

# World Journal of *Stomatology*

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## Angina bullosa hemorrhagica an enigmatic oral disease

Javier Alberdi-Navarro, María Luisa Gainza-Cirauqui, María Prieto-Elías, José Manuel Aguirre-Urizar

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cavity and oropharynx unrelated to any hematological, dermatological or systemic disease. The ABH is an uncommon disease of the oral cavity distinctively affecting adults, with the highest incidence over the 5<sup>th</sup> decade of life. This process is considered nowadays to have a multifactorial etiopathogenesis, where mild oral traumatism can trigger the blisters in susceptible individuals. Certain association on the onset of the lesion with the chronic use of inhaled steroids and, more controversially, with triggering systemic disorders, such as, diabetes or hypertension has been described. Characteristically, the ABH blisters are acute and are located on the lining mucosa, more frequently on the soft palate. Usually, the lesions are solitary and rupture easily, resulting in a superficial ulceration that heals quickly without scarring. The histopathological analysis shows a subepithelial blister containing blood and direct immunofluorescence on the epithelium is negative. The differential diagnosis should consider all oral vesiculo-bullous disorders with hematic content, including mucocutaneous, hematological or cystic pathology. The diagnosis of ABH is clearly clinical, although the biopsy might be helpful on atypical or abnormally recurrent cases. The general prognosis of ABH is good and the treatment is symptomatic.

**Key words:** Angina; Bullosa; Hemorrhagica; Traumatic; Blister

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**Core tip:** Although it is an uncommon disease, the angina bullosa hemorrhagica should be considered in the differential diagnosis of oral vesiculo-bullous processes. Acknowledging this entity will help in differentiating it from important mucocutaneous and hematological diseases such as pemphigus vulgaris, mucous membrane pemphigoid or coagulation disorders. In this review we analyze the main etiopathogenic, clinicopathological, diagnostic and therapeutic aspects of this enigmatic oral condition.

### Abstract

Angina bullosa hemorrhagica (ABH) is an enigmatic oral disorder described for the first time by Badham in 1967 to define blisters with a hematic content in the oral



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## CONCEPT

Angina bullosa haemorrhagica (ABH) is an uncommon and benign subepithelial disorder appearing as hematic blisters on the oral and oropharyngeal mucosa and no relation with any dermatological, haemostatic or systemic condition<sup>[1]</sup>. Badham<sup>[1]</sup> in 1967 defined these lesions with this term, although according to Stephenson *et al*<sup>[2]</sup> in 1987 and Grinspan *et al*<sup>[3]</sup> in 1999, similar lesions had been previously described by other authors such as Haryng<sup>[4]</sup> in 1890 referred to this condition as "Traumatic Oral Hemophlyctenosis" or Baliña<sup>[5]</sup> in 1933 as "Angina Ulcerosa Benigna" 1933. This entity has received multiple names, such as Benign Hemorrhagic Bullous Stomatitis<sup>[6]</sup> or Localized Oral Purpura<sup>[7]</sup>. In 1994 Kirtschig and Happel<sup>[8]</sup> named it "Stomatopompholyx hemorrhagica", as "angina" was an inadequate term for this disease. However, despite all the attempts in changing its name, ABH continues as the most commonly used term in the literature.

## EPIDEMIOLOGICAL AND ETIOPATHOGENIC ASPECTS

The ABH is an uncommon oral pathology, although its real prevalence is unknown. The study performed by Mehrotra *et al*<sup>[9]</sup> in 2010 is the most accurate as they analyze the prevalence of oral pathologies of the soft tissue in a sample of 3030 Indian adults reporting a prevalence of ABH of only 0.03%. Retrospective studies show a prevalence of 0.5% on patients diagnosed with ABH in Oral Medicine and Oral Pathology clinics<sup>[3,10]</sup>. However, many authors<sup>[1,10-13]</sup> estimate a higher prevalence of this disease, justifying its rare diagnosis to its frequent asymptomatic character and the fast resolution of the lesions, which would lead the patient to seek less attention, thus to be undiagnosed.

This disease distinctively affects adult patients from the 3<sup>rd</sup> decade of life, with a peak incidence over the 5<sup>th</sup> decade<sup>[2,3,10,14-17]</sup>.

Regarding the gender distribution, in his first description, Badham<sup>[1]</sup> observed a higher prevalence of ABH in women, although later published series of cases<sup>[2,3,10]</sup> have shown that the differences between genders are non-significant and, some authors<sup>[17]</sup>, even describe a higher prevalence in males.

The etiopathogenesis of this lesion is yet unknown thus being considered nowadays as a multifactorial disease with local trauma on the oral mucosa as the trigger on susceptible individuals<sup>[16]</sup>. Several authors<sup>[1,3]</sup>, have considered ABH an acquired disease without a

recognized genetic component; however, some<sup>[2,18]</sup> have described certain familial predisposition in developing ABH.

Classically, it has been suggested that a loss of cohesion between the epithelium and the chorion can cause the rupture of the subepithelial capillaries after trauma and condition the emergence of a blood-containing blister<sup>[15]</sup>.

### Local trauma factors

An important percentage of the cases (35%-100%) report a known triggering traumatic event, with the intake of hard or crunchy foods as the most cited<sup>[2,10,13,15-17,19]</sup>. Nevertheless, it is worth mentioning that, in a study<sup>[3]</sup>, only 24% of the patients could identify the traumatic factor. We believe that this datum is lower due to the retrospective character of many ABH studies that force the patient to remember the existence of a previous traumatic event<sup>[2]</sup>.

Different foods are associated with ABH, including toasts, chips and hot meals<sup>[1]</sup>. Together with hard and crunchy foods (75%), a previous intake of acidic and citrus fruits has also been reported<sup>[17,18]</sup>. As an anecdote, other hard foods, such as a fish bone or a chicken bone, have been linked<sup>[19]</sup>. Along with food, beverage consumption has been associated with the onset of ABH, although the type and its characteristics are yet to be described<sup>[16]</sup>.

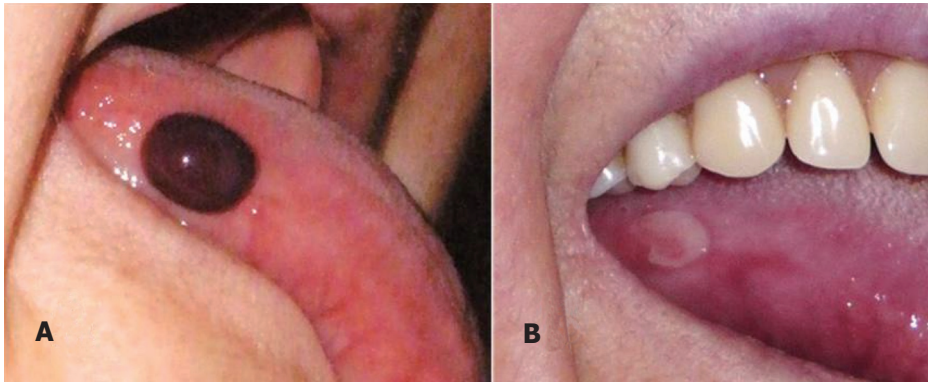
Several clinical cases are associated to trauma from dental procedures, including impressions<sup>[2]</sup>, dental preparations<sup>[20]</sup>, a crown as a traumatic factor<sup>[21]</sup>, certain conservative treatments<sup>[15]</sup>, the injection of local anesthesia<sup>[22-24]</sup> or a periodontal treatment<sup>[25]</sup>. Isolated cases of ABH from other traumatizations have been described, including intubations or endoscopies<sup>[1,26]</sup>, or even after coughing or sneezing roughly<sup>[11,15]</sup>.

In 1987, Stephenson *et al*<sup>[2]</sup> suggested the suction habit as the main cause for the formation of these lesions; although, incidentally, none of the 30 patients from their study described this circumstance. Subsequently, de las Heras *et al*<sup>[27]</sup> described that the suction habit could lead to multiple ABH lesions.

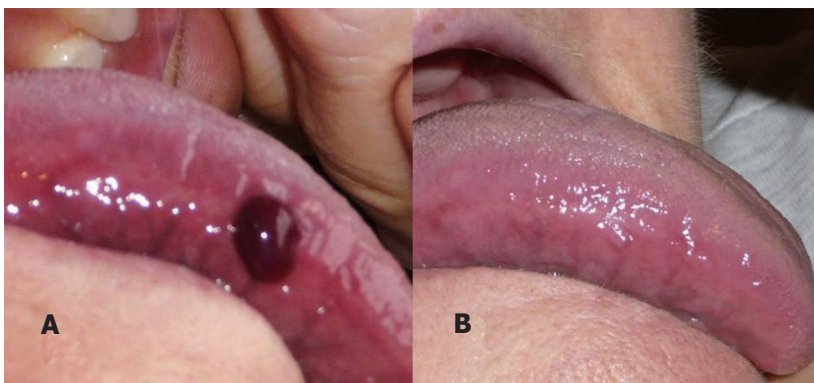
### Drugs

Together with local traumatic factors, certain inhaled drugs, mainly the chronic use of topical corticosteroids, have been associated with the onset of ABH<sup>[28,29]</sup>. High and Main<sup>[28]</sup> performed a study in 1988 in two groups of patients with asthma undergoing treatment with aerosols, one with and one without steroids. When comparing the incidence of ABH, lesions were present only in the group using steroids (35.7%). In these cases, the prolonged contact of the steroid with the oral mucosa may cause epithelial atrophy and may alter the distribution of the chorionic elastic fibers, which would weaken the epithelium-connective tissue junction, and would favor the onset of a subepithelial blister in a local traumatic event<sup>[19,28,29]</sup>.

Another inhaled drug linked to the onset of ABH is



**Figure 1 Clinical presentation of the disease.** A: Blister on the right lateral border of the tongue; B: Superficial ulcer after rupture of the hemorrhagic bulla (4 d of evolution).



**Figure 2 Presentation and resolution of a clinical case.** Blister with blood content (angina bullosa hemorrhagica) on the border of the tongue (A) and full clinical resolution after 14 d of evolution (B).

**Table 1 Association between angina bullosa hemorrhagica and diabetes mellitus and hypertension**

Ref.	n	Diabetes	Hypertension
Grinspan <i>et al</i> <sup>[3]</sup>	54	24 (44%) <sup>1</sup>	0 (0%)
Giuliani <i>et al</i> <sup>[16]</sup>	8	1 (12.5%)	0 (0%)
Yamamoto <i>et al</i> <sup>[13]</sup>	11	4 (36.4%)	3 (27.3%)
Horie <i>et al</i> <sup>[17]</sup>	16	1 (6.25%)	6 (37.5%)
Deblauwe and van der Waal <sup>[11]</sup>	9	1 (11.1%)	0 (0%)
Serra <i>et al</i> <sup>[31]</sup>	4	0 (0%)	2 (50%)
Martini <i>et al</i> <sup>[19]</sup>	4	0 (0%)	2 (50%)
Rosa <i>et al</i> <sup>[10]</sup>	47	4 (8.5%)	17 (32.2%)

<sup>1</sup>Includes patients with altered serological values of glucose and family history of diabetes.

Ipratropium Bromide, an antimuscarinic bronchodilator<sup>[30]</sup>.

### Systemic diseases

Badham<sup>[1]</sup> described in his study certain association between ABH and systemic conditions, including menstruation in some of his patients.

Subsequently, ABH has been linked to different systemic processes, although this is still unfounded as its etiopathogenic base is yet to be described. The main systemic conditions associated with ABH are diabetes mellitus and hypertension (Table 1).

The high prevalence of diabetes, described only by

Grinspan *et al*<sup>[3]</sup> in 1999 is worth mentioning as 44% of the ABH patients showed altered serological levels of glucose or family history of diabetes mellitus. It is possible that considering that both entities share the same age range and that diabetes has a high incidence among adults, it could be a coincidental relation and not a direct pathological association.

Regarding hypertension, several authors<sup>[10,17]</sup> outline circumstances similar to diabetes mellitus. Moreover, several cases of patients with chronic kidney failure are described in the literature<sup>[13,32,33]</sup>.

## CLINICAL CHARACTERISTICS

The characteristic lesion of ABH is a dark red-violet blister with a hematic content<sup>[1]</sup> (Figure 1A and Figure 2A).

Two types of patients have been distinguished according to its clinical presentation<sup>[15]</sup>. Some, the most frequent, have a large solitary lesion located in the soft palate and recurring spaced in time; others, less frequent, have a greater number of lesions in different locations and with a higher recurrence rate. Subsequent studies avoid separating into these subtypes as they distinguish the solitary lesion as the most frequent clinical presentation<sup>[2,3,10,18,16]</sup>. Nonetheless, in 30% of the patients multiple lesions are present, with up to 4

simultaneous lesions being described<sup>[15,34]</sup>.

The formation of the blisters is characteristically acute as the lesions may appear abruptly within seconds<sup>[1,3,15,35]</sup>. The lesions have a diameter of 0.3 to 4 cm, but generally over 1 cm<sup>[2,3,15,17,25,33]</sup>. Despite most authors, Rosa *et al.*<sup>[10]</sup>, in their study on 47 patients, observed that most lesions measured less than 1 cm in diameter.

The lesions might cause mild unspecific discomfort for which it may be diagnosed casually on a dental revision<sup>[3,13,16,19,35]</sup>. However, Rosa *et al.*<sup>[10]</sup>, described pain, mainly of a mild intensity, in 36.1% of their patients.

In some cases, and previous to the blister formation, a burning or itching sensation, or even a stabbing pain has been described<sup>[15,36]</sup>.

Regarding the location of the lesions, there is agreement in suggesting that the most affected site is the soft palate, followed by the borders of the tongue and the buccal mucosa<sup>[2,3,10,13-15,17,19]</sup>. Nonetheless, in addition to the above mentioned locations, cases have been described in the ventral surface of the tongue<sup>[2]</sup>, the lip<sup>[15]</sup> and the floor of the mouth<sup>[3,15,16]</sup>. It is important to point out that all of these locations are part of the "lining mucosa" of the oral cavity which is non-keratinized. Some authors<sup>[2,15,27]</sup> have defended that the keratinized masticatory mucosa (hard palate, gingiva and lingual dorsum) remains unaffected in this pathology. Even so, several cases are described in these locations<sup>[25,32,33]</sup>. In addition to the intraoral involvement, Badham included lesions in the pharynx and esophagus<sup>[1]</sup>.

The time the blister stays complete in the oral cavity is variable, from a few minutes to hours<sup>[2,8,14-16,35]</sup> or even days<sup>[32,34]</sup>, and depends on the location and the size. When ruptured, generally spontaneously or while eating, its hematic content is emptied giving rise to an ulcerated area with minor symptomatology<sup>[2,3,16,19]</sup>. Martini *et al.*<sup>[19]</sup>, described the formation of petechiae in the periphery of the blister immediately after its rupture, which they suggest to be caused by a venous obstruction in the area, although it is unclear if it is a cause or a consequence of the blister. A similar event, although surrounding intact blisters, was described by Hopkins and Walter in 1985<sup>[15]</sup>, defining it as an "ecchymotic halo". Furthermore, Grinspan *et al.*<sup>[3]</sup>, described that the blood in the blister may occasionally be coagulated.

Although the blister is the defining lesion of ABH, it is frail and the patient might seek attention for an unspecific ulcer instead (Figure 1B)<sup>[10,16,19]</sup>. These ulcers heal within 7-14 d without leaving scars (Figure 2B)<sup>[2,3,16]</sup>.

The recurrence of ABH lesions is frequent, between 25% and 100% of the cases<sup>[2,3,10,15,16,19,31]</sup>, with the lesions appearing in the same location or on another area of the oral mucosa<sup>[3]</sup>. It is interesting that, despite most authors, Horie *et al.*<sup>[17]</sup> show no recurrence in a series of 16 cases.

The frequency of recurrence of ABH is variable, with patients reporting lesions only once or twice per

year while others show them continuously<sup>[2,3,15,16]</sup>. Recurrences for more than 24 years have been described<sup>[2,33]</sup>.

## HISTOPATHOLOGICAL CHARACTERISTICS

The cases where the ABH lesions have been biopsied before its rupture show a subepithelial blister with a hematic content and an atrophic squamous epithelium surrounding the lesion<sup>[2]</sup>. A mild perilesional inflammatory infiltrate, generally chronic, is also observed<sup>[2,3]</sup>. In certain cases, an abundant acute subepithelial inflammatory infiltrate with a certain perivascular disposition has been described<sup>[34]</sup>. The biopsy of the ulcer formed after the rupture of the blister shows an unspecific ulcer with chronic inflammatory infiltrate, mainly lymphocytic<sup>[16]</sup>.

Silver special staining has shown a decrease in elastic fibers in the chorion<sup>[29]</sup>. In addition, a capillary vascular hypertrophy, similar to that of patients with diabetes or porphyria, has been described<sup>[3]</sup>.

Studies with direct immunofluorescence may be useful to rule out other oral vesiculo-bullous diseases of an immunological basis and with a poorer prognosis, such as Pempighus Vulgaris or Mucous Membrane Pemphigoid<sup>[14]</sup>. Unlike these diseases, direct immunofluorescence of ABH lesions is negative for IgA, IgG, IgM, fibrinogen and the C3 complement fraction. However, Stephenson *et al.*<sup>[2]</sup> described certain basal positivity for IgG and C3 in some cases.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ABH should be made with all vesiculo-bullous diseases of the oral cavity, including hematological disorders, mucocutaneous immunological pathology and cystic pathology.

Some hematological pathologies, such as thrombocytopenia or the von Willebrand Disease, may present lesions similar to ABH<sup>[14,37]</sup>. Therefore, a complete blood test should always be performed, including coagulation tests which in these cases are altered, while in ABH are normal<sup>[3,14,16]</sup>.

In addition to these pathologies, Serra *et al.*<sup>[31]</sup> mention other hematological entities, including leukemia and vasculitis that should be considered in the differential diagnosis. In these cases, the lesions are usually multiple and widespread appearing in other locations of the body and generally producing systemic symptoms.

The mucocutaneous immunological diseases are the most important differential diagnosis of ABH and should include pemphigus vulgaris, mucous membrane pemphigoid, lineal IgA disease, epidermolysis bullosa acquisita and bullous amyloidosis<sup>[16]</sup>. All of these pathologies have a characteristic immunological basis and sometimes have clinical or even histological



**Table 2 Clinical differential diagnosis of angina bullosa hemorrhagica with mucocutaneous diseases of an immunological basis**

Disease	Type of lesion	Content of the blister	Location	Cutaneous involvement	Involvement of other mucosal membranes
Angina bullosa hemorrhagica	Subepithelial blister	Hematic	LM (soft palate)	No	Oropharynx and esophageal
Mucous membrane pemphigoid <sup>[30]</sup>	Subepithelial blisters and vesicles	Serous and serohematic	MM and LM (gingiva)	Yes	Ocular, genital, oropharynx, nasal and esophageal
Pemphigus vulgaris <sup>[31]</sup>	Intraepithelial blisters and vesicles	Serous	MM and LM (areas of friction)	Yes	Nasal, ocular, esophageal, genital, pharyngeal
Linear IgA disease <sup>[40]</sup>	Subepithelial blisters and vesicles	Serous and serohematic	MM and LM	Yes	Ocular, nasal, genital
Epidermolysis bullosa acquisita <sup>[41]</sup>	Subepithelial blister	Serous, serohematic or hematic	MM and LM	Yes	Ocular, anal, vaginal, esophageal (depending on the subtype)
Bullous amyloidosis <sup>[42]</sup>	Subepithelial blister	Hematic	MM and LM	Yes	Not described

LM: Lining mucosa; MM: Masticatory mucosa.

characteristics similar to ABH. The main clinical characteristics that differentiate these entities are shown in Table 2.

To perform a correct differential diagnosis on these entities, a good medical history is essential, focusing on the presence of lesions in skin or other mucosal membranes<sup>[14]</sup>. The most important differential diagnosis for patients with an ABH ulcer is, without a doubt, pemphigus vulgaris.

In cases of solitary lesions showing the typical characteristics of ABH (acute onset and associated to a traumatic event) a biopsy is often unnecessary<sup>[17]</sup>. The histopathological analysis should be performed only in cases with multiple or recurrent lesions or on atypical lesions. In these cases, together with the conventional hematoxylin and eosin histopathological analysis, it is convenient to perform direct immunofluorescence for IgA, IgG, IgM and C3 in order to exclude other mucocutaneous processes<sup>[2,14,16]</sup>.

