external apical root resorption (EARR) after orthodontic treatment in patients treated at the Department of Orthodontics by postgraduate residents in King Abdulaziz University Faculty of Dentistry and to evaluate the association of EARR with gender, type of treatment, and duration of the treatment.

Materials and Methods

This was a cross-sectional study done in patients attending Dental Clinic of King Abdul Aziz University Hospital for fixed orthodontic treatment. Panoramic radiographs for 226 patients treated in the orthodontic department were screened. The inclusion criteria

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were (1) adult patients, (2) roots with closed apices, (3) no evidence of root reposition before the treatment, (4) healthy patients, and (5) complete records/data and proper panoramic radiographs before and after the treatment. The exclusion criteria were (1) patients who did not complete the treatment.

Fifty-four cases satisfied our inclusion criteria; among the included cases, 31 were females and 23 were males with a mean age of 18 years and the mean treatment duration is 41.5 months. The lower first permanent molars, lower second premolars, and lower first premolars were measured in centimeters on a ruler using ImageJ software version 1.44; (National Institutes of Health, Bethesda, MD, USA). Teeth were measured from the cusp tip to the cementoenamel junction CEJ and from the CEJ to the root apex, and then, the tooth was measured as a whole before and after the treatment. To compensate for any magnification in the panoramic radiographs, the following equation was used on an excel sheet $100 - (X \times 100/Y)$ where X is referred to the mesiodistal width of a magnified permanent tooth in the panoramic radiograph before the treatment and Y is referred to the mesiodistal width of the same tooth in the panoramic radiograph after the treatment.

EARR was classified using four-grade ordinal scale proposed by Scott McNab: grade 0 means no apical root resorption is found, grade 1 blunt root apex, grade 2 moderate resorption of root apex beyond blunting and up to one-third of the root length, and grade 3 severe resorption of root apex beyond one-third of the root length.

Statistical analysis

Data were tabulated and analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Mac, Version 20.0. Armonk, NY: IBM Corp, USA). The Shapiro–Wilk test showed that the data were not normally distributed, so nonparametric tests were used throughout the study. Mann–Whitney tests were used for bivariate comparisons between treatment type and EARR and gender and EARR. Spearman's rank correlation coefficient (rho) was used to establish a correaltion between treatment time and root resorption. A statistical significance was considered at $P < 0.05$.

Results

The case summaries of all the teeth are given in Table 1. Nonparametric tests were used to compare the treatment type whether extraction or not and also between genders. Mann–Whitney tests showed that there were no significant differences in the lengths of the roots for all teeth studied between extraction and nonextraction cases [Table 2] and also between genders [Table 3], $P > 0.05$.

Bivariate correlation was performed between the amount of root resorption and treatment time. The Spearman rho showed no significant correlation between treatment time and the amount of root resorption for the teeth studied ($P > 0.05$).

Discussion

This retrospective study investigated the prevalence of root resorption after orthodontic treatment in relation to age, gender, duration of the treatment, and extraction cases through panoramic radiographs. Although panoramic radiographs have limitations in the evaluation of the root shape and apical area, they were used because periapical radiographs were not available for all patients and because panoramic radiographs are taken by any orthodontist before and after orthodontic treatment.

To compensate for any magnification in panoramic radiographs, a specific equation was used. To discriminate any possibilities of changing in the crown instead of having apical root resorption, teeth were measured from the cusp tip to the CEJ and from the CEJ to the root apex, and then, the tooth was measured as a whole using ImageJ System.