The differential diagnosis with oral cystic pathologies includes superficial mucocele. This lesion often shows acute clinical features generating a subepithelial blister that initially contains mucus but, after traumatic events, may contain blood and be mistaken with ABH<sup>[43]</sup>.

Finally, some genetic syndromes with blisters containing blood in the oral cavity and oropharynx, such as the Kindler syndrome<sup>[44]</sup> or the vascular type of the Ehler-Danlos syndrome, should be excluded<sup>[45]</sup>. It is important to consider that the lesions of ABH are only present in adults, while on these processes, they appear in young people.

## TREATMENT

Given the clinical characteristics of this disease, a specific treatment is unnecessary in most cases, recommending a symptomatic treatment of the lesions<sup>[2,3,15-17]</sup>.

A complete blood test is necessary to rule out a possible systemic compromise while a histopathological analysis would be helpful in those cases with a complicated differential diagnosis.

The benign nature of the process should always be explained to the patients<sup>[2]</sup>. Given the possible traumatic etiology, this should be avoided by establishing general measures and eliminating all possible irritants<sup>[3,17]</sup>. Serra *et al.*<sup>[31]</sup> recommend patients undergoing treatment with inhaled topical steroids to rinse with water after each use as a prevention measure of ABH.

In ABH patients with discomfort or pain, the treatment of the symptoms includes different drugs such as a mouthwash of benzydamine hydrochloride<sup>[2]</sup>, several anti-inflammatory drugs<sup>[28]</sup>, or even topical beclomethasone<sup>[32]</sup>.

To avoid the superinfection of the ulcer resulting from the rupture of the blister, Hopkins and Walker<sup>[15]</sup> recommended rinsing with chlortetracycline. However, most authors<sup>[14,16,28]</sup> support the use of chlorhexidine gluconate mouthwashes in concentrations between 0.12%-0.25%.

To avoid possible recurrences, ascorbic acid and citroflavonoids have been suggested to be administered to the patients<sup>[3]</sup>, without effective results reported.

The general prognosis for ABH is good; however, large lesions and on the soft palate and oropharynx may cause a feeling of suffocation due to a compromise of the upper airway, which leads the patient to seek urgent attention and even compromises his or her life<sup>[2,15,26,32,46]</sup>. Therefore, large blisters are recommended to be ruptured,

mainly those located in the soft palate and oropharynx, as to decrease the possibility of causing obstruction of the upper airway and avoiding an unpleasant choking sensation on the patient<sup>[2,15-17,36]</sup>.

## CONCLUSION

The ABH is an uncommon disease of the oral cavity and oropharynx that should be considered when a blister with a hematic content is observed. It is important for the dentist to acknowledge this condition as to differentiate it from other oral vesicular processes with a poorer prognosis such as Pemphigus Vulgaris, Mucous Membrane Pemphigoid or certain hematological diseases.

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## Melkersson-Rosenthal syndrome

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### Abstract

Melkersson-Rosenthal syndrome (MRS) is a rare, non-caseating granulomatous disorder of unknown etiology and undefined diagnostic criteria. The classical triad of recurrent orofacial edema, relapsing facial paralysis, and fissured tongue, is not frequently seen in its complete form, and many patients remain misdiagnosed or undiagnosed for years. The purpose of this study is to review the findings in the literature describing the

Melkersson-Rosenthal syndrome with aim to identify its clinical and histopathological characteristics and correlate them with definitive diagnostic criteria and effective treatment modalities. A systematic review and analysis of more than 100 publications met eligibility criteria performed by the authors. Orofacial edema of unknown etiology is the most typical clinical feature of the Melkersson-Rosenthal syndrome. Its coexistence with of facial nerve palsy or fissured tongue could be characterized as an oligosymptomatic MRS. Many investigators suggest cheilitis granulomatosa as a monosymptomatic form of MRS, while patients with facial palsy and fissured tongue, without orofacial edema, should not be considered having MRS. Histological evidence is not necessary. Corticosteroids are generally accepted as the mainstay treatment.

**Key words:** Melkersson-Rosenthal syndrome; Orofacial swelling; Cheilitis granulomatosa; Facial nerve palsy; Fissured tongue

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**Core tip:** Orofacial edema of unknown etiology is the most typical clinical feature of the Melkersson-Rosenthal syndrome. Many investigators suggest cheilitis granulomatosa as a monosymptomatic form of melkersson-Rosenthal syndrome (MRS). The coexistence of orofacial edema with facial nerve palsy or fissured tongue could be characterized as an oligosymptomatic MRS. Patients with facial palsy and fissured tongue, without orofacial edema, should not be considered having MRS. Histological evidence is not necessary. Corticosteroids are generally accepted as the mainstay treatment.

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## INTRODUCTION

Melkersson-Rosenthal syndrome is a rare pathological entity of unidentified pathogenesis and equivocal diagnostic criteria<sup>[1]</sup>. All three classical melkersson-Rosenthal syndrome (MRS) signs of orofacial edema, facial nerve palsy and fissured tongue<sup>[2]</sup>, as described by Melkersson<sup>[3]</sup> and Rosenthal<sup>[4]</sup>, are not frequently encountered and many patients remain misdiagnosed or undiagnosed for years due to indefinite syndrome sub-classification<sup>[2,5-8]</sup>.

The annual incidence of MSR is ranging between 0.2 and 0.3 in 100000 per year among various published studies<sup>[2,6,7,9-11]</sup>, but the rarity of the disease in conjunction with the difficulty in diagnosis makes these estimations quite precarious. Although MRS may affect all age groups<sup>[12]</sup>, typically at least one of its symptoms appears before the fifth decade of life<sup>[10,13]</sup>. Many studies show a slight predilection for females<sup>[2,7,13]</sup>, while equal female: male ratio<sup>[10]</sup> or male predominance<sup>[14]</sup> has also been reported.

The etiology of Melkersson-Rosenthal syndrome still remains unidentified. Although Crohn's disease, sarcoidosis, herpes viruses' infection, allergic reactions, and autoimmune diseases have been considered as possible causes of the syndrome<sup>[2,9,10,12,15-28]</sup>, a definite pathogenetic association failed to be demonstrated by solid scientific evidence. Familial inheritance has also been assumed<sup>[5,8,15,29]</sup>.

The purpose of this study is to review the associated with Melkersson-Rosenthal syndrome literature citations with aim to identify its clinical and histopathological characteristics and correlate them with definitive diagnostic criteria and effective treatment modalities.

## STUDY STRATEGY

A systematic review and analysis of more than 100 publications met eligibility criteria performed by the authors. The search of literature references based on the MEDLINE with subject keywords included five main categories: Melkersson-Rosenthal syndrome, orofacial edema, cheilitis granulomatosa, facial paralysis and fissured tongue. Most of these studies have been conducted at departments of dermatology, oral and maxillofacial surgery, oral pathology and plastic surgery.

## RESEARCH

### Diagnosis

The most dominant manifestation of MRS is asymptomatic orofacial granulomatous edema<sup>[5,10,13,14,19,20,24,25,30]</sup>. Lip localization (cheilitis granulomatosa) is perhaps the most frequently encountered type of the MRS associated edema<sup>[10,12,14,30,31]</sup> while cheeks, tongue or eyelids involvement has also been reported<sup>[2,10,13,14,30]</sup>. The patients may experience recurrent short episodes of the edema for many years, which gradually becoming more persistent<sup>[3,8,10]</sup>. It may clinically mimic angioedema, but

it last longer and it does not respond to antihistamines administration<sup>[32]</sup>.

Unilateral or bilateral peripheral facial nerve palsy, indistinguishable from Bell's palsy, is another commonly encountered manifestation of MRS<sup>[7,13,17,30-33]</sup>. Facial nerve involvement could become permanent after recurrent episodes of shorten duration<sup>[13]</sup>. Palsies of other cranial nerves have also been reported<sup>[34]</sup>.

The fissured tongue (lingua plicata), although found in one third to one half of MRS patients, could valuably assists in diagnosis<sup>[9,13,19,20,23-25,30,32,35]</sup>. Fissured tongue is defined the presence of at least 2 mm deep and 15 mm long grooves crossing the dorsum or margins of the tongue<sup>[36]</sup>.

MRS patients may also experience recurring episodes of acute anterior uveitis<sup>[2,37]</sup>. Gastrointestinal symptoms<sup>[2]</sup>, trigeminal neuralgia, psychotic episodes, migraine<sup>[9,12,23-28,30,31,38]</sup> or longstanding immunologic and autoimmune disturbances<sup>[35]</sup>, may also be encountered.

The associated with the MRS histopathological findings include non-caseating granuloma, giant cells and/or lymphocyte infiltration, and fibrosis<sup>[2,5,10,12,26]</sup>, but their present is not necessary for the final diagnosis<sup>[12,34,39]</sup>. However, biopsy proofs could crucially assist in diagnostic process and therefore repeated biopsies during an acute edema episode are generally recommended in case of strong clinical suspicion of MRS with negative or inconclusive histopathological report<sup>[5,12,13,32,39]</sup>.

Imaging investigations and dermatology, immunology, gastroenterology, and ophthalmology consultations are also recommended during differential diagnosis, in order other pathologic entities to be excluded<sup>[5,20,21,23,40-42]</sup>.

### Sub-classification of MRS

The diagnosis of a complete MRS requires the simultaneous or not presence of orofacial swelling, facial nerve palsy and fissured tongue<sup>[2-4,12]</sup>. However the complete form of the syndrome is found in no more than 20% of overall MRS cases<sup>[5,9,10,12-14,17,20,30]</sup>.

The majority of literature evidence demonstrates orofacial edema, as the most important diagnostic feature of MRS, affecting almost all patients<sup>[12,14,34]</sup>. Many investigators suggest cheilitis granulomatosa as a monosymptomatic form of MRS<sup>[10,12,17]</sup>. The coexistence of orofacial edema with facial nerve palsy or fissured tongue could be characterized as an oligosymptomatic MRS<sup>[5,9,20,23,25]</sup>. Other minor and more rare signs and symptoms could also be considered as additional diagnostic criteria of the oligosymptomatic form of the syndrome<sup>[2,30,34]</sup>. Patients with facial palsy and fissured tongue, without orofacial edema, should not be considered having MRS<sup>[12,43]</sup>.

### Management

Although there is no consensus in therapeutic approach, corticosteroids are generally accepted as the mainstay in MRS management<sup>[9,13,20,23,25,35]</sup>. Systemic or intralesional corticosteroid administration has been demonstrated

to keep orofacial edema under control, while pain relievers and/or antibiotics may be also be indicated in some cases<sup>[44,45]</sup>. In case of unacceptable aesthetic consequences, associated with the orofacial edema, facial reconstructive surgery could be taken under consideration<sup>[5,31,46]</sup>.

Corticosteroids are also considered to be the treatment of choice for MRS associated facial nerve paralysis<sup>[9,13,23,25,27]</sup>. Massage and electrical stimulation have also been described but remain of uncertain efficacy<sup>[8,46]</sup>. Follow-up of the patients diagnosed to have MRS should be in a regularly base due to its chronic and gradually progressive nature.

## CONCLUSION

Melkersson-Rosenthal syndrome is a recurrent and gradually progressive pathologic entity of indefinite classification. Even though the etiology still remains unknown and various treatment modalities are often unsatisfactory, it could be relieving to the patients and the involved physicians to have MRS diagnosed.

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## Oral lichenplanus: Etiology, pathogenesis, diagnosis, and management

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condition with periods of remissions and exacerbations. Management of the OLP is diversified with few lesions requiring treatment for years and few others are mild, requiring no treatment.

**Key words:** Mucocutaneous disease; Lichen planus; Oral lichen planus; Autoimmunity; Corticosteroids

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**Core tip:** Oral Lichen planus (OLP) is frequently encountered by the dermatologists and oral physician. Even though, lot of research is carried out on this disease, still the precise etiopathogenesis and treatment is controversial. As there is a risk of malignant potential reported with this disease, early diagnosis and proper management of the patient is necessary. The present article reviews the OLP briefly about its etiology, pathogenesis, diagnosis and various treatment aspects available.

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### Abstract

Oral Lichen planus (OLP) is a common chronic mucocutaneous disorder with an immune mediated pathogenesis. Its appearance may vary from presence of keratotic to erythematous areas. Etiology of OLP is unknown, but it is thought to be the result of an autoimmune process with an unknown predisposing factor. Oral lichen planus is a complex and poorly understood clinical

### INTRODUCTION

Lichen planus is a mucocutaneous disorder which involves various mucosal surfaces either alone or along with involvement of skin. It most commonly involves the oral mucosa when compared with other mucosal sites<sup>[1]</sup>. Oral lichen planus (OLP) is a disease of unknown etiology affecting stratified squamous epithelia<sup>[2]</sup>. In isolated OLP, only oral lesions will exist<sup>[3]</sup>. The disease



Figure 1 Reticular form of oral lichen planus.



Figure 2 Atrophic form of oral lichen planus.



Figure 3 Erosive form of oral lichen planus.

affects 0.5%-2% of the general population. This disease most commonly involves middle aged patients of 30-60 years age group and females are more prone than males with a ratio of 1.4:1. OLP can be seen rarely in children and young adults<sup>[4,5]</sup>. OLP should be considered as a potentially malignant disorder because there is a relationship between oral cancer and OLP, although the degree of risk involved is variable<sup>[6]</sup>.

The purpose of this review is to provide an update of the etiopathogenesis, clinical features, histological features, Diagnosis and management of OLP.

### Clinical features of oral lichen planus

Oral Lichen planus was first described clinically by Erasmus Wilson in 1869 and histologically by Dubdreuilh in the year 1906<sup>[7]</sup>. Cutaneous lichen planus is recurrent, pruritic<sup>[8,9]</sup> and non-contagious<sup>[10]</sup>. Oral lichen planus rarely involves other sites like scalp, nails, esophagus, larynx and conjunctivae. OLP is gradual in onset and patients are unaware of the disease. Initially patients may present with roughening of oral mucosa, burning sensation and pain in oral mucosa to hot and spicy foods. Later red or white patches over the mucosa may appear which gradually progresses to oral ulcerations. The clinical history includes phases of remission and exacerbation<sup>[11]</sup>.

The clinical presentation of oral Lichen planus resembles many other diseases. It can have many clinical presentations. In 1968, Andreasen divided OLP into 6 clinical forms: reticular, papular, plaque like, atrophic, erosive and bullous<sup>[12]</sup>. These forms may present either simultaneously or individually. Based on the predominant clinical morphology it will be labeled as specific form and the predominant morphology may change over time. Older individuals usually presents with more severe forms (erythematous/atrophic, erosive)<sup>[13]</sup>.

The clinical forms described by Andreasen were made simple by other authors who classified lichen planus grossly into three types: Reticular, atropic or erythematous and erosive<sup>[14]</sup>. The reticular form (Figure 1) is the most common type. It clinically presents as papules and plaques with interlacing white keratotic lines (wickham's striae) surrounded by an erythematous border. Wickham's striae are usually bilateral and seen on buccal mucosa, mucobuccal fold, gingiva and rarely on palate, tongue and lips. This type is reportedly more common in males than females and it is usually asymptomatic<sup>[15]</sup>. OLP usually present as a bilateral symmetrical lesion or involves multiple areas individually<sup>[16]</sup>. OLP involving the gingiva is termed as "desquamative gingivitis" which clinically manifest as a fiery red erythema of attached gingiva. OLP lesions which are associated with patchy brown melanin deposits in the oral mucosa are termed as inflammatory melanosis<sup>[5]</sup>.

Reticular form of oral lichen planus is usually asymptomatic. Atrophic/erythematous (Figure 2) and erosive/ulcerative (Figure 3) lesions are symptomatic. Symptoms include mucosal sensitivity, burning sensation and continuous debilitating pain. Oral lichen planus lesions usually persist for many years. OLP patients have periods of exacerbation and quiescence. Periods of exacerbation are generally associated with psychological stress and anxiety and during this time there is increased erythema or ulceration with increased pain and sensitivity<sup>[5]</sup>. OLP resulting from mechanical trauma either during dental treatments or due to cheek biting is termed as koebner phenomenon<sup>[13]</sup>.

Malignant potential is high for atrophic and erosive forms of OLP<sup>[4,6]</sup>, requiring regular follow up of patients. It should be done atleast 3 times in a year with more frequent examinations required for OLP with dysplasia. The symptoms of the disease such as burning sensation, loss of homogeneity in clinical appearance should be assessed thoroughly at each appointment and biopsy should be performed if required<sup>[17,18]</sup>.

### **Etiology and pathogenesis**

The exact etiology of this condition is unknown. Current literature suggests that T cell mediated immune mechanism is mainly implicated in the pathogenesis of OLP<sup>[5,13]</sup>. Pathogenesis of oral lichen planus may be antigen-specific and non-specific. Antigen-specific mechanisms include antigen presentation by basal keratinocytes and non-specific mechanisms include mast cell degranulation and matrix metalloproteinase (MMP) activation in OLP lesions. Both these mechanisms may combine which results in CD8+ cytotoxic T-cell accumulation in the superficial lamina propria followed by basement membrane disruption, intra-epithelial T-cell migration, and keratinocyte apoptosis. OLP chronicity may be due to deficient antigen-specific TGF- $\beta$ 1-mediated immunosuppression. This breakdown of normal oral mucosa could result in OLP<sup>[19]</sup>.

Both endogenous and exogenous factors may cause cell-mediated immunity in a genetically susceptible patient and appears to play a major role in the pathogenesis of OLP<sup>[20]</sup>. The nature of the antigen implicated in OLP is uncertain, however numerous predisposing factors are known to induce OLP are identified. These are systemic medications, dental materials, chronic liver disease and hepatitis C virus, stress, genetics, tobacco chewing, Graft versus Host disease<sup>[16]</sup>.

Systemic medications such as antimalarial drugs, non-steroidal anti-inflammatory drugs, antihypertensive agents, diuretics, oral hypoglycemic agents, beta blockers, penicillins, sulfonamides, tetracyclines, heavy metals, thyroid preparations, antiretroviral medication have been reported to cause OLP<sup>[16,20-22]</sup>.

The association of OLP with chronic liver disease was first suggested by Mokni *et al*<sup>[23]</sup> in 1991. Epidemiological evidences strongly suggest that Hepatitis C Virus may be an etiologic factor in OLP<sup>[24]</sup>. Association of OLP with several different autoimmune diseases such as alopecia areata, dermatitis herpetiformis, myasthenia gravis, *etc.* has been documented<sup>[20]</sup>.

Periods of psychological stress and anxiety are associated with aggravation of OLP in most of the studies conducted so far<sup>[4,16,20,25,26]</sup>. Genetic predisposition also play a role in OLP pathogenesis<sup>[4,16]</sup>. Koebner phenomenon is a characteristic feature of cutaneous LP and is also observed in oral cavity. The erosive OLP lesions are most commonly seen in areas of trauma such as buccal mucosa and lateral surfaces of the tongue. These lesions may decrease in severity with the elimination of trauma<sup>[13,25]</sup>. Smoking, tobacco chewing, and betel

nut chewing has been associated with the development of OLP in studies conducted in indian population<sup>[16,20]</sup>. Grinspan in 1963 found an interesting association between oral lichen planus, diabetes mellitus and hypertension, which he termed as Grinspan syndrome<sup>[27]</sup>.

OLP is a T-cell mediated autoimmune disease in which the auto-cytotoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium. Initially keratinocyte antigen expression or unmasking of an antigen may occur followed by migration of T cells (mostly CD8+, and some CD4+ cells) into the epithelium. These migrated T cells are activated directly by antigen binding to major histocompatibility complex (MHC)-1 on keratinocyte or through activated CD4+ lymphocytes. In OLP, there will be up regulation of MHC-II expression along with increased number of Langerhan cells facilitating the antigen presentation to CD4+ cells, which activate CD8+ T cells through receptor interaction, interferon  $\gamma$  and IL-2. The activated CD8+ T cells trigger the apoptosis of basal keratinocytes by releasing tumor necrosis factor- $\alpha$ , granzyme B and by Fas-FasL mediated apoptosis. This results in loss of integrity of basement membrane. The MMP are principally involved in connective tissue matrix protein degradation<sup>[24]</sup>.

### **DIAGNOSIS**

The diagnosis can be made depending on the history, clinical and histopathological examination. However, in classical lesions, the diagnosis can be arrived based on clinical appearances (Wickham's striae, erythematous area) only. When skin lesions are also present, the accuracy of diagnosis is strengthened<sup>[21,28]</sup>.

Differential diagnosis of reticular OLP includes leukoplakia, lichenoid reactions, lupus erythematosus and graft vs host disease. The differential diagnosis of erosive OLP includes chronic cheek chewing, hypersensitivity mucositis, chronic candidiasis, discoid lupus erythematosus, squamous cell carcinoma, benign mucous membrane pemphigoid, pemphigus vulgaris and erythema multiforme<sup>[21,28]</sup>.

It is sometimes difficult to clinically diagnose "desquamative gingivitis" when lesions in other sites are absent. Mucous membrane pemphigoid, pemphigus vulgaris and OLP may present as desquamative gingivitis of very similar clinical aspect<sup>[29]</sup>. Biopsy is the gold standard for the diagnosis of OLP. The biopsy should include marginal tissue containing both lesional and normal-appearing areas. OLP can be distinguished from other chronic white or ulcerative oral lesions including reactive keratoses, chronic hyperplastic candidosis, epithelial dysplasia, discoid lupus erythematosus, gastrointestinal disease or anemic states with the help of histopathological examination<sup>[5,30]</sup>.

Direct and indirect immunofluorescent studies, direct oral microscopy and enzyme linked immunosorbent assays can be helpful in reaching a diagnosis for



problematic cases and to exclude malignancy. Among these, the most important being the Immunofluorescent studies which are helpful in making a diagnosis in cases of OLP that may resemble other diseases<sup>[20,28,29,31,32]</sup>.

### **Histopathological features**

The histological features of OLP are similar to cutaneous lichen planus. These were first described by Dubreuill in 1906 and later by Shklar<sup>[16,33]</sup>. The histopathological features of OLP are characterized by a dense sub-epithelial lympho-histiocytic infiltrate, increased numbers of intra-epithelial lymphocytes and degeneration of basal keratinocytes. Degenerating basal keratinocytes form colloid bodies which appear as homogenous eosinophilic globules<sup>[5]</sup>. Colloid/civatte/cytoid/hyaline bodies are round and are seen either in the lower layers of the epithelium or within the upper layers of the connective tissue. These represent degenerated epithelial cells or phagocytosed epithelial cell remnants within macrophages<sup>[33]</sup>. The ultrastructure of colloid bodies revealed that these are apoptotic keratinocytes and the end-labeling method demonstrated DNA fragmentation in these cells. Epithelial basement membrane changes are also common in OLP and consist of breaks, branches, duplications and disruption of the basal keratinocyte anchoring elements (hemidesmosomes, filaments and fibrils). These changes like degeneration of basal keratinocytes, disruption of the epithelial basement membrane and basal keratinocyte anchoring elements together lead to produce weakness at the epithelial-connective tissue interface which results in histological cleft formation (Max-Joseph space) and blisters in oral mucosa. Parakeratosis, acanthosis and "saw-tooth" rete peg formation may be seen<sup>[5]</sup>.

Absence of basal cell liquefaction, atypical cytomorphology, heterogeneous population of infiltrate, nucleus enlargement, blunted rete ridges, increased mitotic figures, absence of civatte bodies, abnormal keratinization will help to rule out the definitive diagnosis of OLP<sup>[34]</sup>. One study suggested that Colloid bodies can be helpful to differentiate oral lichen planus from oral lichenoid reaction. The location of colloid bodies is either in epithelium or connective tissue but usually close to the epithelium-connective tissue junction in case of OLP, while these were mostly seen in lower spinous layer of epithelium in case of oral lichenoid reaction<sup>[35]</sup>. Certain times, the histopathological features are equivocal or do not agree with clinical picture. Another biopsy may be necessary to confirm the diagnosis of OLP by immunofluorescence<sup>[21]</sup>.

Direct Immunofluorescent examination of tissue in case of OLP demonstrates deposition of fibrinogen along the basement membrane zone<sup>[21]</sup> and colloid bodies stain for immunoglobulins IgA, IgG, and IgM<sup>[33]</sup>. Although the existence of fibrin deposition at the mucosal submucosal interface, within vessels and the presence of colloid bodies is highly sensitive for a

diagnosis of LP, but it lacks specificity<sup>[31]</sup>. The sensitivity of direct immunofluorescence is positive for 65.8% of the patients with OLP<sup>[28]</sup>. Direct immunofluorescence is most sensitive when the tissue taken from buccal floor, upper labial mucosa, hard palate and mucosa of the cheek. It is less sensitive when the tissue taken from the gingiva and the dorsum of the tongue. Use of punch biopsy technique instead of conventional biopsy is better to detect the disease in direct immunofluorescence<sup>[28]</sup>. There is no difference in the sensitivity of direct immunofluorescence between biopsies performed in perilesional tissue (radius of up to 1 cm from the lesion) and distant tissue (radius greater than 1 cm). This occurs because the immune deposit may be present in the entire oral tissue, not only close to the lesion. Distant sites also provide more sample options when tissue extraction is difficult<sup>[28]</sup>.

Direct oral microscopy technique is noninvasive which helps in clinical examination of oral cavity. This is based on the principle of colposcopy used by gynecologists and dermoscopy used by the dermatologists. This is used in a study conducted by Drogoszewska *et al.*<sup>[32]</sup> for determining the site for biopsy and for clinical diagnosis of OLP. The principle behind usage of oral microscopy is to reveal precancerous lesion of oral mucosa in subclinical phase in order to begin the treatment as early as possible and to prevent malignant transformation. In their study they have done the direct oral microscopy by using a Leisegang colposcope, model BG/LED Y/C type 3ML. The results of their study showed that direct oral microscopy provides an alternative to clinical examination with the naked eye for choosing most appropriate biopsy site so that it is helpful in early detection of malignant changes of OLP and helps in early intervention of malignancy<sup>[32]</sup>.

### **Management of OLP**

As the immunopathogenesis of OLP is unclear, the clinical management of OLP poses considerable difficulty to the dermatologist and oral physician<sup>[36]</sup>. Currently there is no cure for oral lichen planus<sup>[2,13,21,37]</sup>.

Reticular OLP is often asymptomatic and require no treatment<sup>[4,16,36]</sup>, whereas atrophic, erosive forms can cause symptoms. Symptomatic OLP require therapy and treatment of OLP should be initiated after careful evaluation of patient's medical history, psychological state, treatment compliance and possible drug interactions while evaluating the cost effectiveness of any treatment modality<sup>[36]</sup>. When a medication is suspected that it is causing oral lichenoid lesions, then that drug should be discontinued<sup>[36,37]</sup>. OLP with involvement of the gingiva may be associated with deposition of plaque and calculus. Maintaining good oral hygiene by effective plaque control measures like supragingival scaling, oral hygiene instruction is essential which can enhance healing of the lesions and also decreases the painful symptoms of OLP<sup>[36,38]</sup>. Mechanical trauma of dental procedures, rough dental

restorations, friction from sharp cusps and poorly fitting dental prostheses can be exacerbating factors of symptomatic OLP and these factors should be corrected<sup>[16,36]</sup>.

Transformation of OLP to squamous cell carcinoma is most commonly seen in cases of OLP involving the palatal arch, tongue, labial mucosa and gingiva. Therefore, it is essential to differentiate lesions of OLP as OLP with dysplasia and without dysplasia<sup>[34]</sup>. It has been suggested that regular follow-up of patients with OLP without dysplasia should be performed for at least every 4 mo. More frequent examinations should be considered for patients of OLP with dysplasia<sup>[34]</sup>. Before initiating treatment for OLP, it should be confirmed by biopsy. Oral candidiasis can be caused by different treatment modalities used for OLP, therefore it is important to take care of oral candidiasis before initiating treatment and also during treatment of OLP<sup>[21]</sup>. Current treatment modalities are palliative and have varied efficacy. The usage of specific medication depends on the potential benefit vs side effect and it differs from patient to patient based on patient condition and physicians choice<sup>[13]</sup>. No treatment modality has proved to be curative for OLP. Therefore different drugs are used in a single patient which suggests the insufficiency of any one agent to provide relief to the patient<sup>[2]</sup>. Various treatment regimens are available for the management of symptomatic oral LP.

### **Treatment of inflammatory/symptomatic OLP**

**Corticosteroids:** Corticosteroids till today remain the first line of treatment for OLP. These drugs can be administered topically, intralesionally or systemically.

The most widely accepted treatment of OLP involves use of topical or systemic corticosteroids<sup>[2]</sup>. Topical corticosteroids remain the mainstay and first line of OLP treatment<sup>[13]</sup>. The combination of systemic and topical steroid therapy is often effective in certain severe cases of OLP. Localized OLP lesions are treated with topical steroids either in the form of ointment or paste which can be applied two to four times daily after meals. Topical preparations are also available as lozenges or as a mouthwash or through an inhaler with a special adapter. The dosage and specific preparations are based on the individual patient's needs. Steroid mouthrinse twice daily after food is effective method of treating generalized oral lesions<sup>[5,37,39]</sup>. Commonly used preparations include 0.025% or 0.05% clobetasol propionate gel, 0.1% or 0.05% betamethasone valerate gel, 0.05% fluocinonide gel, 0.05% clobetasol butyrate ointment or cream, 0.1% triamcinolone acetonide ointment<sup>[16,21,36,39-41]</sup>, an aqueous suspension of triamcinolone acetonide 0.1% or 0.3% or 0.5% as oral rinse<sup>[37,42]</sup>, dexamethasone elixir (5 mL of a 5 mg/5 mL suspension) as a mouth rinse<sup>[13]</sup> or 0.1% mouthwash<sup>[43]</sup>, Hydrocortisone hemisuccinate in aqueous solution, betamethasone valerate pellets or aerosol or clobetasol propionate mouthwash<sup>[36,40]</sup>.

Patients are advised to apply a thin layer of the prescribed topical corticosteroid, 3 times a day. The gel or ointment can be applied either directly or indirectly by mixing with equal parts of Orabase, a gelatin-pectin-sodium carboxymethylcellulose-based oral adhesive paste which facilitates adhesion to the gingival tissues. The choice of delivery vehicle can be changed depending on clinician and patient preference. Oral application with a gel preparation is superior compared to other routes of administration. In patients with widespread symptomatic lesions, mouthwashes and aerosols are advised as direct mucosal application of topical medication will be uncomfortable to the patient. Patients should be instructed to gargle with 5 mL of the solution for 2 min after meals and at bedtime<sup>[21]</sup>. The topical steroid application is superior compared to systemic administration because of few side effects. Adverse effects include discomfort on application, thinning of the oral mucosa and candidiasis. Topical preparations of more potent corticosteroids can cause adrenal suppression. The signs and symptoms of OLP are usually improved within 8 wk of therapy with the use of topical steroid preparations<sup>[21,40]</sup>. Prolonged use of topical steroids mainly leads to development of oral candidiasis, so use of antifungal agents along with topical steroids is recommended. Fungal cultures also should be taken before, during and after the treatment<sup>[40,44]</sup>.

Overall, topical steroids are used as a gel, cream, ointment with orabase, mouthwash, oral rinse, etc. The efficacy of the different topical steroid formulations are shown different results in various studies<sup>[36,40-44]</sup>.

Persistent localized erosive OLP lesions are treated with Intralesional and perilesional injection of steroids with caution. Use of local anaesthetic with the preparation reduces the pain during injection. Candidiasis and atrophy of tissue are potential local complications. Intralesional injections of dexamethasone, hydrocortisone, triamcinolone acetonide, and methyl prednisolone are generally used<sup>[2,4,5,13,21,29,36,37,39]</sup>.

Systemic corticosteroids should be reserved for diffuse erosive OLP, multisite disease and generalized atrophic or erosive OLP that do not respond to topical therapy. Depending on the severity of the disease, doses of prednisone 30-60 mg are given once daily for two to four weeks<sup>[36,39]</sup>. These drugs should be gradually tapered and potential adverse effects should be monitored during the treatment<sup>[13]</sup>. Clinical improvement of the OLP lesions is usually seen in majority of patients undergoing systemic prednisone therapy. Topical agent can be given in patients who are using prednisone once control is established<sup>[2]</sup>.

Concurrently prescribing levamisole (150 mg/d) with prednisone will reduce the dose of prednisone. Use of Levamisole and prednisolone 25 mg/d for 3 consecutive days each week for 4-6 wk showed beneficial results in the management of erosive OLP<sup>[45,46]</sup>.

Contraindications of steroid therapy include Hypers-

ensitivity, hypertension, viral infection, tuberculosis, diabetes mellitus and stomach ulcers<sup>[5]</sup>.

In summary, most of the patients can be managed with corticosteroids. Use of Topical or intralesional or systemic steroid preparation is based on severity of the disease, systemic condition and adverse effects during the treatment. Intralesional agents are used in cases of ulcerations which do not respond to topical agents. Systemic agents are restricted for multisite disease, diffused disease and for OLP lesions which do not respond to topical agents.

### **Calcineurin inhibitors**

Calcineurin is a protein phosphatase which activates transcription of Inter Leukin-2 there by stimulates the growth and differentiation of T-cell response. Cyclosporine, tacrolimus and pimecrolimus are calcineurin inhibitors are generally used in treatment of OLP<sup>[24]</sup>.

Cyclosporine A is an immunosuppressive agent which is beneficial in cutaneous lichen planus<sup>[36]</sup>. Cyclosporine (100 mg/mL solution, 5 mL swish and spit three times daily) can be used as a mouth rinse in OLP patients who do not respond to topical corticosteroids<sup>[47-49]</sup>. Oral Cyclosporin A (5 to 6 mg/kg per day) is very effective in recalcitrant severe forms of the disease<sup>[48]</sup>. Recent studies compared the efficacy of cyclosporine solution and triamcinolone acetonide 0.1% in orabase in oral lichen planus lesions, these studies concluded that cyclosporine was not effective when compared with triamcinolone acetonide 0.1% in orabase<sup>[50,51]</sup>. Side-effects with cyclosporine include transient burning sensation, itching, swelling lips and petechial haemorrhages. These side effects, cost of the drug and also questionable efficacy of cyclosporine limits its use in OLP<sup>[49-51]</sup>.

Tacrolimus is a potent immunosuppressive agent which can be used in topical form that can control symptoms of refractory erosive OLP. Studies showed that Tacrolimus ointment 0.1% is well tolerated and it is very effective in erosive OLP that did not respond to topical steroids. Most common adverse effect is local irritation due to burning sensation. Tacrolimus can be used as safe alternate to steroids when the lesions are resistant to the conventional treatment as there are less adverse effects with this drug. Topical tacrolimus helps to release the stress and improves the quality of life of patients suffering from OLP. Topical tacrolimus should be used for short period of about one month, as relapse of the lesions are seen within 6 to 12 mo of treatment cessation. Therefore prolonged or intermittent use of topical tacrolimus ointment in patients with symptomatic OLP may be recommended with constant monitoring. The United States Food and Drug Administration have recommended tacrolimus to be used for short periods of time because of a potential cancer risk from prolonged use. The efficacy of usage of tacrolimus remains to be clearly established in large, well-designed clinical studies<sup>[52-56]</sup>.

Studies using 1% topical cream of pimecrolimus showed significant results in reducing ulceration and inflammation of lesion with better tolerance and relief from pain. Pimecrolimus has significant anti-inflammatory activity with low systemic immunosuppressive potential. Burning sensation is the common complaint experienced by the patients with the use of pimecrolimus<sup>[52,57,58]</sup>. Ibrahim *et al*<sup>[58]</sup> also observed the decreased expression of Fas in the immunohistochemical specimens after the treatment with pimecrolimus. Fas is an important molecule which is involved in apoptosis.

### **Retinoids**

Various Topical retinoids such as 0.1% vitamin A, 0.05% tretinoin ointment, isotretinoin 0.1% gel, etretinate and fenretinide, with their immunomodulating properties are effective in OLP. Irritation, burning sensation are commonly observed with application of topical retinoids. Temporary reversal of white striae can be achieved with topical retinoids<sup>[13,24,36,42]</sup>. Systemic retinoids such as isotretinoin, temarotene, tretinoin have been used in cases of severe lichen planus with varied degree of success. The positive effects of retinoids should be weighed against their significant side effects<sup>[36]</sup>.

### **Azathioprine**

Azathioprine has potent immunosuppressive effects, can be used in the treatment of erosive OLP. There is a risk of malignancy with the long-term use of this drug. Azathioprine cannot be considered as better alternative to systemic steroids alone or systemic steroids in conjunction with topical steroids<sup>[36,39]</sup>.

### **Lycopene**

Lycopene is a fat-soluble carotenoid. It has antioxidant activity, also acts by inhibition of cancer cell proliferation and interference with growth factor stimulation. It has shown to be effective in the management of oral leukoplakia and in chemoprevention of oral cancer. Supplementing with 8 mg/d of lycopene for 8 wk showed favorable results of reduced burning sensation and decreased signs and symptoms of OLP in patients, in a placebo controlled study<sup>[59]</sup>.

### **Aloe vera**

Aloe vera (*Aloe barbadensis* Miller) is cactus like plant and it is a member of the Liliaceae family. There are few studies conducted using aloe vera gel or aloe vera in a aqueous suspension and it is also compared with the triamcinolone gel which showed beneficial effects in relieving symptoms of OLP. Further studies are required to prove the efficacy of aloe vera in the treatment of OLP<sup>[60-62]</sup>.

### **Hyaluronic acid**

Hyaluronic acid (HA) is a linear polymer of glucuronic

acid, N-acetylglucosamine disaccharide which helps in tissue healing. HA in the form of 0.2% gel showed transient improvement in decreasing the soreness associated with OLP in a placebo controlled double blind study<sup>[63]</sup>.

#### ***Bacillus Calmette-Guerin polysaccharide nucleic acid***

Bacillus Calmette-Guerin polysaccharide nucleic acid (BCG-PSN) is the third-generation BCG extract with various immunologic active materials including polysaccharide and nucleic acid. It has the ability to regulate the Th1/Th2 cytokine secretion in peripheral blood mononuclear cells (PBMC) of the OLP patients. In a study which compared the effectiveness of intralesional 0.5 mL BCG-PSN injection every alternative day with 10mg triamcinolone injection every week for about 2 wk showed equal effectiveness of both agents for erosive OLP. So BCG-PSN injections could be a promising therapeutic alternative for erosive OLP, especially for those insensitive or even resistant to glucocorticoids<sup>[64]</sup>.

#### ***Anthocyanins***

Anthocyanins are polyphenolic groups which block the spread of free radicals and are considered the main antioxidants of the plant kingdom. The extracts of grape seeds and grape skins contain anthocyanins. These are also present in other fruits, vegetables, chocolate, tea. Rivarola de Gutierrez *et al.*<sup>[65]</sup> conducted a prospective, non-randomized study in 52 patients. Anthocyanins were administered in 100 mg/doses diluted in 5 mL of water, mouth rinses, during 5 min and spit, three times a day in 26 patients and control group received CP-NN cream (100 g of commercial preparation containing: 17-clobetasol propionate (micronized) 0.050 g, Neomycin (as sulfate) 0.350 g; Nystatin (micronized) 100.000 U/g. This was applied three times daily locally on lesions. There is improvement in the pain relief in patients with anthocyanins when compared with patients receiving CP-NN treatment<sup>[65]</sup>.

Pharmacological agents like dapsone, doxycycline, griseofulvin, hydroxychloroquine sulphate, adalimumab, mycophenolates, efalizumab, cyclophosphamide, hydrochloroquine, phenytoin, mesalazine, interferon, glycyrrhizin, amitriptyline, amlexanox, curcuminoids, thalidomide, ignatia, purslane reported in the treatment of OLP. However, the main concerns with these are local and systemic side effects and lesion recurrence following withdrawal of treatment as fewer studies are reported with these agents. The cost-benefit and the safety profile of these drugs have to be more carefully considered and randomized controlled trials of these agents in larger groups of patients with OLP are recommended to clarify their effectiveness and safety profile<sup>[2,24,29,34,36,48,66,67]</sup>.