Out of 54 cases, only 11 cases had EARR. These results showed no statistically significant relationship between EARR and gender as in previous studies of Pandis *et al*.,[12] Krieger *et al*.,[13] and Sunku *et al*.[14]

Further, there was no statistically significant relationship between EARR and the type of the treatment whether extraction or not; this is similar to a study done by Pandis *et al*.[12] Another study done by Sunku et al. reported that there is an association between EARR and cases treated with extraction.[14]

In addition, the current study showed no statistical significance between EARR and duration of the treatment; this is contrary to the study of Pandis *et al*., which concluded that there is statistical significance between the duration of the treatment and EARR.[12]

As regards the management of root resorption during orthodontic treatment, many researchers tried to introduce means to control this root resorption other than postponement of treatment. A group of researches tried medical agents such as echistatin,[15] bisphosphonates,[16] and lithium chloride,[17,18] while others tried the use of physical means such as low-intensity pulsed ultrasound.[19-21]

Limitations

One of the limitations in the study was the small sample size because some of the patients records had incomplete data; in addition, most of the panoramic radiographs

Table 1: Case summaries of resorption measurement (cm)

Gender	Treatment	Premolar				Molars			
		Premolar 45	Premolar 44	Premolar 35	Premolar 34	Molar 46 distal root	Molar 46 mesial root	Molar 36 distal root	Molar 36 mesial root
Male	Nonextraction								
	n	16	16	16	16	16	16	16	16
	Mean (SD)	0.0625 (0.2500)	0.2500 (0.5773)	0.1875 (0.4031)	0.000 (0.000)	0.063 (0.250)	0.063 (0.250)	0.063 (0.250)	0.000 (0.000)
	Extraction								
	n	7	2	7	2	5	5	6	6
	Mean (SD)	0.2857 (0.4879)	0.500 (0.7071)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	Total								
	n	23	18	23	18	21	21	22	22
	Mean (SD)	0.1304 (0.34435)	0.2778 (0.5745)	0.1304 (0.3443)	0.000 (0.000)	0.048 (0.218)	0.048 (0.218)	0.046 (0.213)	0.000 (0.000)
Female	Nonextraction								
	n	24	24	24	23	22	22	22	22
	Mean (SD)	0.0417 (0.2041)	0.0417 (0.2041)	0.125 (0.3378)	0.1304 (0.3443)	0.000 (0.000)	0.000 (0.000)	0.046 (0.213)	0.000 (0.000)
	Extraction								
	n	7	1	7	1	7	7	7	7
	Mean (SD)	0.000 (0.000)	0.000 (-)	0.000 (-)	0.000 (-)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	Total								
	n	31	25	31	24	29	29	29	29
	Mean (SD)	0.0323 (0.180)	0.04 (0.200)	0.0968 (0.301)	0.125 (0.338)	0.000 (0.000)	0.000 (0.000)	0.035 (0.186)	0.000 (0.000)
Total	Nonextraction								
	n	40	40	40	39	38	38	38	38
	Mean (SD)	0.05 (0.221)	0.125 (0.404)	0.150 (0.362)	0.0769 (0.270)	0.026 (0.162)	0.026 (0.162)	0.053 (0.162)	0.026 (0.226)
	Extraction								
	n	14	3	14	3	12	12	13	13
	Mean (SD)	0.1429 (0.363)	0.333 (0.577)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	Total								
	n	54	43	54	42	50	50	51	51
	Mean (SD)	0.0741 (0.2644)	0.1395 (0.4130)	0.111 (0.317)	0.0714 (0.261)	0.020 (0.141)	0.020 (0.141)	0.039 (0.196)	0.000 (0.000)

SD: Standard deviation

Table 2: Bivariate comparisons=Grouping variable: Treatment (extraction vs. nonextraction)

				*P**			
Molar 46 distal root	Molar 46 mesial root	Bicuspid 45	Bicuspid 44	Molar 36 distal root	Molar 36 mesial root	Bicuspid 35	Bicuspid 34
0.574	0.574	0.258	0.247	0.403	1.000	0.128	0.622

*P>0.05 is considered statistically significant

Table 3: Bivariate comparisons=Grouping variable: Gender

				*P**			
Molar 46 distal root	Molar 46 mesial root	Bicuspid 45	Bicuspid 44	Molar 36 distal root	Molar 36 mesial root	Bicuspid 35	Bicuspid 34
0.240	0.240	0.177	0.066	0.843	1.000	0.0700	0.124

*P>0.05 is considered statistically significant

were not clear. Furthermore, periapical radiographs and cone-beam computed tomography would be more useful to evaluate EARR than panoramic.