## **NON-PHARMACOLOGICAL MODALITIES**

Phototherapy or light therapy or heliotherapy has been

widely used as an alternative therapy for the management of OLP. Different kinds of phototherapy include Ultra Violet (UV) phototherapy, photodynamic therapy and lasers<sup>[68]</sup>.

#### ***UV Phototherapy***

UVA treatment usually comprises UVA radiation (long wave length 315-400 nm Ultra Violet light) combined with a sensitizer (a chemical that increases the effect of UVA) called 8-methoxy psoralen. This form of treatment is referred to as PUVA (psoralen + UVA). To avoid PUVA side effects, photosensitization with topical 0.01% trioxsalen can be used for the treatment. Various side effects include nausea, eye symptoms, dizziness, paraesthesia and headache. PUVA therapy may be useful for severe forms of erosive OLP that do not respond to conventional treatment. Photochemotherapy with solar radiation has been introduced as an effective and cheaper alternative to PUVA. PUVA therapy has shown oncogenic potential, therefore it is not widely used and is discontinued for the treatment of OLP<sup>[4,16,36,68]</sup>.

#### ***Photodynamic therapy***

Photodynamic therapy (PDT) uses a photosensitizing compound (photosensitizer) which is activated at a specific wavelength of laser light which is known to destroy the targeted cell. PDT has shown positive results in management of head and neck tumors. The immunomodulatory activity of PDT also helpful in controlling the inflammation in OLP<sup>[2,16]</sup>. PDT with the use of different photosensitizers (methyl 5-aminolevulinate, phenothiazine dye methylene blue, Photolon®, a novel chlorin e6-derived photosensitizer) are used for the treatment of OLP and showed promising results in the treatment of OLP. The only PDT side effect reported was photosensitivity. However, further well-designed randomized controlled trials with larger numbers of patients with long follow-ups will be needed to evaluate the effectiveness of PDT in the treatment of OLP<sup>[68,69]</sup>.

#### ***Lasers***

Use of lasers for treatment of OLP is not recommended as the first choice of treatment, but it is suggested for use in patients who are unresponsive to topical corticosteroids<sup>[68]</sup>. Low-level laser therapy (LLLT; photobiostimulation, photobiomodulation) has physiological effects such as vasodilatation, enhancement of blood flow and lymph drainage, increased cellular metabolism, aggregation of prostaglandins, immunoglobulins and lymphokines, resulting in reduction of inflammation, immune response, and pain. Various low level lasers with different wavelengths, intensities, powers, durations, number of sessions, and therapeutic approaches (with or without tissue absorbent) have been used to treat oral lichen planus<sup>[70]</sup>. Few studies also reported the use of CO<sub>2</sub> laser, excimer laser for the treatment of OLP<sup>[68,71,72]</sup>. Use of LLLT, CO<sub>2</sub> lasers and excimer lasers are to be confirmed in well-designed



controlled trials with large number of patients<sup>[68]</sup>.

### Surgery

Surgical excision has been recommended for isolated plaques or non-healing erosions as it may cure the disease and also provides tissue for histopathologic examination. Surgical excision is not recommended in erosive and atrophic forms because of erosions in these forms and also due to recurrence of inflammation. Cryosurgery has been successful in cases of erosive OLP resistant to other treatment modalities. Recurrences are common with the use of cryosurgery<sup>[2,37,36]</sup>.

### Treatment of dysplastic OLP

The inflammatory component of OLP is treated with various above mentioned methods and additional approaches are required for assessing and treating dysplastic component in these cases<sup>[34]</sup>.

## CONCLUSION

Oral lichen planus is a chronic disease of oral mucosa. Patients of oral lichen planus have longer periods of disease activity with periods of remission and exacerbations and also there is a risk of malignant transformation over a long time. Therefore early diagnosis and treatment is mandatory with periodical follow up of the patients.

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## Unraveling the role of epidermal growth factor receptor in oral lesions: Key to non surgical treatment modes

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diverse roles in maintaining homeostasis and recent molecular advances identify that EGFR mutations are linked to several carcinomas. EGFR plays important roles in the development and maintenance of various oral structures, tooth development, eruption and morphogenesis. EGFR expression has also been studied in diverse oral pathologies like squamous cell carcinomas, potentially malignant lesions, lichen planus, salivary gland tumors and odontogenic cysts and tumours. The present review delves into the various general features of EGFR with an insight into its physiological and pathological role in the oral cavity. The clinical implications and upcoming role of EGFR inhibitors in the nonsurgical treatment of oral lesions has also been discussed.

**Key words:** Epidermal growth factor; Epidermal growth factor receptor; Oral pathology; Cetuximab

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**Core tip:** This review addresses the importance and need to understand epidermal growth factor receptor (EGFR) related pathogenesis in oral lesions and the possible effectiveness of anti-EGFR agents in treating these conditions.

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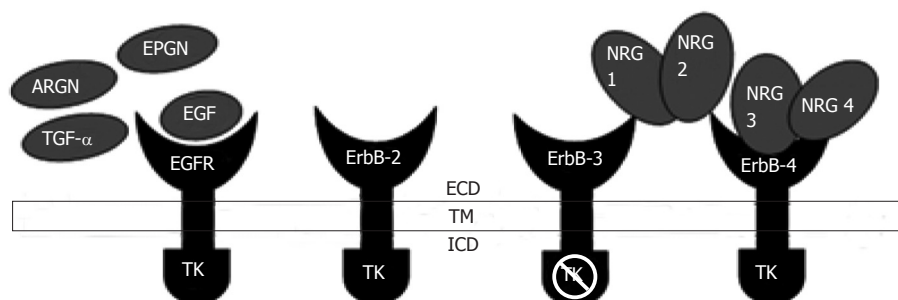
### Abstract

Epidermal growth factor receptor (EGFR) is a transmembrane receptor with tyrosine kinase activity, mediating actions of various growth factors including EGF, transforming growth factor- $\alpha$ , and neuregulins. Protein binding to ligand induces receptor modification, tyrosine autophosphorylation leading to cell signaling resulting in cellular proliferation. This receptor plays

### INTRODUCTION

The epidermal growth factor receptor (EGFR) is nowadays being studied because of the possible role of





**Figure 1 Epidermal growth factor receptor structure: Extracellular domain, transmembrane pass, intracellular domain, ligand binding, cysteine-rich domains.** Intracellular domain includes the kinase domain and cytoplasmic tail. EGFR: Epidermal growth factor receptor; ECD: Extracellular domain; TM: Transmembrane pass; ICD: Intracellular domain; ARGN: Amphiregulin; EPGN: Epiregulin; TGF- $\alpha$ : Transforming growth factor alpha; TK: Tyrosine kinase; NRG: Neuregulin.



**Figure 2 Epidermal growth factor receptor and its major ligands epidermal growth factor, transforming growth factor alpha, neuregulin, amphiregulin and epiregulin.** ECD: Extracellular domain; TM: Transmembrane pass; ICD: Intracellular domain; LB: Ligand binding; CR: Cysteine-rich; KD: Kinase domain; CT: Cytoplasmic tail.

using EGFR inhibitors in the cancer chemotherapy<sup>[1]</sup>. EGFR is the prototypal member of four homologous transmembrane proteins and was the first protein in this family to have been sequenced and identified to have tyrosine kinase activity<sup>[2-5]</sup>. EGFR is also referred to as HER (human EGF receptor) and c-erbB1 and is encoded by the *EGFR* gene located on chromosome 7p12. This transmembrane glycoprotein comprises of 1186 amino acids having three main parts; extracellular domain (ECD), transmembrane pass (TM) and intracellular domain (ICD)<sup>[2]</sup> (Figure 1).

In vertebrates, among the four EGFR family members (ErbB1, ErbB2, ErbB3 and ErbB4), overall similarity among the amino acids is about 50%<sup>[6]</sup>. The receptors EGFR family are together create an interacting system that receives and processes information that results in multiple cellular functions. EGFR binds to EGF, amphiregulin and TGF- $\alpha$  and ligands like betacellulin, heparin-binding EGF and epiregulin bind to the EGFR as well as ErbB4. The ErbB2/HER2/neu does not bind ligands and ErbB3/HER3 has an inactive kinase domain, and these receptors are thought to serve as co-receptors. Neuregulins 1 (NGR1) and Neuregulins 2 (NGR2) bind preferentially to ErbB3 and ErbB4 and the ligands NGR3 and NGR4 bind to ErbB4 (Figure 2). Ligand bonding initiates shape alteration that unmasks a "dimerization loop," thereby triggering receptor homo-dimerization or hetero-dimerization which causes tyrosine trans-phosphorylation leading to activation of downstream signaling cascades<sup>[7]</sup>. These pathways are often functionally interlinked and ideally should not be considered in isolation; however, for the sake of simplicity most authors discuss them individually<sup>[7-10]</sup>.

The EGFR family is a diverse signaler and plays

important physiological roles in determining cell lineage, organ morphogenesis, cell adaptation, motility, proliferation and apoptosis<sup>[5,7]</sup>. Damjanov *et al.*<sup>[11]</sup> in 1986 conducted a study to identify EGFR in various tissues in human oral mucosa and suggested that membrane EGFR location depicts a more responsive cell than cytoplasmic EGFR localization. This study said that it is likely that differential distribution of the EGFR to specific cell types and cellular compartments may signify adaptations that permit growth factor responsiveness in the surroundings of available ligand<sup>[11]</sup>. EGFR also interacts with RANK resulting in RANKL signaling pathways which helps in osteoclast differentiation and survival<sup>[12]</sup>.

In general pathology EGFR plays a major role in human cancers. Aberrant EGFR signaling are initiated by several events, such as altered ligand production, receptor mutations or deletions and continuous signaling leading to uncontrolled cell multiplication, invasion, increased angiogenesis and metastasis<sup>[7,13-15]</sup>. EGFR also plays an important role in stopping autophagic cell death induced by death receptors which is one of the mechanisms that initiate cancer<sup>[14]</sup>. Another recent EGFR mechanism that was identified is the tyrosine kinase independent mode in which EGFR prevents cancer cells from apoptosis by regulating the basal intracellular glucose level via the sodium/glucose co transporter 1<sup>[15]</sup>. EGFR has varied effects in the prognosis of various cancers<sup>[13]</sup>. This is speculated to be an important reason for the aggressiveness and resistance to chemotherapy noticed in EGFR related epithelial tumors<sup>[16-19]</sup>. EGFR levels in normal cells usually ranges between 40000 and 100000 receptors per cell<sup>[19]</sup>. Enhanced EGFR expression are a notable characteristic of many epith-

elial carcinomas like glioblastoma, Non-small cell lung cancer, breast, colorectal, bladder, prostate and ovarian carcinomas<sup>[11,16-19]</sup>.

## EGFR IN ORAL PHYSIOLOGY

To understand EGFR related pathogenesis a proper understanding of its significance in physiology needed. EGFR plays important roles in the development and maintenance of various oral structures, tooth development, eruption and morphogenesis.

Hernández *et al*<sup>[20]</sup> in 1992 elicited the localization of epidermal growth factor and its receptor during tooth formation in rat embryos during embryonic days (E-16 to E-21) immunohistochemically. Another study by Heikinheimo *et al*<sup>[21]</sup> on role of EGFR in tooth development and few neoplastic odontogenic neoplasms concluded that that regulation of EGFR expression is developmentally determined in human odontogenesis. Furthermore, the odontogenic epithelium is the main target tissue for EGF, TGF- $\beta$  and TGF- $\alpha$  and they may also be involved in odontogenic tumorigenesis<sup>[21]</sup>. Several authors like Wise *et al*<sup>[22]</sup>, Shroff *et al*<sup>[23]</sup> and Cdhill *et al*<sup>[24]</sup> have proven that tooth follicle with the presence of EGFR and their ligands is essential for tooth eruption. EGFR and its ligands also mediates tooth morphogenesis as claimed by Hu *et al*<sup>[25]</sup>.

On assessment of EGFR expression by Thesleff *et al*<sup>[26]</sup> it was seen that they intensely bind to the epithelial cell rests of Malassez concluding that they are responsive to the actions of EGF. Her study speculated that these epithelial rests may be activated whenever there is local rise of EGF ligand in that tissue milieu<sup>[26]</sup>. Another immunohistochemical analysis was performed in normal and pathological human gingival epithelia by Nordlund *et al*<sup>[27]</sup> which showed that basal layers of gingival proliferating cells in inflamed adult periodontitis cases, as well as the epithelial cell rests of Malassez bound to the antibody intensely signifying that EGF moderates epithelial growth and differentiation in periodontal tissues.

Also in recent research by O Häärä *et al*<sup>[28]</sup> it was evident that EGFR plays a role in formation of salivary gland by supporting the growth and development of the epithelium and survival of the mesenchyme.

## EGFR IN ORAL PATHOLOGY

Various studies have analyzed EGFR expression in diverse oral lesions like squamous cell carcinomas<sup>[18,29-32]</sup>, potentially malignant lesions<sup>[32-34]</sup>, lichen planus<sup>[35,36]</sup> salivary gland tumors<sup>[37-39]</sup> and odontogenic cysts and tumours<sup>[40-44]</sup>.

### EGFR in head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is increasing at an alarming rate with about 600000 patients being newly diagnosed annually. It was noted

that most cases showing remission and metastasis are associated with poorer prognosis and a multitude of research is now being concentrated on understanding this disease and its relationship with EGFR pathways<sup>[18,19]</sup>. Heightened EGFR expression is observed in about 80%-90% HNSCC and often correlates with poorer prognosis, higher recurrence rate, advanced tumor stage and increased possibility of metastasis<sup>[13,18,19]</sup>.

The HER 3 receptor was identified as most prognostic value in assessing tongue squamous cell carcinoma<sup>[31]</sup>. EGFR has been a recent target of anticancer therapies due to its critical roles in cellular homeostasis. EGFR mutations are found in four exons of the EGFR gene, exons 18 to 21. Exon 19 deletions and exon 21 mutations account for most of these mutations. On genetic analysis it is seen that the EGFR mutation of deletion in exon 19 was implicated with squamous cell carcinoma development in few of the cases<sup>[45]</sup>.

### EGFR in potentially malignant lesions

EGFR over expression is an initial event in the squamous cell carcinoma of the head and neck carcinogenesis. On investigation done by Rautava *et al*<sup>[34]</sup> in dysplastic, developing and malignant oral epithelium it was seen that all the four family of EGFR receptors was seen in developing oral epithelium and to a lesser extent in mature oral epithelium<sup>[34]</sup>. An increase in EGFR immunoreactivity was seen in 61% and 54% of dysplasias and OSCC respectively. Its increased presence is also noted in "apparently normal" mucosa from cancer patients, when compared to healthy controls (field cancerization) and this over expression is observed to steadily increase analogous to observed histological abnormalities, from dysplasia to carcinoma *in situ*<sup>[34]</sup>. In normal mucosa EGFR positivity was seen only in the basal layers, whereas in leukoplakia the spinous and basal layers showed positivity and squamous cell carcinomas showed intense and increased positivity<sup>[46]</sup>. Another similarly designed study in dysplasias and SCC showed nearly all cells of the dysplastic epithelium showing positivity and in oral squamous cell carcinomas, the positivity in the tumor cells correlated inversely with cellular differentiation<sup>[47]</sup>. In other potentially malignant lesions like OSMF, it was found that there was a definite increase in EGFR expression along the differentiated layers of the oral epithelium<sup>[33]</sup>. In certain lesions like lichen planus, increased EGFR expression in the epithelial cells as well as the infiltrating lymphocytes are hypothesized to play a significant role in disease development<sup>[35,36]</sup>.

### EGFR expression in salivary gland lesions

EGFR expression has also been analyzed in various salivary gland lesions<sup>[37-39]</sup>. In a study done by Yamada *et al*<sup>[37]</sup> 1989 the immunohistochemical localization of EGFR was classified into two types, one the cell membrane-positive type found in epithelial tumor cells, and the other is the cytoplasm positivity seen in normal ductal

cells and luminal tumor cells of pleomorphic adenomas and mucoepidermoid carcinomas. In a recent study<sup>[38]</sup> done on pleomorphic adenomas (PA), mucoepidermoid carcinoma (MC) and adenoid cystic carcinoma (ACC), it was found that all of them expressed EGFR family receptors. ErbB-2 was seen to be commonly expressed and both membrane and cytoplasmic staining is noted. Enhanced scores of ErbB-2 membrane were more common in MEC as compared to ACC and PA suggestive of their role in pathogenesis of salivary gland neoplasms. Another study done in carcinoma ex Pleomorphic adenoma (CXPA), showed intense EGFR expression in the outer borders of CXPA, indicating that this receptor may be related to cell detachment and invasive potential of CXPA<sup>[39]</sup>.

### EGFR expression in odontogenic lesions

Numerous investigations have been done in odontogenic epithelium and related lesions in reference to EGFR expression<sup>[40-44]</sup>. Based on the various studies conducted in odontogenic cysts and tumors and it has been suggested that EGFR is related to the proliferative mechanisms in these lesions. Shrestha was one of the first to study the expression of EGFR in odontogenic lesions and he found increased expression of EGFR in these odontogenic cysts and tumors but no positivity in ameloblastomas<sup>[42]</sup>. Based on these findings the author then concluded that the proliferative pathways in ameloblastomas were diverse. However, most of the studies done later in ameloblastoma showed diverse results with most ameloblastomas giving EGFR positive immunoexpression<sup>[41,43]</sup>. EGFR expression was studied in the physiological odontogenic epithelium represented by the pericoronal follicle by da Silva Baumgart *et al.*<sup>[42]</sup> and he hypothesized that understanding the staining patterns of EGFR in the follicles could provide vital clues to the origin of various odontogenic cysts and tumors. Other studies by Vered *et al.*<sup>[43]</sup> and de Vicente *et al.*<sup>[44]</sup> also give diverse findings.

## METHODS OF EVALUATION OF EGFR

EGFR quantification can be done at the DNA, RNA or protein level<sup>[45]</sup>. EGFR mutations are known to occur in various carcinomas and they are studied by analyzing the chromosomes and DNA<sup>[46]</sup>. EGFR amplification which is noted in various lesions can be studied by gene amplifications assay which analyze at the DNA, RNA and the protein levels in tissue<sup>[47,48]</sup>. mRNA based methods of detection are prone to problems with RNA degradation and contamination.

EGFR protein levels quantified by western blot analysis and enzyme immunoassay, measure total receptor protein and provide no data on their location in the cell<sup>[49]</sup>. Immunohistochemistry is commonly used to evaluate EGFR protein levels and is arguably the most convenient method for analyzing clinical samples and give an idea about the cellular localization. However,

the main disadvantage of immunohistochemistry is its lack of sensitivity and specificity in comparison to other methods. Further there is still no consensus of standard scoring criteria for the quantifying EGFR positivity in tissue specimens. Downstream markers and their analysis may also provide EGFR related information. The EGFR molecule has various downstream pathways of action and these molecules are of significance in studying specific lesions. Some of the most common downstream markers of significance are EGFR, p-EGFR, p-Akt, p-Erk, p-STAT3<sup>[50,51]</sup>.

## EGFR AND ITS CLINICAL IMPLICATIONS

The identification of chemo-therapeutic agents in the treatment of specific malignancies like leukemias and lymphomas have simplified and inspired new treatment perspectives of neoplasms. Since the advent and success of these treatment strategies, researchers all over the world are trying to open more avenues in the treatment of other malignancies. Ever since the discovery of EGF in 1960 and the isolation of EGFR by Cohen *et al.*<sup>[52]</sup> in 1980 numerous studies are done to elucidate its role in cancer pathogenesis. Based on the work of many pioneers on EGFR agents John Mendelsohn conducted research focusing on EGFR and proposed EGFR as an anticancer target, especially in various carcinomas<sup>[17,53]</sup>. Control of EGFR signaling is likely to open new avenues of treatment in three main areas that include cell yield, organ restoration and management of cancer.