Conclusion

Within the limitation of the current study, no statistically significance relationship between EARR and gender, type of treatment, and treatment duration was found. Individual susceptibility could be one the main risk factors for root resorption in adults.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Impact of Tooth Loss Position on Oral Health-Related Quality of Life in Adults Treated in the Community

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Abstract

Background: Tooth loss is known to have negative effects on both functional and psychological oral health-related quality of life (OHRQoL), but the impact of the position of the tooth loss (i.e. anterior or posterior) on the different psychosocial dimensions of OHRQoL has yet to be examined. Here, we examined how the position of lost teeth impacts the different dimensions of OHRQoL. **Methods:** This was a cross-sectional epidemiological study of adults aged 18 years and older attending routine examinations at primary care dental centers in Jeddah, Kingdom of Saudi Arabia. Demographic information was collected, and OHRQoL was assessed using the Oral Health Impact Profile-14 (OHIP-14) (Arabic form). Differences in total and subdomain OHIP-14 scores between individuals without tooth loss and those with ≥1 anterior or posterior missing teeth were assessed using Student's *t*-test, and analysis of covariance was used to assess the association between the presence and absence of missing teeth in each compartment and total and subdomain OHIP-14 scores after controlling for age, gender, and income. **Results:** The overall prevalence of tooth loss was 76%. In multivariate analysis controlling for age, gender, and income as covariates, anterior missing teeth were significantly associated with higher OHIP-14 total, physical pain, physical disability, psychological disability, and social disability scores, accounting for 6%–12% of the score variance. However, posterior missing teeth were only associated with total OHIP-14 and functional limitations domain scores, accounting for 6% and 7% of the variance, respectively. **Conclusions:** Here, we show for the first time the impact of the location of missing teeth on different OHRQoL dimensions. Anterior tooth loss has a wide-ranging impact on both physical and psychosocial functioning compared to posterior tooth loss, suggesting that anterior tooth restoration should be prioritized when treatment planning. The position of lost teeth must be considered in addition to the number of losses when examining the impact of tooth loss and its treatment on OHRQoL.

Keywords: *Oral health-related quality of life, psychosocial functioning, tooth loss, tooth position*

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Introduction

Quality of life (QoL) is an important parameter to consider when assessing health status and treatment outcomes in dental patients. Oral health-related QoL (OHRQoL) describes the impact of orofacial conditions and dental interventions as perceived by the patient.[1] OHRQoL is a multidimensional concept that is influenced by physical health, psychology, social interactions, and the environment and as a consequence, standardized instruments have been designed to capture the different composite domains of OHRQoL.[1] One of the most widely used is the Oral Health Impact Profile-14 (OHIP-14), a short

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form self-reporting questionnaire comprising 14 items divided into seven dimensions of impact (functional limitation, pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap).[2] The OHIP-14 has been shown to be reliable,[2] sensitive to changes,[3,4] and have cross-cultural consistency[5] including in Arabic.[6]

Tooth loss remains a significant public health burden in Saudi Arabia, with a recent study reporting a 69% prevalence of tooth loss in a convenience sample of over 600 subjects in Riyadh, Saudi Arabia.[7] Since teeth are vital to mastication, speech, and facial esthetics, tooth loss can have a significant impact both on the individual and society. In meta-analyses and systematic reviews, tooth loss has been shown to have negative effects on both functional and psychological OHRQoL independent of the instrument used or the social context.[8-11] Furthermore, in our recent analysis of occlusal traits and OHRQoL, we found that tooth loss was the only independent predictor of high total OHIP-14 scores in a community sample of adults attending primary care clinics in Jeddah, Saudi Arabia, even when controlling for factors such as age, gender, and income.[12]

However, few studies have examined how the position of the tooth loss (i.e. anterior or posterior) affects OHRQoL or how different tooth loss locations affect the different functional and psychosocial dimensions of impact. Therefore, here, we examined how the position of lost teeth impacts the different dimensions of OHRQoL, hypothesizing that teeth lost from different areas of the mouth will have a differential impact on OHRQoL dimensions.

Methods

Study design

This was a cross-sectional epidemiological study of adults aged 18 years and older attending routine examinations at primary care dental centers in Jeddah, Kingdom of Saudi Arabia. The local institution's ethical board review approved the study protocol, and all patients gave written informed consent after reading the study details.

Inclusion criteria, exclusion criteria, and sampling

The primary health-care centers were geographically located in five areas of the city (north, south, west, east, and center) according to the KSA Ministry of Health. The inclusion criteria were patients aged 18 years and above who were medically healthy and syndrome free. Subjects who had received previous orthodontic treatment were excluded.

Sampling and assessment metrics

A cluster sampling approach was employed to recruit twenty participants from each geographical area, resulting in a total sample of 100 participants. Collected data included demographic information and OHRQoL assessed using the OHIP-14 (Arabic form).[6] Age was subcategorized into three groups (18–40, 41–60, and >60), while income levels were categorized into six groups. Each OHIP question is answered on a five-point Likert scale (0–4), and total scores were obtained by summing the scores of each of the 14 questions. Mean domain scores were calculated by dividing the sum of the subdomain score by the number of questions in that subdomain. Higher OHIP-14 scores indicated worse OHRQoL.

The presence of missing teeth and their location, where the incisors and canines were regarded as anterior teeth and the premolars and molars were regarded as posterior teeth, were recorded during clinical examination by three calibrated examiners. Clinical examination was completed in the clinic's dental chair with an examination kit.

Statistical analysis

Each subject was assigned a unique identifier code, and data were deidentified. Data analysis was conducted using the Statistical Package for the Social Sciences program v. 22 (IBM SPSS Inc., Chicago, IL, USA). Differences in total and subdomain OHIP-14 scores between tooth loss groups (no missing teeth vs. ≥1 missing teeth) were assessed using Student's *t*-test. Analysis of covariance was conducted to assess the association between presence and absence of missing teeth in each compartment and total and subdomain OHIP-14 scores after controlling for age, gender, and income as confounding variables. Results were considered statistically significant if the $P < 0.05$.

Results

All invited participants agreed to participate but, after exclusion of patients who had received previous orthodontic treatment and patients with missing data, 87 patients were available for final analysis. 54% were male and 46% were female [Table 1]. Participants were fairly evenly distributed across all income brackets (15%–20%) except for the lowest and highest income brackets, comprising 28.7 and 1.1% of participants, respectively [Table 1].

The overall prevalence of ≥1 missing teeth was high (76%). Although the prevalence of missing teeth was about equal according to gender, there was a particularly high prevalence of missing teeth in the

19–40-year age group (90.3% vs. approximately 70% in the older age groups) and in income level 0 and 1 groups (80% and 93.8%, respectively) compared to higher income levels groups (~65%).

Since we previously showed that missing teeth were the only occlusal trait associated with total OHIP-14 scores,[12] we next examined how the position of the missing teeth influenced OHRQoL according to both total OHIP-14 scores and subdomain scores. In univariate analysis [Table 2], one or more missing anterior teeth was significantly associated with higher (i.e. worse OHRQoL) total scores (17.2 vs. 25.1; $P = 0.04$) and physical pain (1.9 vs. 3.4; $P = 0.02$) and social disability (2.3 vs. 4.3; $P = 0.008$) domain scores. One or more missing posterior teeth were associated with higher functional limitation (2.1 vs. 3.9; P - 0.008) and psychological discomfort (2.9 vs. 4.2; $P = 0.04$) scores. Total and domain OHP-14 scores were not significantly different according to gender, age, or income, except for the psychological disability domain, which was significantly higher younger patients. In multivariate analysis controlling for age, gender, and income as covariates [Table 3], anterior missing teeth were significantly associated with higher OHIP-14 total, physical pain, physical disability, psychological disability, and social disability scores, accounting for 6%–12% of the variance in scores. However, posterior missing teeth were only associated with total OHIP-14 and functional limitations domain scores, accounting for 6% and 7% of the variance, respectively.