EGFR is the receptor most often found up regulated and its gene mutations are evident in a wide variety of human tumors like head and neck cancers, renal carcinomas, breast carcinomas, gliomas, colon cancers, non-small-cell lung carcinomas and pancreatic carcinomas<sup>[7,13,18,19,30,45,54,55]</sup>. Herbst *et al.*<sup>[55]</sup> in 2002 stated that EGFR is one of the most important receptors critical for cell proliferation, differentiation and survival and related its dysregulation to be of significance in suppressing apoptosis, mediating neoplastic angiogenesis, increasing metastatic ability and resisting chemo and radiotherapy<sup>[55]</sup>. Several ongoing clinical trials on humans are presently testing anti-EGFR antibodies with many of them showing promising results for the future. The rationale behind EGFR therapies is that they compete with endogenous growth factors like EGF and transforming growth factor- $\alpha$ , for binding sites. Once bound EGFR blocks crucial downstream pathways thereby interfering with the growth of neoplasms expressing EGFR.

The rationale of using anti-EGFR agents in head and neck cancers is that EGFR is expressed in more than 90% of head and neck carcinomas and studies have shown that EGFR over expression is associated with decreased survival<sup>[1,18,29-32,49]</sup>. Also it is noted that increased EGFR expression occurs initially in carcinogenesis and is present even in premalignant oral lesions<sup>[32-34]</sup>. Finally

studies have also shown that inhibition of EGFR-TK pathway slows the growth of xenograft tumour models of head and neck. EGFR based chemotherapy can involve various methods<sup>[56]</sup>. This can be achieved by using directly acting anti-EGFR agents, by using tyrosine kinase inhibitors (TKIs) or agents that inhibit the downstream molecules in the EGFR pathway<sup>[56]</sup>. Amongst these, EGFR antibody Cetuximab and TKIs like Erlotinib and Gefitinib are being trialled in HNSCC. Understanding the molecular pathogenesis of the neoplasm will help in choosing the ideal therapeutic agent. For example EGFRvIII is caused by frame deletion mutations and is seen in 42% of HNSCC leading to growth of the tumor and provides resistance to antibody based treatment interventions.

In such situations, patients with EGFRvIII HNSCCs would possibly benefit better from tyrosine kinase inhibitors rather than EGFR antibody based treatment strategies<sup>[56,57]</sup>.

Another important treatment possibility of the EGFR neoplasms is that anti-EGFR agents increase the radiosensitivity of several neoplasms. In a recent randomised phase III clinical trial attempted by Bonner *et al.*<sup>[58]</sup> it was seen that simultaneous radiotherapy and chemotherapy with Cetuximab in head and neck cancer patients showed improved local tumour containment compared to radiotherapy alone<sup>[58]</sup>. The cause for increased radiation effects when combined with EGFR therapy are still obscure. Numerous other studies studying the efficacy of anti-EGFR agents are in the phase three trial<sup>[1,7,54,55,58]</sup>. Antisense oligonucleotides, ligand conjugates and immunoconjugates of EGFR are also used to inhibit EGFR activity. Other EGFR inhibitors like cetuximab-C225 are being extensively studied in head and neck carcinomas and are in the third phase of trial. However till date no drastic changes in treatment modalities have been experienced. Moreover, there are a lot of side effects associated with the use of EGFR which has rendered it use, unacceptable.

Vered in his article<sup>[43]</sup> mentions that adverse effects of anti-EGFR agents like C225 and ZD-1839 is usually observed in less than 15% of patients, and these effects may not occur with ameloblastoma, as these side effects could be avoided by intralesional administration of the anti-EGFR agents. Recently, a fully human anti-EGFR monoclonal antibody, vectibix-EGF was developed as a possible treatment for surgically compromised cases of ameloblastoma. However, clinical trials are yet to take place<sup>[43]</sup>.

## CONCLUSION

The EGF receptor is an important molecule in maintaining various pathways and homeostasis within an organism. It plays varied roles and its dysregulation is identified to be a key factor in various oral pathologies, especially HNSCC and ameloblastomas. Identifying ideal therapeutic target will enable the transition of treating these lesions using a non surgical modality thereby

significantly reducing the mortality and morbidity of the patient. The receptor mediates its action through various pathways and the proper understanding of these will enable us to develop ideal treatment strategies to combat the various lesions. Several studies are now targeting these pathways, however, till now significant success has not been achieved in clinical trials using anti-EGFR agents in HNSCC. Several reasons suggested for this insensitivity are the multifactorial aetiology of head and neck carcinomas and lack of proper understanding of the various molecular pathways. More research needs to be focussed on the understanding of this molecule in future in order to bring the treatment of several debilitating neoplasms from the bench to the bedside.

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## Unusual aggressive behavior of central giant cell granuloma following tooth extraction

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in jaws. Its etiopathogenesis is unclear; however it is suggested that it can arise as a reactive response to trauma. This report describes an aggressive variety of CGCG which raises a question; can extraction of tooth modify the behavior of CGCG? A 46 years old male had reported with a rapidly increasing intraoral and extraoral swelling of lower jaw following tooth extraction. Radiographic examination revealed a large multilocular lesion involving the body and ramus of mandible which had been proved to be aggressive CGCG on histopathological examination. The importance of radiographic examination prior to extraction of teeth and importance of inclusion of CGCG in jaw swellings associated with mobility of teeth or failure of healing sockets is emphasized.

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**Key words:** Aggressive; Central giant cell granuloma; Mandibular swelling; Extraction of teeth; Jaw

**Core tip:** This report describes an aggressive variety of central giant cell granuloma (CGCG) after extraction which raises a question; can extraction of tooth modify the behavior of CGCG? The importance of radiographic examination prior to extraction of teeth and importance of inclusion of CGCG in jaw swellings associated with mobility of teeth or failure of healing sockets is emphasized. Literature about clarity in clinical behavior, radiographic features and various treatment modalities of this one of the bony lesion of jaws are reviewed.

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### Abstract

Central giant cell granuloma (CGCG) is found exclusively

## INTRODUCTION

Central giant cell granuloma (CGCG) has unpredictable biologic behavior, non-specific radiographic features and is amenable to a plethora of treatment alternatives. A reactive response to trauma is the most accepted etiopathogenesis of CGCG<sup>[1-3]</sup>. This report describes a case of an aggressive variety of CGCG which was augmented following extraction of teeth. This is a rare presentation of CGCG and it suggests two important things, as delay in diagnosis has an important implication on morbidity and mortality of the patient. (1) The necessity of radiographic examination prior to extraction of teeth; and (2) importance of early histopathological examination, if extraction socket fails to heal should not be underestimated. Though abundant literature is available regarding this well known entity, case reports are still considered to be the source of information.

## CASE REPORT

A 46 years old male reported to the Department of Oral Diagnosis and Medicine at Sharad Pawar Dental College and Hospital, Wardha, India, with a chief complaint of progressive extraoral and intraoral swelling on lower right back region of the jaw since 2 mo. History of present illness revealed that approximately three months ago patient had noticed mobility of the teeth in same region and all his molars were extracted from that quadrant. This had resulted in failure of healing of the extraction socket and development of rapidly enlarging extraoral and intraoral swelling 1 mo post-extraction. There was associated pain too. As a result of intraoral swelling the patient had difficulty in chewing, swallowing and speaking as these processes were aggravating the pain. There was no history of discharge from the swelling. The patient was of moderate build and healthy weight. The general systemic examination did not reveal any major illness.

On extraoral examination, there was diffuse swelling on lower right side of face resulting in marked facial asymmetry as shown in Figure 1. Palpation elicited that the swelling was bony hard, non-tender, fixed to the underlying structures and with no pulsations. Local Temperature was not raised. There were no signs of loss of sensory function.

Intraoral examination revealed missing lower right molars with an exophytic soft tissue growth from the residual socket and well-circumscribed ovoid swelling of approximately 4 cm × 6 cm in posterior region of right side of the mandible causing bucco-lingual expansion of the jaw with marks of indentation on overlying mucosa. (Figure 2). The swelling was firm in consistency, slightly tender and was fixed to underlying structures. On the basis of history and clinical features, provisional diagnosis was malignant tumor. Investigations were carried out to evaluate the case.

Lateral mandibular occlusal view showed single



Figure 1 Diffuse swelling on lower right side of face.

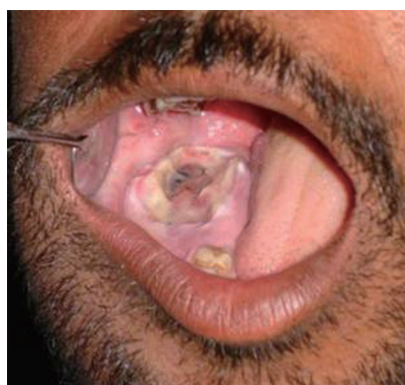


Figure 2 Swelling in molar region with marks of indentation on overlying mucosa.

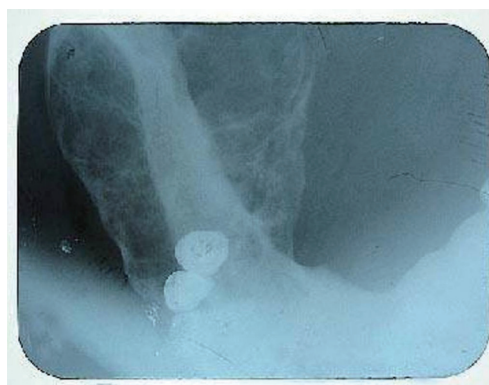


Figure 3 Mandibular lateral occlusal view showing predominantly buccal and lingual expansion with thinning of cortical plates.

large multilocular radiolucent lesion having well defined periphery with predominant buccal and lingual expansion and thinned-out of cortical plates (Figure 3). A panoramic radiograph revealed a single large multilocular radiolucent lesion involving the body (honey comb appearance) and ramus (soap bubble appearance) on right side of mandible extending anteroposteriorly from the canine to posterior border of ramus and superoinferiorly from sigmoid notch to inferior border of mandible in ramus region and from alveolar crest to inferior border of mandible in body



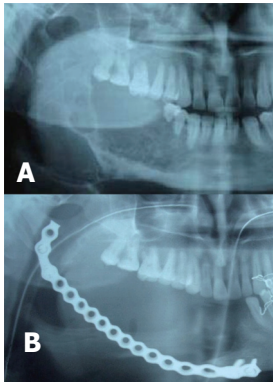


Figure 4 Cropped orthopantomograph showing (A) a multilocular lesion in body and ramus of mandible on right side (B) a surgical defect and radioopaque image of reconstruction plate.

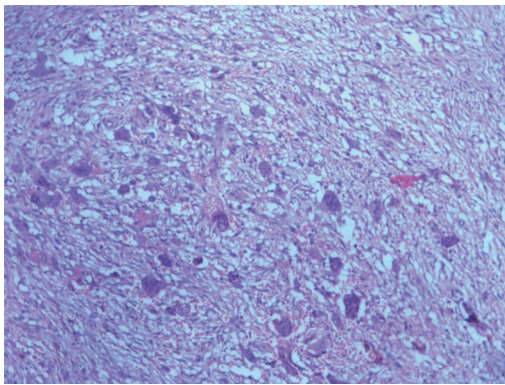


Figure 5 Photomicrograph showing multinucleated giant cells and spindle cells (10 ×).

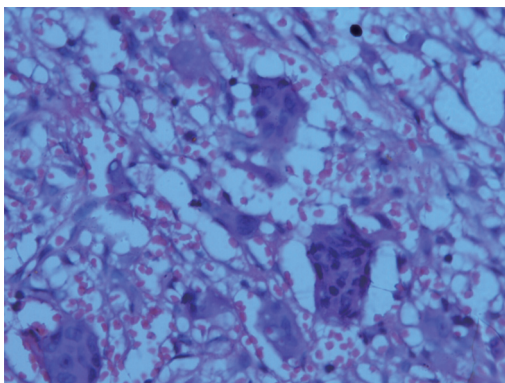


Figure 6 Photomicrograph showing multinucleated giant cells (40 ×).

region as illustrated in Figure 4A. The periphery of the lesion was well defined and scalloped. There was resorption and thinning of superior and inferior cortices, roots resorption as well as expansion at the inferior border of mandible.

On the basis of radiographic findings, probability of ameloblastoma was considered while various benign tumors and multilocular cysts were considered in differential diagnosis. The lesion was subjected to fine needle aspiration biopsy which was non productive.

Then an incisional biopsy of the lesion was performed. Results of the biopsy showed the features suggestive of CGCG. An attempt was made to exclude the brown tumor of the hyperparathyroidism by undergoing biochemical tests (serum calcium, phosphorus, alkaline phosphates, and parathyroid hormone) which were within normal limits.

As surgery is the most accepted and traditional form of treatment for CGCG especially in the aggressive type and as there was absence of any systemic disease which could complicate the surgical treatment, surgery was chosen as a treatment of choice in this case.

Under general anesthesia the surgical excision of the lesion was performed by hemimandibulectomy and a reconstruction plate was inserted to repair the defect (Figure 4B). Post-operative healing was uneventful. The specimen was sent for histopathological examination. Hematoxylin and Eosin stained section showed highly cellular fibrous connective tissue stroma, which consisted of many plump fibroblasts, extravagated blood elements and numerous multinucleated giant cells, containing nuclei ranging from 5-20 in numbers and uniformly scattered throughout the lesion (Figures 5 and 6). The clinic-pathological diagnosis was compatible with aggressive CGCG. To confirm the origin of giant cells, the tissue was analyzed by immunohistochemistry by cytokeratin expression and giant cells were found to be positive for cytokeratin which confirmed the diagnosis (Figure 7). Clinical and radiographic examination after six months following surgery revealed uncomplicated recovery and no recurrence.

## DISCUSSION

CGCG is an intra-osseous destructive lesion of jaws which has definite predilection for mandibular anterior region and has a tendency to cross the midline though controversial results also exist<sup>[4-7]</sup>. It rarely occurs in areas elsewhere other than the jaws like maxillary sinus, temporal bone, cranial vault and other bones of the craniofacial complex<sup>[4]</sup>.

The etiopathogenesis of CGCG can be an exacerbated reparative process related to previous trauma and intraosseous hemorrhage that triggers the reactive granulomatous process<sup>[8,9]</sup>. In the present case, we can assume that trauma due to extraction might be responsible for change in behavior (rapid progress) of the lesion since the lesion grew rapidly and perforated intraorally after molar extractions. Similar such cases are rarely reported in the literature<sup>[9,10]</sup>. However, this type of clinical presentation is commonly observed in oral malignancy which was ruled out by radiographic examination in the present case.

Basically CGCG is a benign entity but based on its clinical behavior and radiographic features, it has been classified into non-aggressive and aggressive variety<sup>[1,11]</sup>. Aggressive CGCG is found in younger patients while in this regards, the present case was

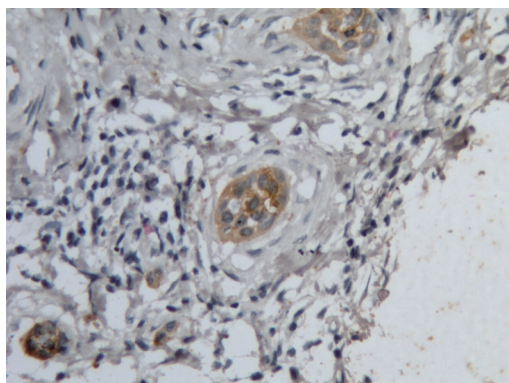


Figure 7 Immunohistochemical expression of cytokeratin in giant cells.

distinct showing features of aggressive variety at advanced age.

Although aggressive lesion is expansive and invasive, paresthesia is usually not observed in these patients. However, Whitaker *et al*<sup>[5]</sup> reported paresthesia in 6% of their cases. Bataineh *et al*<sup>[12]</sup> have suggested the remedy to avoid distressing paresthesia or painful dysesthesia.

Amongst aggressive and non-aggressive types of CGCG, the controversial reports are observed in histologic differences. Few authors stated that there are no histologic differences between aggressive and non aggressive varieties<sup>[1,11]</sup>. Ahuja *et al*<sup>[13]</sup> reported high cellularity and a vesiculated fibroblastic population in aggressive CGCG while a minimal-moderate cellularity and a non vesiculated fibroblast population in non-aggressive cases<sup>[13]</sup>. Shetty *et al*<sup>[14]</sup> explained that the number of giant cells and number of nuclei within alone does not determine aggressive nature and recurrence of CGCG.

CGCG can present different radiological features, from small unilocular radiolucent lesions to extensive multilocular radiolucent areas. Wood *et al*<sup>[6]</sup> reported that the lesion may initially occur as a solitary-cyst like radiolucency and as it grows larger it may develop architecture of a soap bubble or honeycomb type of multilocular radiolucency. Presence of wispy trabeculae within the lesion is the most significant radiographic sign associated with CGCG<sup>[2,5,6]</sup>. Though radiolucent is the commonest radiographic internal structure of CGCG (87.5%), Kaffe *et al*<sup>[7]</sup> have observed mixed (10%) and radiopaque (2.5) appearances too. Generally the periphery of CGCG is well defined but many times it presents with ill defined, diffused borders<sup>[7,15]</sup>. There may be a cortical radiopaque halo and dental displacement or root resorption<sup>[1,2]</sup>. Stavropoulos *et al*<sup>[16]</sup> and Jose *et al*<sup>[15]</sup> have found radicular resorption in 37% and 15.4% of cases respectively.

Overall above description suggests that the clinical and radiographic features of CGCG are non pathognomic and are often confused with several other lesions of the jaws that pose challenge to oral diagnostician. In this case also the provisional diagnosis considered

was oral malignancy and radiological diagnosis was ameloblastoma. The present case justify radiographic examination before extraction of molars as failure of which resulted in an extensive lesion involving the body and ramus entirely due to modification in behavior of lesion following extractions. It also suggests inclusion of CGCG in jaw swellings associated with mobility of teeth and failure of healing sockets.

It is equally important to exclude brown tumors associated with hyperparathyroidism from CGCG as they share identical clinical and radiological features<sup>[15]</sup>. This differentiation depends on laboratory tests for investigating serum levels of calcium, phosphorus and alkaline phosphatase which, in cases of hyperparathyroidism, present alterations<sup>[2]</sup>. Ahuja *et al*<sup>[13]</sup> presented difficulty in diagnosing aggressive CGCG from Giant cell tumors with which they share similar histopathology, behavior and prognosis. Histologically, CGCG is indistinguishable from other giant cell lesions of the bone like cherubism and aneurysmal bone cyst too. But, in the present case immunohistochemical expression of cytokeratin in giant cells helped to confirm the diagnosis. In multiregional cases of CGCG, cherubism, neurofibromatosis type 1 and Noonan syndrome must be considered in differential diagnosis<sup>[6,17]</sup>. A combination of CGCG with some other lesions like fibro osseous lesions called as hybrid lesions is also reported in the literature<sup>[18,19]</sup>.

Traditionally the most accepted treatment of CGCG of the jaws is surgical while successful medicinal treatment modalities are also reported in the literature; each has got its own advantages and disadvantages<sup>[20-22]</sup>. Surgical approach may result in loss of teeth, disfigurement and loss of dental germs (in younger patients)<sup>[12,23]</sup>. Whitaker *et al*<sup>[5]</sup> have mentioned the recurrence rate of CGCG as 4% to 20% and the reasons were larger lesion and incomplete removal of the tumor. Radiation therapy is contraindicated in CGCG<sup>[3]</sup>.

An alternative nonsurgical approaches are intralesional corticosteroid injections, calcitonin injections and subcutaneous interferon injections<sup>[20,23,24]</sup>. Weekly intralesional injections of corticosteroids are believed to inhibit the bone resorption by controlling proliferation and differentiation of osteoclasts. However, this is contraindicated in certain conditions like diabetes mellitus, peptic ulcer and immunocompromised state<sup>[21,23,24]</sup>. Calcitonin act by inhibiting the calcitonin receptors that are present on giant cells thereby inhibiting osteoclastogenesis<sup>[17,25]</sup>. Interferons have anti-angiogenic effect and inhibition of bone resorption<sup>[1]</sup>. Nalan *et al*<sup>[26]</sup> have used the combination of surgical and medicinal treatment in their patient. Non surgical treatment options are simple, inexpensive, save vital structures and avoid facial deformity<sup>[2,23]</sup>.

In conclusion, though the classic presentation of CGCG is a slow growing benign lesion in mandibular anterior region in a young patient, variable clinical appearances exist. Thus, it is still a topic of keen interest

to study about clarity in clinical behavior, radiographic features and various treatment modalities of this one of the bony lesion of jaws.