Discussion

Here, building on our previous study of the impact of occlusal traits on OHRQoL,[12] we provide granularity to the impact of missing teeth on the OHRQoL of adult patients in the primary care setting. While both anterior and posterior missing teeth had an impact the overall OHRQoL as measured by the OHIP-14 instrument, the position of the missing tooth had a differential impact on the patient. While posterior missing teeth only impacted function, anterior missing teeth had a much broader impact on patients, not only affecting them in terms of pain and physical disability but also in the psychosocial dimensions. Although the magnitude of the effect of missing teeth was small (<0.2 according to Cohen's guidelines[13]), these data nevertheless confirm our own and previous studies that unrestored missing teeth have a significant effect on patients' QoL[8,9,12,14] and suggest that restoration planning should prioritize anterior teeth to optimize QoL outcomes. The prevalence of missing teeth in our population (76%) was high and similar to previous

Table 1: Clinical and demographic features of the study participants

Variable	*n* (%)	Prevalence of≥1 missing teeth (%)
Gender		
Male	47 (54.0)	76.6
Female	40 (46.0)	75.0
Age (years)		
18-40	31 (38.3)	90.3
41-60	38 (46.9)	71.1
>60	12 (14.8)	75.0
Income level		
0	25 (28.7)	80.0
1	15 (17.2)	93.8
2	14 (16.1)	64.3
3	14 (16.1)	64.3
4	18 (20.7)	66.7
5	1 (1.1)	100

Table 2: Univariate analysis of associations between missing tooth position and total and subdomain oral health impact profile-14 scores

	n	Mean	SD	*P*
Total score				
Posterior				
No missing	36	15.8889	15.48783	0.061
≥1 tooth	42	22.4524	14.98650	
Anterior				
No missing	56	17.1786	15.46622	0.041
≥1 tooth	22	25.1364	14.28051	
Total				
No missing	17	13.7647	16.34598	0.088
≥1 tooth	61	21.0000	14.98221	
Functional limitation				
Posterior				
No missing	40	2.1000	2.52982	0.008
≥1 tooth	45	3.8889	3.43261	
Anterior				
No missing	61	2.9836	3.13311	0.769
≥1 tooth	24	3.2083	3.27014	
Total				
No missing	20	2.1000	2.24546	0.125
≥1 tooth	65	3.3385	3.34607	
Physical pain				
Posterior				
No missing	39	2.1795	3.08538	0.648
≥1 tooth	44	2.4545	2.37677	
Anterior				
No missing	59	1.8814	2.57364	0.019
≥1 tooth	24	3.4167	2.81172	
Total				
No missing	19	1.8947	2.92299	0.435
≥1 tooth	64	2.4531	2.66625	

Contd...

Table 2: Contd...

	n	Mean	SD	*P*
Psychological discomfort				
Posterior				
No missing	38	2.9211	2.88876	0.036
≥1 tooth	44	4.2273	2.64895	
Anterior				
No missing	58	3.3448	2.76920	0.168
≥1 tooth	24	4.2917	2.89646	
Total				
No missing	19	3.0526	3.04546	0.319
≥1 tooth	63	3.7937	2.75423	
Physical disability				
Posterior				
No missing	40	3.1250	3.40578	0.961
≥1 tooth	44	3.1591	2.89300	
Anterior				
No missing	60	2.7333	3.00207	0.057
≥1 tooth	24	4.1667	3.26599	
Total				
No missing	20	2.9000	3.44735	0.693
≥1 tooth	64	3.2188	3.04708	
Psychological disability				
Posterior				
No missing	39	2.2051	3.01033	0.193
≥1 tooth	43	3.0930	3.10003	
Anterior				
No missing	59	2.4068	2.86548	0.215
≥1 tooth	23	3.3478	3.52406	
Total				
No missing	19	1.8421	2.79410	0.181
≥1 tooth	63	2.9206	3.12793	
Social disability				
Posterior				
No missing	40	2.5500	2.53134	0.355
≥1 tooth	44	3.1591	3.36841	
Anterior				
No missing	61	2.3443	2.60055	0.008
≥1 tooth	23	4.2609	3.55755	
Total				
No missing	20	2.3500	2.51888	0.378
≥1 tooth	64	3.0313	3.13186	
Handicap				
Posterior				
No missing	40	2.7250	3.49349	0.578
≥1 tooth	44	3.1364	3.26070	
Anterior				
No missing	60	2.7000	3.13699	0.302
≥1 tooth	24	3.5417	3.86713	
Total				
No missing	20	3.0000	3.85255	0.928
≥1 tooth	64	2.9219	3.22345	