## COMMENTS

### Case characteristics

A 46 years old male had reported with a rapidly increasing intraoral and extraoral swelling of lower jaw following tooth extraction.

### Clinical diagnosis

Extraorally bony hard, non-tender swelling on lower right side of face and exophytic soft tissue growth from the residual socket intraorally.

### Differential diagnosis

Provisional diagnosis was malignant tumor.

### Laboratory diagnosis

Serum calcium, phosphorus, alkaline phosphates, and parathyroid hormone which were within normal limits. Thus, exclude the brown tumor of the hyperparathyroidism.

### Imaging diagnosis

Lateral mandibular occlusal view and a panoramic radiograph showed single large multilocular radiolucent lesion having well defined periphery with predominant buccal and lingual expansion and thinned-out of cortical plates suggested benign tumor like ameloblastoma.

### Pathological diagnosis

Biopsy showed highly cellular fibrous connective tissue stroma, which consisted of many plump fibroblasts, extravagated blood elements and numerous multinucleated giant cells. These features were diagnostic of central giant cell granuloma (CGCG).

### Treatment

Surgery was chosen as a treatment of choice.

### Related reports

Immunohistochemistry by cytokeratin expression and giant cells were found to be positive for cytokeratin which confirmed the diagnosis of CGCG.

### Term explanation

An aggressive variety of CGCG which was augmented following extraction of teeth is described.

### Experiences and lessons

The necessity of radiographic examination prior to extraction of teeth, and the importance of early histopathological examination, if extraction socket fails to heal should not be underestimated.

### Peer-review

The case report shows some valuable information to understand the diagnosis and treatment for this disease in future. The manuscript is written well and organized reasonable.

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## Controversy of silver amalgam as a restorative material

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**Core tip:** This editorial highlights the importance of silver amalgam restoration in restorative dentistry.

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### INTRODUCTION

The most widely used dental restorative material for posterior teeth is silver amalgam. Amalgam is naturally adhesive to teeth and is long-lasting, for these reasons Amalgam has served the dental profession for decades. Although there has been scientific and political efforts to stop Amalgam being used as a dental restorative material (Minamata Convention on Mercury, January 2013)<sup>[1]</sup>. The continued use of Amalgam in dentistry is controversial since many people believe its use should be prohibited. However, attempts to completely replace Amalgam with composite resins and other dental materials has failed because no other materials can match Amalgam in terms of its low cost, ability to withstand wear and breakage, and its longevity as a restorative material. These are the properties which makes Amalgam the first choice of most of the Worlds dentists for posterior restorations. Silver amalgam has distinctive qualities which endears itself to the clinician. Considering its uniqueness as a substantial restorative material, compared to other commercially available tooth colored/esthetic materials, which can also be toxic<sup>[2,3]</sup>. The advantages of amalgam must generally outweigh its dangers, because it is still widely used, even though some countries have prohibited its use in dentistry. Very few articles in the, scientific literature associate dental amalgam with toxic effects

### Abstract

Silver amalgam contains mercury leading to concerns about the potential toxic effects of amalgam on the health of dental patients. The debate over the toxicity of silver amalgam restorations has divided the dental profession for over a century. The use of amalgam restorations for anterior teeth have been declining worldwide due to patient's safety concerns and preference for tooth colored restorations. Nevertheless, amalgam has served the dental profession for decades and benefited hundreds of millions of patients because of its longevity as a dental restorative material. Amalgam is still the World's most widely used restorative material for posterior teeth.

**Key words:** Esthetic resorations; Silver amalgam; Toxicity



or damage to the health of patients, therefore it seems over-reactive to prohibit the use of Amalgam for the restoration of teeth. Instead, researchers should be developing improved formulations of Amalgam to reduce its potential for toxicity and to improve its clinical performance.

Toxic materials are sometimes needed in dentistry. Sodium hypochlorite is extremely toxic<sup>[4,5]</sup>, but is the most widely used root canal irrigating solution in endodontics<sup>[4,5]</sup>. Radiation used to take x-rays can be dangerous in high doses. Some wavelengths of light, such as ultraviolet light can cause damage to eyes, and can be linked to deleterious health effects like cancer, depressions, heart disease, etc<sup>[6]</sup>. Despite the potential health risks, toxic materials and radiation are still commonly used in dentistry, because similar to Amalgam the risks can be managed to avoid causing harm to patients. This explains why even with so much controversy, that Amalgam is still the most widely used restorative material for posterior teeth.

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## Periosteal pedicle graft for the treatment of gingival recession: A viable alternative to sub-epithelial connective tissue graft

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**Core tip:** The periosteal pedicle graft (PPG) is an emerging technique to treat gingival recession defects and has advantages over subepithelial connective tissue graft (SCTG). The technique not only provides a viable treatment option to manage gingival recessions without involving two surgical sites and additional cost but also produced results which have raised the question whether PPG can replace SCTG in near future?

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### Abstract

Treating gingival recessions is important to satisfy the functional and aesthetic needs of the patients. Among various available techniques to treat gingival recessions, the subepithelial connective tissue graft technique is still considered to be the best despite its inherent disadvantages. The recent innovation utilising periosteum as a pedicle graft to treat gingival recession defects has drawn considerable attention and may provide a viable alternative to subepithelial connective tissue graft.

**Key words:** Periosteal pedicle graft; Gingival; Recession;

### INTRODUCTION

Gingival recession defect (GRD) is among the most common condition for which the patients seek professional dental care. If neglected, gingival recession may not only result in functional problems like dentinal hypersensitivity and root caries but may also lead to unaesthetic facial appearance. The consequences of gingival recession defects are well recognized by the dental professionals and numerous treatment options have been suggested to resolve GRD. Among all the techniques utilised to treat GRD, ranging from restorative to prosthetic to surgical measures, the mainstay of treatment is still the periodontal plastic surgery. The surgical techniques applied to cover denuded root surfaces mainly utilize soft tissue autografts, which may be either free or pedicle and

harvested adjacent to the GRD or from the palate. Although many techniques have been proposed for the treatment of GRD, a detailed review of the scientific literature clearly rates the Sub-epithelial connective tissue graft (SCTG) better than all other techniques owing to the excellent post treatment aesthetic outcomes and sustained long term results associated with the SCTG<sup>[1]</sup>. Despite the fact that SCTG is considered to be the gold standard for the treatment of GRD the search for a technique which eliminates the inherent limitations associated with SCTG (two surgical sites, increased patient trauma, postoperative complications) is still on. The use of acellular dermal matrix graft and GTR membranes has also been proposed to improve patient centred outcomes in addition to clinical outcomes but the techniques have failed to gain the popularity due to the associated increased cost of treatment and uncertain predictability of these procedures<sup>[2]</sup>. Recently, the use of periosteum has been suggested for the treatment of GRD and has drawn considerable attention<sup>[3]</sup>. Although the use of periosteum in regenerative therapies is not new and it has been used successfully in the treatment of bony defects by the oral and maxillofacial surgeons, orthopaedicians and periodontal surgeons<sup>[4,5]</sup> but the idea to utilize the periosteum as a pedicle graft for treatment of soft tissue defects like GRD is innovative and interesting. The detailed technique utilizing the periosteum as a pedicle and the term "Periosteal Pedicle Graft (PPG)" for the treatment of single tooth GRD were first published in the Australian dental journal in 2009<sup>[3]</sup> and later the technique was successfully used to treat adjacent multiple gingival recession defects for the first time in 2011<sup>[6]</sup>.

Since the invention of the PPG technique multiple studies have been done and have shown encouraging results both in terms of root coverage and patient satisfaction<sup>[7-11]</sup>, the reasons suggested for the successful treatment outcomes include: (1) PPG can be harvested adjacent to the GRD eliminating the use of second surgical site thus minimising intra-operative trauma and postoperative complications; (2) There is no limitation to the amount of the graft that can be harvested in case of PPG hence PPG can be used effectively to treat multiple adjacent gingival recession defects; (3) Since periosteum is highly vascular and PPG is ideal for placement over avascular root surfaces; (4) Owing to the presence of stem cells in the periosteum there is an actual possibility of new attachment during the healing period; and (5)

Patients are more satisfied with procedures which require minimum intra-operative trauma and postoperative complications hence PPG scores better in terms of patient satisfaction over SCTG.

Considering the above facts and current evidence it may be concluded that PPG has emerged as a viable option for the treatment of GRD with a great possibility to regenerate the lost periodontal tissues and form a new attachment at the treated gingival recession site, although it is still uncertain whether it will achieve the status at par with SCTG because for that to happen the technique will have to pass the test of time.

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## Platelet preparations in dentistry: How? Why? Where? When?

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**Core tip:** Autologous platelet concentrates (platelet-rich plasma, platelet rich fibrin, plasma rich in growth factors, concentrated growth factor), are blood derivatives, prepared from patient's own blood, reach in platelets, growth factors and cytokines, which can be used to promote guided tissue regeneration in dentistry and oral surgery.

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### Abstract

The aim of this article is to review the outcomes of platelet preparations in dentistry. A structured electronic search discovered 348 articles, which described the use of autologous platelet concentrates with a relevance to clinical dentistry. Among these articles, 220 articles investigated platelet rich plasma, 99 investigated platelet rich fibrin, 22 investigated plasma rich in growth factors and 7 investigated the use of concentrated growth factors. Several studies reported beneficial treatment outcomes in terms of enhanced bone and soft tissue regeneration.

### INTRODUCTION

Bone and soft tissue regeneration is frequently required in dentistry, mainly but not exclusively for implantology and periodontology. Tissue regeneration is a complex process of healing and tissue growth, which involves different biological elements and strategies. These include the use of bone grafts<sup>[1,2]</sup>, biomaterials and growth factors<sup>[3]</sup>, natural or synthetic scaffolds and more recently the use of stem cells<sup>[4,5]</sup>. Nowadays, a whole range of modern surgical procedures and a variety of dental materials are available. These are performed to reconstruct bony defects of the upper and lower jaw and for augmentation of lost structures of the residual alveolar ridge. Autologous platelet concentrates are a promising and innovative therapeutic approach in various medical fields, including dentistry<sup>[6-10]</sup>. Platelets play a crucial role not only in hemostasis, but also in the



wound healing process, as they are reservoirs of growth factors and cytokines, which in turn are key promoters for bone and soft tissues regeneration. After platelets are activated, they become trapped within a fibrin matrix and release growth factors. Together the fibrin can form a scaffold and the growth factors can stimulate tissue healing and regeneration repair responses. An improved understanding of the physiologic properties of platelets in wound healing over the last two decades, has led to more successful therapeutic applications, especially in oral surgery.

### **Platelet concentrates**

Platelet concentrates are blood derivatives<sup>[11,12]</sup>, prepared from the patient's own blood and containing autologous platelets, growth factors and cytokines involved in the key processes of tissue regeneration, including cell proliferation and differentiation, extracellular matrix synthesis, chemotaxis and angiogenesis. Platelets are packed with secretory granules, which are necessary to fulfill their functions. There are three types of secretory granules,  $\alpha$  granules are the most abundant and have a high protein content. The granules contain cytokines and growth factors, such as vascular endothelial growth factor, epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, hepatocyte growth factor and the insulin-like growth factor as well as several others. The release of these growth factors from activated platelets can promote healing in both soft and hard tissues.

Most platelet concentrate preparations used in guided tissue regeneration surgery are termed Platelet-Rich Plasma (PRP), even if they differ slightly according to their preparation from a patient's peripheral blood. These variations include differences in centrifugation speeds and times, differences in adding chemicals, and differences in the selection of supernatants and precipitates. These variations can cause differences in fibrin network structures and in platelets, leucocyte and growth factors content. Therefore the term PRP alone can be non-specific, because it does not define the actual preparation protocol. Depending on the leukocyte content and fibrin architecture, five main categories of PRPs can be defined: (1) Pure Platelet-Rich Plasma, such as cell separator PRP, Vivostat platelet rich fibrin (PRF)<sup>[13]</sup> or Anitua's PRGF<sup>[14,15]</sup>; (2) Leukocyte and Platelet-Rich Plasma; (3) Pure Platelet-Rich Fibrin, such as Fibrinet; (4) Leukocyte- and Platelet-Rich Fibrin, such as Choukroun's PRF; and (5) Concentrated growth factors (CGF). In the following paragraphs, the use of PRP, PRF, plasma rich in growth factors (PRGF) and CGF in dentistry and oral surgery will be reviewed.

### **PRP**

PRP is blood plasma that has been enriched with platelets and it was the first generation of platelet concentrates to be used in clinical practice by Marx in 1998<sup>[16]</sup>. PRP has a platelet concentration of  $1000 \times 10^9/L$  in 5 mL of plasma, which is 3-5 times higher

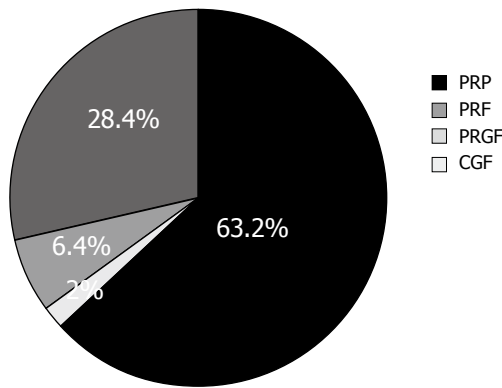
compared to the normal whole blood platelet count ( $150-400 \times 10^9/L$ ). PRP contains (and releases through platelet degranulation) several growth factors and cytokines that can stimulate bone and soft tissue healing<sup>[17-19]</sup>. PRP is prepared by drawing peripheral venous blood from a patient's arm. The fresh blood is immediately mixed with an anti-coagulant to prevent clotting and then the platelets are concentrated using a two-step gradient centrifugation method<sup>[20]</sup>. In this method, the first spin (called the hard spin) separates the red blood cells (RBCs) from the plasma containing platelets, leukocytes and clotting factors, the second spin (called the soft spin) is used to delicately separate the platelets and leukocytes, from the plasma. The soft spin produces PRP and separates it from the platelet-poor plasma (PPP), free from the interference associated with large number of red blood cells. Commonly, with commercially available systems, a one-step method is used to separate the RBCs, buffy coat and plasma into three distinct layers. The buffy coat contains platelets and leukocytes and is often collected as PRP. The top plasma layer is often called PPP, which is discarded, leaving the PRP to be injected into surgical sites to accomplish guided tissue regeneration.

### **PRF**

PRF consists of an intimate assembly of cytokines, glycanic chains, structural glycoproteins enmeshed within a fibrin network, and is considered to be the second generation of platelet concentrates<sup>[21-23]</sup>. The cytokines, glycanic chains, structural glycoproteins can have synergetic effects on tissue healing processes. The PRF pioneers were Choukroun *et al.*<sup>[24,25]</sup>, who used it to promote the osseointegration of dental implants. Several studies have demonstrated the clinical effectiveness of autologous PRF to regenerate defects in hard and soft tissues. The preparation of PRF is similar to PRP and consists in collecting peripheral venous blood from the patient's arm. Except that no anti-coagulant is used during blood harvesting. After the blood is collected it is immediately centrifuged for 10 min to activate the platelets, leading to the initiation of a coagulation cascade. After centrifugation, the blood is separated into three different layers: acellular PPP (platelet poor plasma) on top, a PRF clot in the middle and RBCs at the bottom of the test tube. The PRF clot obtained after centrifugation is collected, 2 mm below the lower dividing line and the other layers are discarded. The clinical success of the PRF protocol is dependent on a quick collection of blood and its transfer to the centrifuge. Because no anti-coagulant is used, the blood sample begins to coagulate almost immediately, and a failure to accomplish the quick preparation of PRF could cause a diffuse polymerization of fibrin, which is not ideal for tissue healing.

### **PRGF**

PRGF is prepared from peripheral venous blood drawn from a patient's arm. PRGF is prepared using



**Figure 1** Number of studies with platelet rich plasma, platelet rich fibrin, plasma rich in growth factors and concentrated growth factors in dentistry up to January 2015. PRP: Platelet rich plasma; PRF: Platelet rich fibrin; PRGF: Plasma rich in growth factors; CGF: Concentrated growth factors.

a modified PRP protocol developed by Anitua<sup>[26-28]</sup>. The difference between PRGF and PRP is that PRGF is optimized to deliver a more sustained release of growth factors. PRGF can create a three-dimensional fibrin scaffold which can be injected into a tissue defect, to maintain the regenerative space and can be used as a scaffold for cells to accomplish tissue regeneration. The Leukocyte content of PRGF is eliminated to prevent the pro-inflammatory effects of the proteases and acid hydrolases contained within these cells. PRGF is prepared from a small volume of patient's peripheral venous blood and is collected by a one-step centrifugation using sodium citrate as the anti-coagulant (Endoret System, Biotechnology Institut, Minano, Alava, Spain). After activation, PRGF progressively releases a pool of proteins and growth factors, which accelerate soft tissue healing as well as bone regeneration. Different formulations of PRGF with therapeutic potential can be obtained from a patient's blood depending on the degree of coagulation and activation of the samples. PRGF supernatant can be used as conventional eye-drop solution and cell culture media solution; liquid PRGF can be used to coat dental implant surfaces to promote osseointegration; the fibrillar and cellular scaffold-like PRGF can be used to fill tissue defects as part of ulcer treatment, sealing tooth sockets after tooth extraction, and promoting the epithelialization of soft tissues.

### CGF

CGF, first developed by Sacco, in 2006, is an autologous fibrin network, rich in leukocytes and platelets<sup>[29,30]</sup>. CGF also contains autologous osteo-inductive growth factors derived from platelets and an osteo-inductive fibrin matrix. Similar to PRF, CGF is created using a one-step centrifugation method, but it requires a special programmed centrifuge (Medifuge MF200, Silfradent srl, Forli, Italy), which uses plastic tubes, coated with silica particles, and without the addition of exogenous substances. The final blood product is separated into three layers, two are discarded, and the CGF is collected

**Table 1** Number of different studies published in the literature using platelet rich plasma, platelet rich fibrin, plasma rich in growth factors and concentrated growth factors in dentistry

Study type	Platelets concentrates			
	PRP	PRF	PRGF	CGF
Clinical trials	116	50	13	1
Animal studies	46	13	5	1
<i>In vitro</i> studies	20	17	2	1
Technical report	3	1	0	2
Case report	35	18	2	2

PRP: Platelet rich plasma; PRF: Platelet rich fibrin; PRGF: Plasma rich in growth factors; CGF: Concentrated growth factors.

from the buffy coat layer, which consists of a dense fibrin matrix that is rich in growth factors.

## STUDY STRATEGY

A structured electronic search of scientific papers up to January 2015, was conducted using two medical databases (PubMed and the Cochrane Library) and specific keywords: "platelet concentrates in dentistry", "PRF", "Platelet rich fibrin Choukroun", "platelets in dentistry and maxillofacial surgery", "PRP", "CGF", "PRGF", "periodontal regeneration". For each of these platelet concentrate categories, their therapeutic potential in dentistry was evaluated according to the following inclusion criteria: (1) clinical trials; (2) animal studies; (3) *in vitro* studies; (4) case reports; and (5) technical reports. Subsequently, the articles for each type of platelet concentrate (PRP, PRF, PRGF and CGF) were classified according to these inclusion criteria and study type.

## RESULTS

A total of 563 articles were identified as meeting the inclusion criteria of investigating the clinical use of autologous platelet concentrates in dentistry. However, after all the studies not relevant to dentistry, or containing no data were excluded, 348 articles were included in this review. Of the 348 articles, 220 articles (63.2%) were about PRP, 99 articles (28.4%) investigated PRF, 22 articles (6.4%) investigated PRGF and 7 articles (2%) were about CGF (Figure 1).

The articles were classified according to the type of platelet preparations in dentistry and the type of research performed in the article, which are briefly described below and summarized in Table 1: (1) PRP: from 220 articles, 116 were human clinical trials, 46 regarded animal studies, 20 were about *in vitro* investigations, 3 were technical reports and 35 were case reports; (2) PRF: from 99 articles, 50 were human clinical trials, 13 regarded animal studies, 17 were about *in vitro* experiments, 1 was a technical report about PRF general properties and 18 were case reports; (3) PRGF: from 22 articles, 13 were human clinical trials, 5 regarded

animal studies, 2 were about *in vitro* experiments and 2 were case reports; and (4) CGF: from 7 articles, 1 was a human clinical study, 1 regarded an animal study, 1 was about an *in vitro* study, 2 were technical reports about CGF properties and its application in dental implantology and 2 were case reports.