SD: Standard deviation

studies reporting similarly high prevalence of missing teeth in other populations (Saudi Arabia and the UK) of between 62.5 and 94.4%.[7,15,16]

Missing teeth, and in particular the number of missing teeth, have generally been shown to have a negative impact on QoL, particularly in younger adults.[9] In their meta-analysis of similar studies using OHIP instruments to measure OHRQoL, Gerritsen *et al*.[8] reported that the impact on OHRQoL was proportional to the number of teeth lost, with a marked deterioration in OHRQoL in individuals with <17 teeth from three cross-sectional surveys representing over 13,000 individuals.[17,18] Similarly, in their recent study of 152 adults attending dental clinics in Riyadh, Saudi Arabia, Anbarserri *et al*.[14] reported that OHIP-14 scores were proportional to the number of teeth lost. Here, we compared complete dentition with tooth loss of one or more teeth, similar to Lawrence *et al*.,[19] who similarly found using the OHIP-14 that loss of one or more teeth was significantly associated with OHRQoL after adjusting for sex and "episodic" dental care.

However, fewer studies have examined the impact of the position of tooth loss on OHRQoL. Pallegedara and Ekanayake,[20] although examining elderly individuals with large numbers of missing teeth rather than our younger population with as few as only one missing tooth, found that individuals with anterior spaces were significantly more likely to have higher OHIP-14 scores. Using the OHIP-49, Walter *et al*.[21] similarly found that missing anterior teeth were independently and most strongly associated with impaired OHRQoL in adjusted analysis of adult patients attending dental outreach clinics. Similarly, Batista *et al*.[22] found that having one or more missing teeth including one in the anterior position had a greater impact on OHRQoL than fully dentate adult patients.

Our data now add to this growing body of evidence that the location of missing teeth impacts OHRQoL, with anterior tooth loss having a greater impact than posterior tooth loss (11% of the variation vs. 6% of the variation in adjusted analyses), not only on function but also psychosocial domains. It has been suggested that the greater impact of anterior missing teeth reflects the importance of esthetics and appearance in dictating the psychosocial morbidity associated with tooth loss.[22] Indeed, when examining the domains most affected by tooth loss location, we found that anterior loss affected psychological disability and social disability scores, while posterior loss did not, objectively supporting this hypothesis. Few studies have examined the specific domains affected by tooth loss. While Anbarserri *et al*.[14] found that tooth loss significantly affected the functional limitation and social disability domains, which we found were impacted most by posterior and anterior tooth loss, respectively, they did not examine tooth loss position

Table 3: Analysis of covariance analysis of associations between missing tooth position and total and domain oral health impact profile-14 scores

	F statistic	*P*	ηp2
Total score			
Anterior	8.0	0.006	0.11
Posterior	4.4	0.04	0.06
Functional limitation			
Anterior	0.001	0.98	0.00
Posterior	6.0	0.02	0.07
Physical pain			
Anterior	8.2	0.006	0.10
Posterior	4.2	0.61	0.008
Psychological discomfort			
Anterior	1.96	0.17	0.03
Posterior	2.8	0.10	0.04
Physical disability			
Anterior	4.0	0.05	0.05
Posterior	0.004	0.95	0.00
Psychological disability			
Anterior	4.2	0.05	0.06
Posterior	3.1	0.08	0.04
Social disability			
Anterior	9.5	0.003	0.12
Posterior	0.83	0.37	0.01
Handicap			
Anterior	0.98	0.33	0.01
Posterior	0.13	0.72	0.002

in relation to OHIP-14 subdomains. Similarly, in their meta-analysis of twenty study samples with missing teeth, Schierz *et al*.[11] established that the impact of missing teeth on oral function, as measured by OHIP scores for the physical disability domain, was typically around 1.9 units, but these data were not separated by tooth position. Our data support that missing teeth impact both functional and psychosocial OHRQoL but that tooth position is a critical determinant of exactly how individuals are affected.

Our study has a number of limitations. This was relatively small sample from a single city, so the results may not be generalizable; however, we used a cluster sampling approach to attain a representative population. The OHIP-14 is a self-reported instrument, so may be subject to bias; however, the OHIP-14, despite being a short questionnaire, has been shown to be reliable,[2] sensitive to changes,[3,4] and have cross-cultural consistency.[5] Our study is strengthened by adjusting for the effect of gender, age, and income, which are known to impact OHRQoL.[23,24] Future studies should include other covariates such as educational level and caries experience to further establish the relative contributions of these factors in overall OHRQoL.

Conclusions

Here, we show for the first time the impact of the location of missing teeth on different dimensions of OHRQoL. Anterior tooth loss has a more wide-ranging impact on both physical and psychosocial functioning than posterior tooth loss, suggesting that anterior tooth restoration should be prioritized when treatment planning. The position of lost teeth must be considered in addition to the number of losses when examining the impact of tooth loss and its treatment on OHRQoL.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Perceived Impact of the COVID-19 Pandemic on Orthodontic Practice in the Middle East

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Abstract

Background: With COVID-19 announced as a global pandemic, a countrywide lockdown was executed in many countries, including the Middle East. With no foregoing warning or expectation, orthodontic treatments were temporarily canceled as dental clinics and colleges were indefinitely closed. To the best of our knowledge, no study addresses the orthodontist perspective in such testing times, where they are entirely restricted to the confines of their homes. The study aims to assess the impact of the COVID-19-related lockdown on orthodontists and orthodontic postgraduate students' treatment and psychology. **Materials and Methods:** The survey participants consist of 315 orthodontists and orthodontic postgraduate residents from different Middle East countries. A pretested self-administered questionnaire was sent to the consenting participants through an online data collection platform (Google forms), covering participants' sociodemographics and participants' perceived impact of the COVID-19 pandemic. **Results:** A majority of the participants (87.61%) stated that the pandemic would permanently change their way of practicing orthodontics and also will lead to the reduction in the number of orthodontic patients in the future (78.73%), and a significant number of orthodontists (67.61%) has an opinion that the pandemic will not affect the viability of their profession. The majority of the respondents (88.57%) commented about the negative economic impact of COVID-19 on their income, and regarding the effect of COVID-19 on psychosocial well-being, 73.01% had experienced anxiety and depression, 88.25% were excited about the future of the profession, and 68.57% enjoyed the life with their family due to lockdown, and when asked about their social life with the family and friends, majority of the participants (66.34%) had an opinion that it has improved due to the increased free time. **Conclusions:** Most of the respondents reported perceived economic, psychosocial, and social impacts due to the pandemic.

Keywords: *Challenges, COVID-19, dental care, orthodontics, social change*

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Introduction

SARS-CoV-2, commonly as COVID-19, was initially notified in Wuhan, China, in December 2019, which then emerged as a pandemic infecting more than 110 million people.[1-3] Even though coronaviruses primarily infect animals, human contamination can occur if the animal-human species barrier is breached, and pangolins and snakes are considered the in-between hosts in the case of COVID-19.[1,4-6] COVID-19 spreads from continent to continent due to widespread transportation modes, and the WHO declared COVID-19 a pandemic on March 11, 2020. COVID-19 can currently