### **PRP studies in dentistry**

PRP was used to treat periodontal intrabony defects in fifteen studies<sup>[31-45]</sup>. Nine studies described the use of PRP in cyst enucleations/periapical surgeries<sup>[46-54]</sup>. Forty-eight studies investigated PRP in sinus floor elevation treatments<sup>[55-101]</sup>. Twenty-two studies reported the use of PRP for the treatment of periodontal and periimplant defects<sup>[102-123]</sup>. Four studies used PRP for covering the roots of teeth<sup>[124-127]</sup>. Six studies investigated the efficacy of PRP for the treatment of gingival recession<sup>[128-133]</sup>. Four studies evaluated the benefits of using PRP to repair furcation defects<sup>[134-137]</sup>. Twenty-five studies investigated PRP for the repair of mandible/maxilla fractures<sup>[138-160]</sup>. Thirty-one studies investigated the use of PRP in endodontic surgery<sup>[161-188]</sup>. Eighteen studies investigated the use of PRP for dental extraction socket preservation before implant placement<sup>[189-206]</sup>. Twenty-two studies investigated the stimulating effect of PRP on alveolar bone regeneration and reconstruction<sup>[207-224]</sup>. Eight studies investigated the use of PRP to improve the healing and regeneration of soft tissues<sup>[225-231]</sup>, mostly for periodontal ligament repair, and reducing the incidence of complications. Eight studies investigated PRP using *in vitro* protocols to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts<sup>[232-237]</sup> (Figure 2).

### **PRF studies in dentistry**

PRF was used in six studies to treat periodontal intrabony defects<sup>[238-243]</sup>. Four studies used PRF to regenerate tissue following cyst enucleations, and periapical surgeries<sup>[244-246]</sup>. Eleven studies investigated the ability of PRF to regenerate tissues following sinus floor elevation<sup>[247-256]</sup>. Eight studies investigated the use of PRF to treat periodontal and periimplant defects<sup>[257-263]</sup>. One study tested PRF as a potential root coverage repair treatment<sup>[264]</sup>. Two studies investigated the efficacy of PRF in gingival recession treatment<sup>[265,266]</sup>. Four studies investigated PRF to treat furcation defects<sup>[267-269]</sup>. Eight studies applied PRF to heal mandible or maxilla fractures<sup>[270-276]</sup>. Twenty one studies investigated the usefulness of PRF as part of endodontic surgery to repair periapical tissues<sup>[277-293]</sup>. Eleven studies investigated the ability of PRF to preserve tooth sockets after tooth extraction in preparation for dental implant placement<sup>[294-302]</sup>. Nine studies investigated the ability of PRF to stimulate alveolar bone regeneration and reconstruction<sup>[303-309]</sup>. Ten studies investigated the ability of PRF to improve the healing and regeneration of soft tissues, especially periodontal ligament, reducing complications<sup>[310-319]</sup>. Four studies investigated the

*in vitro* effects of PRF to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts<sup>[320-323]</sup> (Figure 2).

### **PRGF studies in dentistry**

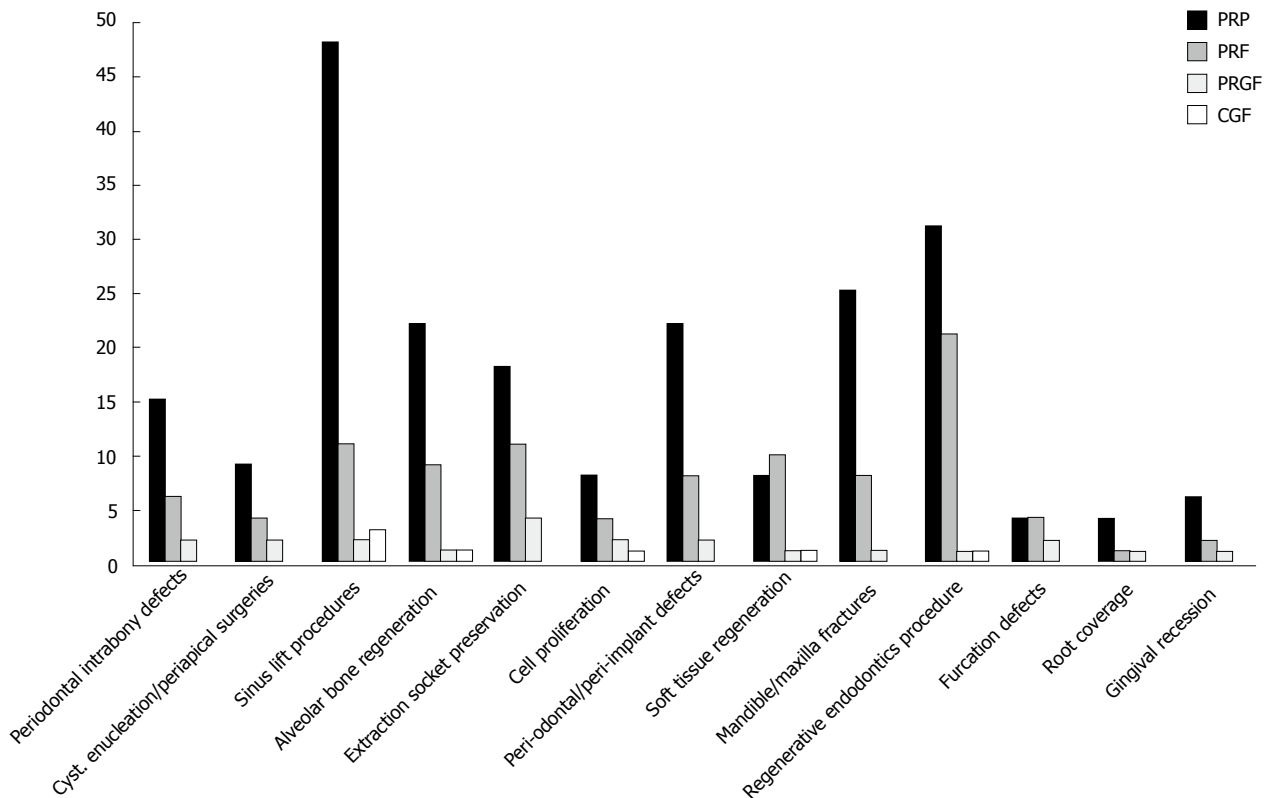
PRGF was investigated in two studies to treat periodontal bone defects<sup>[324,325]</sup>. PRGF was investigated in two studies to regenerate tissues following cyst enucleations and periapical surgeries<sup>[326,327]</sup>. The potential of PRGF to heal tissues following sinus floor elevation treatment<sup>[328,329]</sup> was reported in two studies. Two studies reported that PRGF had a positive effect on the healing of periodontal and periimplant defects<sup>[330,331]</sup>. One study investigated the use of PRF to cover the roots of teeth<sup>[332]</sup>. One study investigated the efficacy of PRGF to heal tissues following gingival recession treatment<sup>[333]</sup>. Two studies investigated the benefits of PRGF for the treatment of furcation defects<sup>[334,335]</sup>. One study investigated the effectiveness of PRGF to heal mandible/maxilla fractures<sup>[336]</sup>. One study investigated the effectiveness of PRGF to heal periapical soft tissues following endodontic surgery<sup>[337]</sup>. Four studies investigated the clinical potential of PRGF to preserve tissue in tooth extraction sockets prior to dental implant placement<sup>[338-340]</sup>. One study investigated the stimulating effect of PRGF on alveolar bone regeneration and reconstruction<sup>[341]</sup>. One study investigated the ability of PRGF to improve the healing and regeneration of soft tissues, especially the periodontal ligament<sup>[342]</sup>. Two studies investigated the *in vitro* effect of PRGF to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts<sup>[343,344]</sup> (Figure 2).

### **CGF studies in dentistry**

Compared to the other platelet articles, only a few had investigated the use of CGFs as part of dental treatment. A reason for the lack of CGF articles may be because it is newest of the platelet protocols and there has not been enough time for many articles to be published. Three studies were found which investigated CGF for tissue regeneration following sinus floor elevation<sup>[345-347]</sup>. One study investigated the *in vitro* effectiveness of CGF to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts<sup>[348]</sup>. One study investigated the healing effects of CGF for tissue repair following endodontic surgery<sup>[349]</sup>. Two studies investigated soft tissue and periodontal ligament healing after using CGF to accomplish guided tissue regeneration<sup>[350,351]</sup> (Figure 2).

## **DISCUSSION**

Dentists have different types of biomimetic biomaterials to help guided bone and soft tissue regeneration. All these biomaterials have advantages and limitations and no single type of biomaterial has all the properties needed to be the universal dental regeneration biomaterial. A natural scaffold regeneration material is the blood clot, and several protocols have been



**Figure 2** Platelet rich plasma, platelet rich fibrin, plasma rich in growth factors and concentrated growth factors application in dentistry up to January 2015. PRP: Platelet rich plasma; PRF: Platelet rich fibrin; PRGF: Plasma rich in growth factors; CGF: Concentrated growth factors.

developed to improve the scaffold and growth factor properties of the blood clot (PRP, PRF, PRGF and CGF). These platelet rich preparations have been shown to improve healing, quicken tissue regeneration, improve the quality of tissues that are regenerated, and to reduce the incidence of complications. Alternatively, there are also many studies, which have shown that platelet rich preparations had little or no effect on tissue healing in comparison to biomimetic scaffolds. This explains the need to carefully investigate the uses of platelet concentrates as part of dental treatments.

After the careful analysis of the literature, the follow questions could be asked: (1) How is platelet rich fractions of blood prepared? (2) Why use platelet concentrates in dentistry? (3) Where to use platelet concentrates in dentistry? and (4) When to use platelet concentrates in dentistry?

The answer to the first question about how platelet rich fractions of blood are prepared, was answered in the previous paragraphs. All the techniques involve the centrifugation of the patient's peripheral venous blood and the use of fractions containing fibrin, platelets, leukocytes and growth factors. Red blood cells are discarded.

The answer to the second question about why platelet concentrates are used in dentistry is because they are cheap natural scaffolds and source of growth factors to stimulate tissue regeneration. Platelet concentrates are biocompatible and can sometimes

offer potential benefits including rapid wound healing and bone regeneration. A controversial advantage is a reduction of postoperative pain and an unequivocal advantage is the lack of risk of infectious disease transmission. Sometimes platelet concentrates cannot be used where a patient does not want to donate their own blood, or when a special-needs patient or child refuses to cooperate with the collection of their blood.

The answer to the third question about why autologous platelet concentrates are used in oral and maxillofacial surgery and periodontal regenerative therapy is because of some promising results for tissue regeneration following sinus floor elevation (especially with PRP and CGF)<sup>[55-101,345-347]</sup>, bone filling of periodontal intrabony defects<sup>[102-123,238-243,324,325]</sup>, regeneration of alveolar ridges<sup>[207-224,303-311,343]</sup>, dental extraction socket preservation<sup>[189-206,294-302,338-340]</sup>, gingival recession treatment<sup>[128-133,265,266]</sup>, mandibular and maxilla fractures<sup>[138-160,270-276,333]</sup>. Platelet concentrates have been used to manage bisphosphonate-related osteonecrosis of the jaw to enhance wound healing and bone maturation<sup>[271,272,352]</sup>.

The answer to the fourth question about when to use platelet concentrates is the most difficult to reach for most dentists. A general rule of guidance is to use platelet concentrates, scaffolds, or biomaterials, in surgical situations where the prognosis for tissue repair is poor in the absence of a tissue regeneration scaffold and addition of growth factors<sup>[225-231,310-319]</sup>.



## CONCLUSION

In conclusion, platelets concentrates represents innovative tools in dentistry. The results, demonstrate that these concentrates are effective at improving bone and soft tissues healing. Moreover, well-enhanced bone regeneration can be obtained when PRP, PRF and CGF are used together with autogenous bone, with recombinant human growth factors such as recombinant BMP and also with other biomaterials (as for example Bio-Oss- Geistlich-Switzerland and Hydroxyapatite)<sup>[95-96]</sup>. However, the definition and validation of accurate protocols is a key issue for the long-term development of these techniques. So for further research is required to establish a standardized protocol for the use of these concentrates in the treatment of tissue regeneration.

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## Salivary gland disorders: A comprehensive review

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viral, bacterial, rarely fungal or its ductal obstruction which may cause painful swelling or obstruction, affecting their functions. The salivary gland may also be affected by a various benign and malignant tumours. This review article briefly describes about the various salivary gland disorders, diagnostic techniques and their management including the recent advances and the future perspective.

**Key words:** Salivary gland disorders; Xerostomia; Salivary biomarker; Salivary diagnostics; Exocrine glands

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**Core tip:** The aim of this article was to analyse detailed aspects of various salivary gland disorders, their diagnostic and therapeutic advances in the prevention and management of salivary gland diseases of the oral cavity, including the recent developments and their future perspective.

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### Abstract

Salivary glands are complex in nature. They could be either tubulo acinar, merocrine or exocrine glands secreting mainly saliva. Salivary gland is one of the main soft tissue structures in the maxillofacial area. Saliva is a clear, slightly acidic muco serous fluid that coats the teeth, mucosa and thereby helps to create and maintain a healthy environment in the oral cavity. Salivary glands may be affected by a number of diseases: local and systemic and the prevalence of salivary gland diseases depend on various etiological factors. The glands may be infected by

### INTRODUCTION

A gland consists of specialized type of cells, wherein they produce products which are used elsewhere in the body. Salivary glands are complex, tubulo acinar, exocrine or merocrine glands secreting mainly saliva. Saliva is the product of the major and minor salivary gland dispersed throughout the oral cavity. It is a complex mixture of organic, inorganic components and water, carrying out several functions. There are three pairs of major salivary glands namely parotid, sub mandibular and sublingual glands in addition to numerous minor salivary glands in the oral cavity<sup>[1]</sup>.

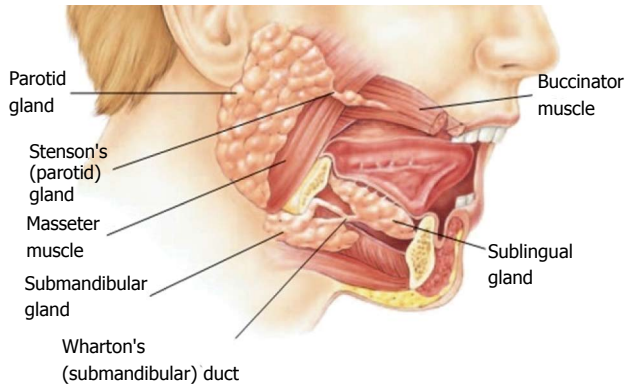


Figure 1 Major Salivary Glands and their related structures.

## SALIVARY GLANDS DEVELOPMENT AND ANATOMY

The development of the parotid gland starts from 4-6<sup>th</sup> week, the submandibular gland at 6<sup>th</sup> week and the sublingual gland including minor salivary glands develops at 8-12 wk of embryonic life. The various developmental stages are: Bud formation, Epithelial cord formation, Branching and glandular differentiation, canalization and cyto differentiation. The parotid is ectodermal while the submandibular and sublingual glands are endodermal in their origins. The parotid represents the largest of the salivary gland which is situated between the external acoustic meatus between the ramus of the mandible and sternocleidomastoid muscle. Each gland is encapsulated and is composed of fat tissue and cells that secrete mainly the serous fluids. The major duct of each parotid gland is called Stensen's duct which opens into the vestibule of the mouth opposite the crown of the upper second molar tooth. The parotid gland being primarily serous in secretion secretes watery serous saliva<sup>[2]</sup>.

The submandibular glands are located along the side of the lower jawbone in the anterior part of digastric triangle. Each gland has a major duct called Wharton's duct which opens on the floor of the mouth, on the summit of sublingual papilla at the side of frenulum of the tongue. Each of these glands is covered by a capsule which gives off mixed serous and mucous secretion in nature. The sublingual glands are the smallest of the major salivary glands which lies above mylohyoid and below the mucosa of the floor of the mouth. They are not covered by a capsule and are therefore more dispersed throughout the surrounding tissue. Their secretions are drained by many small ducts known as Rivinus's ducts that exit along the sublingual fold at the floor of the mouth. Sometimes, few anterior ducts may join to form a common duct called Bartholin's duct, their secretion being mixed in nature which empties into Wharton's duct. The sublingual and minor salivary glands are primarily mucous in nature.

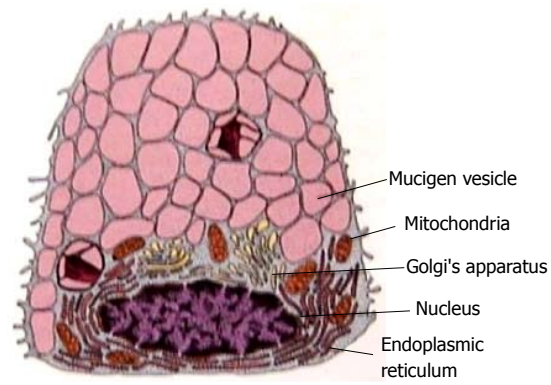


Figure 2 Mucous secreting cell showing Mucigen vesicle.

### Types

Salivary glands can be classified according to size as major and minor glands. The major salivary glands are of three pairs namely the parotid, submandibular and sublingual glands are shown in Figure 1. There are a numerous minor glands present in labial, buccal, glosso palatine, palatine and lingual areas in the oral cavity.

Based upon the type of secretion salivary glands may be predominantly serous, mucous or mixed depending on the type of secreting cells. Parotid and Von Ebners glands are purely serous while minor salivary glands like glosso palatine, palatine and anterior lingual glands are purely mucous. The mixed types of salivary glands are submandibular, sublingual, labial, buccal and posterior lingual glands.

### Histology of salivary glands

Each gland has the secretory unit which is mainly composed of acinus, myoepithelial cells, intercalated duct, striated and excretory ducts. The acinus could be serous, mucous or mixed. These acini contain amylase granules in serous and granules with mucin in mucous glands and are responsible for producing primary secretion is shown in Figures 2 and 3. The secretory granule in mixed salivary glands contains serous demilunes, capping mucous acinar cells (Demilunes of Gianuzzi or Heidenham) producing sero mucous saliva. The ductal system of the salivary gland has a varied network. The three classes of ducts are intercalated, striated, and excretory each with different structure and function.

**Saliva:** It is mainly secreted and produced by the salivary gland. The total volume of saliva secreted daily in an adult person is 600-1000 mL out of which 60% is secreted by the submandibular glands, 30% by the parotid, 5% by the lingual and 7% by the minor salivary glands with a pH in the range of 6.0-7.0. However, the salivary secretion is a reflex action arising from the salivary centres dependent on afferent stimulation. The sublingual and minor salivary glands spontaneously secrete saliva though the bulk of this secretion is nerve

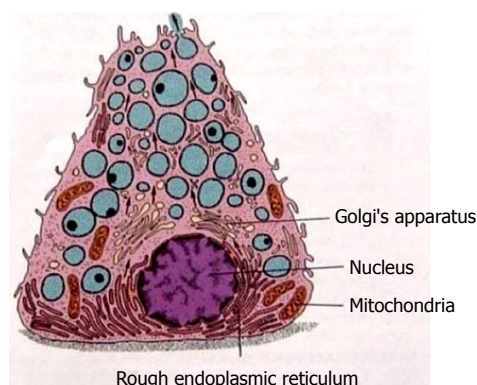


Figure 3 Serous secreting cell with secretory granules.

mediated. The normal average salivary flow rate ranges from 0.1-0.3 mL per minute<sup>[3]</sup>.