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spread within towns through neighborhood spread from a carrier individual or community spread, where its origin is unknown. COVID-19 had been confirmed in more than 110,605,084 cases in 183 countries as of February 28, 2021, for more than 2,194,204 people died.[7] Despite ages, people are affected by COVID-19, reports recent studies. However, the risk of infection is high in those having close contact with positive cases and asymptomatic carriers also medical professionals and other hospitalized patients.[8]

Due to strict COVID-19 rules and public health interventions such as travel restriction and home isolation,[9] many dental workers opted for teleconferencing for patient interactions.[10,11] Altogether, the above-said changes in job and living due to COVID-19 can significantly influence health professionals, including nonfrontline workers.[12] This research aimed to determine the impact of the COVID-19 pandemic on orthodontists and orthodontic postgraduate students, especially in terms of their current and future orthodontic practice as their financial, emotional, and social well-being.

Materials and Methods

The consenting participants were received a self-assessed questionnaire through an online data collection platform (Google forms) between April and December 2020. The methodology adopted was purposive sampling. We included orthodontists and orthodontist residents (postgraduates) from different Middle East countries. A list of the participants was made first and was reached using the social media platform and through direct personal messages.

The questionnaire consisted of two parts, Part A comprised participants' sociodemographics, and part B documented participants' COVID-19 impact on their orthodontics treatment, particularly with reference to patients' seen during the pandemic, infection control training, and their perceptions on the longer-term viability of orthodontics as a specialty following the pandemic. Respondents were also asked if the pandemic would change the way, they currently practiced orthodontics and what changes they might be making if any. In addition, the questionnaire also assessed the perceived economic, psychosocial, and social impacts of the pandemic on the lives of respondents. A pilot study was done. The questionnaire was distributed to ten orthodontists and five orthodontic students to assess the validity of the instrument. These were not included within the overall samples used for the study. The ideal sample size computed for the study was 315, based on a confidence interval of 90%, a margin of error of 5%, and a study population of 350.

The information was coded, entered, and analyzed utilizing SPSS 23.0 version (IBM Corp., Armonk, NY, USA). Descriptive statistics, frequencies, and percentages were utilized to sum-up, information. Descriptive analysis was carried out by frequency and proportion for categorical variables. Categorical outcomes were compared between study groups using the Chi-square test/Fisher's exact test. $P < 0.05$ was considered statistically significant. IBM SPSS version 23 was used for statistical analysis by an independent biostatistician.

Results

A total number of 315 orthodontists and orthodontic residents in the state taken part in the survey, made up of 205 (65%) males and 110 (35%) females with the majority in the age group 31–40 years. We had participants from Saudi Arabia (49.2%), United Arab Emirates (17.8%), Oman (14.3%), Kuwait (12.1%), and Qatar (6.7%). Most of them, 144 (45.71%), were consultant orthodontists, while 101 (32.06%) of them were orthodontic residents. A total of 133 (42.22%) completely resumed their orthodontic practice after the lockdown and 52 (16.50%) reported that they have not resumed their practice yet [Table 1]. As shown in Table 2, majority of the participants (85%) stated that they have got instruction on infection control in dentistry but not regarding COVID-19 (55%). Furthermore, a majority of them (87.61%) stated that the COVID-19 will perpetual change in their way of practicing orthodontics and also will lead to decrease in the number of orthodontic patients in the future (78.73%), and a significant number of orthodontists (67.61%) has an opinion that the pandemic will not affect the viability of their profession. When we assessed the relationship of these effects with the country of practice, it was found that there was no statistically significant association except that 80% ($n = 124$) of participants from Saudi Arabia, and 75.5% ($n = 34$) from Oman believed that COVID-19 would lead to the decrease in the number of orthodontic patients in the future more than other countries ($P = 0.018$).

As shown in Table 3, majority of the respondents (88.57%) commented about the negative economic effect of COVID-19 on their income, and regarding the effect of COVID-19 on psychosocial well-being, 73.01% had experienced anxiety and depression, 88.25% were excited about the future of the profession, and 68.57% enjoyed the life with their family due to lockdown and when asked about their social life with the family and friends, majority of the participants (66.34%) had an opinion that it has improved due to the increased free time. Participants