### Composition

Saliva is mainly composed of the following components. Electrolytes like sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, thiocyanate, and fluoride. Secretory proteins/Peptides like Amylase, proline rich proteins, mucins, histatin, cystatin, peroxidase, lysozyme, lactoferrin, glycoproteins, lysozyme, defensins, and cathelicidin LL37. They also contain secretory immune globulins-(IgA), IgG, IgM, organic components like, glucose, amino acids, urea, uric acid, and lipid molecules. The other components that are present are epidermal growth factors, epithelial cells, insulin, cyclic adenosine monophosphate, binding proteins and serum albumin. In addition, biologically active peptides such as leptin, ghrelin and endothelin which are identified in saliva are of supreme importance to general health and also oral health in particular<sup>[4-9]</sup>. Functions: saliva mainly helps in lubrication for the movement of oral tissues against each other and the food, aids in digestion, in taste perception, neutralises by its buffering action the bacterial acids and thereby promotes remineralisation by reducing dissolution of enamel by inhibition of calcium phosphate precipitate. The saliva over all protects the teeth and the oral mucosa by the presence of immunoglobulin's tissue repair factors and antibacterial system<sup>[4]</sup>.

### Oral diagnostic approaches to the patients with salivary gland disorders:

(1) Past and Present History: to enquire about the history of patient who had undergone any surgery/radiotherapy, or have any underlying systemic problems/the patient is under any medications, etc. A thorough medical history and physical examination are also essential; and (2) Clinical Examination; a study by Navazesh suggests four clinical measures to diagnose the hypo function in the salivary gland. They are dryness of the lips and buccal mucosa, absence of saliva produced by the gland, bimanual palpation, and DMFT scores<sup>[5]</sup>.

For evaluations of Dry mouth and a salivary mass or enlarged salivary gland, the following diagnostic

approached may be applied: (1) Imaging of salivary glands; (2) Sialography; (3) Special imaging; (4) Sialochemistry; and (5) Biopsy and culture.

**Salivary gland disorders:** (1) Developmental-Aplasia, Atresia, Aberrancy; (2) Functional Disorders-Xerostomia, Sialorrhea (Ptyalism); (3) Inflammatory-infectious conditions; acute and chronic bacterial infection; Sialadenitis, Viral infection; Mumps, Human immunodeficiency virus associated salivary gland disorder; Post irradiation Sialadenitis, chronic sclerosing Sialadenitis, cheilitis glandularis; (4) Traumatic/Obstructive-Mucocele, salivary duct cyst (mucose retention cyst, Ranula), Nicotinic stomatitis, Sialolithiasis; (5) Autoimmune-Sarcoidosis, Sjogrens syndrome, Mikulicz's disease; (6) Neurological-Frey's syndrome; (7) Degenerative-idiopathic Sialolithiasis; (8) Non inflammatory non neoplastic-Sialadenosis; (9) Vascular-Necrotizing sialometaplasia; (10) Neoplastic-Benign: Papillary Cystadenoma Lymphomatosum, Pleomorphic Adenoma, BasalCell Adenomas, Oncocytoma, Canalicular Adenoma, Myoepithelioma, Sebaceous Adenoma, and Ductal Papilloma. Malignant: Adenoid Cystic Carcinoma, Hyalinising Clear Cell Carcinoma, Mucoepidermoid Carcinoma, Acinic Cell Carcinoma, Adeno carcinoma, Carcinoma<sup>[3,6]</sup>; and (11) Classification of Salivary Gland Tumours according to WHO 2005 is listed in Table 1.

### Developmental disorders

Atresia is the congenital occlusion or absence of salivary ducts which leads to xerostomia or mucous retention cyst.

Aplasia is the complete absence of one or more salivary gland which leads to xerostomia, and affected patients are more susceptible to dental caries. This condition could be an isolated finding or associated with other disorder like hemi facial microsomia or Treacher Collins syndrome. Recent studies suggest that mutation in fibroblast growth factor 10 (FGF10) affecting the FGF receptor signalling, has been linked with this condition<sup>[7]</sup>. Enamel hypoplasia, extensive occlusal wear of teeth or congenital absence of teeth are other oral manifestations of salivary agenesis. However the treatment is supportive.

**Aberrancy:** it is an anatomic variant wherein the normal salivary gland develops at an abnormal position. Sometimes they are found adjacent to lingual surface of the mandible within a depression. Ex: Staphne's bone cyst or Staphne's bone cavity: It is thought to be created by an ectopic portion of salivary gland tissue which causes remodelling of the mandibular bone. This creates an apparent cyst like radiolucent area seen on the radiographs<sup>[8]</sup>. It appears below the inferior alveolar nerve canal in the posterior region of the mandible.

This lesion is not discovered during routine examination, as it causes no symptoms and do not require intervention. However, surgical intervention is recommended in atypical

**Table 1 World Health Organization 2005 Classification of salivary gland tumors**

Epithelial tumors
Benign epithelial tumors
Pleomorphic adenoma
Myoepithelioma
Basal cell adenoma
Oncocytoma
Canalicular adenoma
Warthins tumors
Cystadenoma
Papillary cyst adenoma
Mucinous cyst adenoma
Benign sebaceous neoplasm
Sebaceous adenoma
Sebaceous lymphadenoma
Ductal papilloma
Intraductal
Inverted ductal
Sialadenoma papilliferum
Malignant epithelial tumors
Mucoepidermoid carcinoma
Acinic cell carcinoma
Adenoid cystic carcinoma
Polymorphous low grade adenocarcinoma
Epithelial myoepithelial carcinoma
Clear cell carcinoma
Basal cell adenocarcinoma
Oncocytic carcinoma
Myoepithelial carcinoma
Adenocarcinoma NOS
Carcinoma ex pleomorphic adenoma
Metastatising pleomorphic adenoma
Carcinosarcoma
Salivary duct carcinoma
Cyst adenocarcinoma
Low grade cribriform cystadenocarcinoma
Sialoblastoma
Malignant sebaceous tumor
Sebaceous adenocarcinoma
Sebaceous lymphadenocarcinoma
Squamous cell carcinoma
Mesenchymal tumors
Benign
Haemangioma
Haemangiopericytoma
Lipoma
Neurofibroma
Schwannoma
Malignant
Fibrosarcoma
Malignant fibrous histiocytoma
Liposarcoma
Malignant lymphoma
Metastatic tumor

regions in which the diagnosis is unclear and a tumor is suspected.

### Functional disorders

**Xerostomia:** It is defined as the subjective sensation of oral dryness that may or may not be associated with a reduction in salivary output. The condition may be transient, prolonged or permanent depending upon the duration of the condition.

**Aetiology:** Temporary causes are: (1) Psychological causes due to anxiety and depression; (2) Drug therapy- Drugs that exert anti-anticholinergic and decrease the volume of serous saliva are: anticholinergic ex: atropine, anti-hypertensive ex: reserpine, methyl dopa, antihistamine ex: diphenhydramine, antidepressant: amitriptyline, antipsychotics: diazepam, anti parkinsonian drugs: procyclidine, anti-emetics: hyoscine and antispasmodics: tizandine. Drugs that exert sympathomimetic action and produce more viscous mucinous saliva with less volume are: Nasal decongestants, appetite suppressants, bronchodilators, and amphetamines. Some drugs may also exert their neural effects in higher centres of the brain, by stimulation of adreno receptors in the frontal cortex that can produce inhibitory effects on salivary nuclei's; (3) Duct calculi: a blockage of the duct of a major salivary gland (submandibular) can produce dryness on the affected side with pain and swelling in the gland on stimulation. If left untreated it can cause progressive fibrosis of the gland and permanent xerostomia; (4) infections; Sialadenitis is the inflammation of the salivary gland, acute infections like mumps and post-operative parotitis, chronic conditions like swellings related to nutritional deficiency, and iodine hypersensitivity, wherein in all these conditions causes hypo salivation<sup>[3,9]</sup>.

**Permanent causes:** (5) Salivary gland aplasia, Sjogrens syndrome: causes dry eyes, dry mouth and often associated with rheumatoid arthritis. Other systemic disorders like diabetes mellitus, Parkinson's disease, cystic fibrosis, sarcoidosis, vitamin A, riboflavin, nicotinic acid deficiencies and in anaemia's; (6) Surgery or trauma to the ducts may also impair secretion; and (7) Radiotherapy: hypo salivation occurs on exposure of major salivary glands to radiation bilaterally in head and neck cancer. At radiation doses > 3000 cGy, the patient is at risk if all major glands are in the field of radiation. Irreversible effects occur at a dose of 6000 cGy for 5 wk. Radiation causes acinar cell atrophy and fibrosis, changes in vascular connective tissue and neurologic function. The degree of salivary gland alteration depends on dose volume factor, patient age, and time of exposure to radiation. Serous acini are affected before mucous acini resulting in thick viscous secretion. Depending on the amount of salivary tissue in the field, xerostomia may resolve within 6 mo and sometimes may be permanent. There can also be changes in salivary composition, decreased secretory IgA and buffering capacity with increased magnesium, calcium, potassium and sodium chloride in post radiotherapy cases<sup>[9-11]</sup>.

**Signs and symptoms:** Lips are often cracked, peeling and atrophic; Buccal mucosa may be corrugated and pale: (1) Tongue may be smooth and reddened, cracked or fissured, with loss of papillation; (2) Increase in erosion and caries, particularly decay on root surfaces and even cusp tip involvement; (3) Erythematous form



of candidiasis is frequent; (4) Lipstick sign: occurrence of shed epithelial cells on the labial surfaces of maxillary anterior teeth as the mucosa adheres to the teeth due to reduced saliva; (5) Tongue blade sign: when held against buccal mucosa, the tissue adheres to the tongue blade as it is lifted away; (6) Viscous sticky saliva with difficulty in speaking and swallowing; (7) Halitosis, altered taste and smell, gingivitis; (8) Complaint of burning mucosa, lips or tongue; (9) Ulceration of oral mucosa; (10) No accumulation of saliva in the floor of the mouth; (11) Poorly fitting prosthesis; and (12) Enlargement of salivary glands.

**Xerostomia associated problems are:** Dental Caries, Dry mouth, Dysgeusia, Dysphagia, oral Candidiasis, and Bacterial infections<sup>[12]</sup>.

**Treatment of xerostomia associated problems:** Dental caries; use of fluorinated dentifrice (0.05% NaF)/fluoride gel in the concentration of 1% NaF, 0.4% Stannous fluoride application of 0.5% sodium fluoride varnish to teeth, regular use of re mineralising tooth paste. Dental examination every 6 mo and bitewing radiograph once a year for early diagnosis of dental caries. The recent advances in chair side diagnostics test kits are GC Salivary check-Buffer Kit that identifies, measures, and assesses patient for caries risk based on saliva conditions like hydration, consistency, pH of resting saliva and flow, and buffering capacity of stimulated saliva<sup>[13]</sup>. GC Saliva Check Mutans Kit is another chair side diagnostic kit used for rapid detection of high levels of *S.mutans* without the need for incubation is possible within 15 min. In a study, Gopinath *et al*<sup>[14]</sup> evaluated the effect of salivary testing in dental caries assessment using salivary testing kit (GC Asia Dental Pvt Ltd, Japan) and recommended adopting this test in patients with high caries risk.

A similar study conducted by Wennerholm *et al*<sup>[15]</sup> compared Saliva-Check Mutans and Saliva-Check IgA Mutans with the Cariogram for caries risk assessment and the data suggested that the combination of Saliva-Check Mutans and Saliva-Check IgA Mutans could be used for caries risk assessment.

Kanehire *et al*<sup>[16]</sup> aimed to develop a simple screening technique for the diagnosis of hypo salivation by estimation of capsaicin-stimulated salivary flow using filter paper. Five spots containing starch and potassium iodide on filter paper with or without capsaicin and a colouring reagent was designed in this assay system. The study suggested that this test would be useful for evaluating the retained functional ability of salivary glands and screening of hypo salivation with dry mouth.

Dry Mouth should be hydrated regularly using water or lozenges with citric acid to stimulate salivation, artificial salivary substitutes, lubricants such as lanolin based product Vaseline, olive oil, vitamin E or lip balm, oral gels such as oral balance, Dry mouth gel (GC Asia Dental Pvt Ltd, Japan) which can be applied on buccal

and lingual surfaces of teeth and oral mucosa which can be applied any time during the day as needed. Even mouthwashes and sprays, sugar free gums, mints water or ice chips are recommended<sup>[16,12,17]</sup>. Sialogogues like pilocarpine 5 mg 3 times a day, cevimeline 30 mg 3 times a day, bromhexine, bethanecol, and anethole trithione are prescribed. Use of Salivary substitute's solutions mainly containing electrolytes stimulates natural saliva, example Salivart, Oralube, Xerolube, Plax may also be recommended.

Application, in children 1 spray whereas in adult 2-3 sprays should be directed into the back of the mouth and tongue for the relief of dry mouth symptoms. The characteristics features that these substitutes possess are that they have electrolytes and pH similar to saliva and low viscosity allowing electrolytes particularly calcium to travel through matrix of saliva substitute which helps in remineralisation process. Mucin containing saliva orthana and Glycerate polymer are also suggested for xerostomia. There are studies suggesting the role of acupuncture therapy for improvement in salivation as a treatment option for patients responding to muscarinic agonists<sup>[17]</sup>.

Measuring biofilm activity is possible by using recently introduced simple chair side adenosine triphosphate (ATP) bioluminescence test, CariScreen (Oral BioTech, Albany, Ore) the caries susceptibility test to assess cariogenic bacterial activity and their levels in caries free and caries active patients in about 15 s measurement with a meter<sup>[18]</sup>.

### Inflammatory

Sialadenitis is an inflammation condition affecting the salivary glands. Parotid salivary glands are most commonly affected in adolescents and in children, debilitated adults, or patients with medication on tricyclic antidepressants and tranquilizers.

**Aetiology:** The main etiologic factors for sialadenitis can be either infectious or non-infectious factors. Bacterial and viral agents can cause of sialadenitis. Bacterial sialadenitis is caused because of retrograde spread of infection secondary to decreased salivary flow or ductal obstruction. Decreased salivary flow can be secondary to medications, dehydration or debilitating conditions. Ductal obstruction can be due to sialolithiasis, strictures within the ductal system and common in submandibular salivary glands or due to pressure effect from adjacent tumors.

*Staphylococcus aureus* is the most common etiologic agent for acute bacterial parotitis in addition *Staph. Pyogenes*, *Strep. Viridians* and other microorganisms can also cause sialadenitis. Viruses causing sialadenitis include paromyxo viruses (mumps-most common), Coxsackie virus, cytomegalo virus, etc. The patient may present with fever and dehydration<sup>[19]</sup>. Clinical features: clinically there is sudden pain at the angle of the jaw which is unilateral with glandular enlargement

and tender to palpation with purulent discharge over Stensens duct.

Treatment includes administration of salivary stimulants, antibiotics and surgical drainage.

**Acute postoperative parotitis:** Aetiology is a form of sialadenitis which occurs after a major surgical procedure where in the patient depends only on intravenous fluids. In addition these patients are on atropine which is a pre anaesthetic medication for drying the secretions and this may contribute to dryness of mouth and subsequent inflammation of parotid salivary glands. Non-infectious causes of salivary gland inflammation are sarcoidosis and Sjogrens syndrome.

**Clinical features:** Parotid gland is the most common salivary gland involved in acute bacterial sialadenitis. The patient presents with painful, usually bilateral swelling of the parotid salivary glands with low grade fever. In addition the patient may also complain of difficulty in opening the mouth. On clinical examination the skin over the parotid region may be inflamed and intra orally purulent discharge may be observed from parotid duct. Treatment-The condition usually resolves in about 48 h. However, symptomatic treatment is recommended.

Mumps is an acute paramyxovirus induced infection of parotid salivary glands. Aetiology- It is a contagious infection spreading through airborne droplets or direct contact of saliva. The peak incidence of mumps is reported during winter and spring season<sup>[20]</sup>. Clinical features: The infectivity of the mumps virus ranges from 3 to 4 d after the onset of the disease<sup>[21,22]</sup>. During the prodromal phase of the disease, the patient may complain of low grade fever, muscle pain, headache and malaise<sup>[20]</sup> followed by unilateral or bilateral enlargement of parotid salivary glands associated with pain which is severe during mastication. The inflammation of the salivary gland starts reducing by the end of 1<sup>st</sup> week and the patient returns to normal by 10 d<sup>[21]</sup>. Epididymo-orchitis, Oophoritis, pancreatitis and acute meningitis are the complications of mumps<sup>[21]</sup>. Treatment is symptomatic and Mumps vaccination (MMR) may decrease the incidence of this infection and considered as preventive measure.

**Chronic recurrent parotitis:** The proposed aetiology for this disorder includes congenital<sup>[23,24]</sup> and acquired factors like ductal obstruction secondary to inflammation infection and autoimmune diseases<sup>[25,26]</sup>.

**Chronic sclerosing sialadenitis:** Also known as Kuttner's tumour was identified by Kuttner in 1896. Aetiology-The condition is a chronic inflammatory reaction secondary to ductal obstruction and subsequent salivary stasis. However, salivary flow obstruction is proposed to be the main factor in the pathogenesis of this disorder<sup>[27]</sup>.

**Clinical feature:** Clinically the condition presents as a painful, hard swelling of submandibular salivary gland. The pain and swelling may be present for a variable duration of time. The differential diagnosis includes chronic sialadenitis, sialolithiasis, and benign lymphoepithelial lesions. Treatment-The condition is managed by surgical excision of the involved gland and chances of recurrence of the lesion or changing into malignancy is found to be rare<sup>[27]</sup>.

**Hepatitis C virus associated sialadenitis:** Aetiology-hepatitis C virus (HCV) is found to affect the salivary glands and cause the glandular inflammation. Clinical feature: The affected patients may present with mild swelling of the parotid gland with minimum or no symptoms of dry eyes and dry mouth<sup>[27,28]</sup>. The diagnosis of HCV is by the detection of HCV DNA and anti HCV antibodies. Treatment- Hepatitis associated sialadenitis is treated symptomatically<sup>[29]</sup>.

**Human immunodeficiency virus infection:** In Human immunodeficiency virus (HIV) infected patients salivary gland lesions commonly occur which may be neoplastic or non-neoplastic in nature. AIDS related tumours such as lymphoma and Kaposi's sarcoma and a Sjogrens syndrome like condition occurs in these patients and are described as "HIV salivary gland disease" (HIV-SGD) is considered to be due to reactivation of a latent virus. Various studies have expressed the strong association between salivary gland dysfunction seen in HIV affected patients and Human Cytomegalovirus (CMV) saliva. Clinical feature: The condition is characterised by xerostomia with unilateral or bilateral salivary gland enlargement with reduced tear production. Diagnosis is by biopsy of the major gland which shows the presence of hyperplastic lymph nodes with lymphocytes and cystic cavities obtained from patients affected from HIV-SGD<sup>[6,28]</sup>. Treatment-Administration of oral sialagogues/frequent sipping of water are recommended for xerostomia. Anti-retroviral therapy may be administered for the management of HIV. Rarely radiotherapy and parotidectomy may be beneficial in advanced condition.

**Iodine 131 induced sialadenitis:** Aetiology-high dose of oral Iodine 131 in treatment of thyroid carcinomas can adversely affect the salivary glands leading to sialadenitis. The incidence of acute salivary gland inflammation ranges from 24%-67% and that of chronic salivary gland inflammation ranges from 11%-43%<sup>[29-31]</sup>. Clinical feature: The patients present with pain and swelling of the salivary glands with or without dry mouth condition<sup>[32]</sup>. Treatment- Administration of oral sialagogues/oral hydration, serotonin receptor blocker and dexamethasone are recommended.

**Sialadenosis:** Sialadenosis also known as sialosis is an enlargement of salivary glands which is non-inflammatory and non-neoplastic more commonly affecting the parotid

salivary glands.

**Etiology:** This condition can be associated with: Endocrine disorders: (1) Diabetes mellitus and insipidus; (2) Accromegaly; (3) Hypothyroidism; and (4) Pregnancy. Nutritional status: (1) Anorexia nervosa; (2) Bulimia; (3) Chronic alcoholism; and (4) General malnutrition. Medication induced sialadenosis<sup>[33]</sup>: (1) Psychotropic medications; (2) Antihypertensive drugs; and (3) Sympathomimetic drugs. Clinical features- Patient presents with a slowly progressing bilateral (rarely unilateral) swelling of parotid salivary glands which may be asymptomatic<sup>[34]</sup>. Rarely patients may complain of reduced salivary flow. Treatment-Management of underlying systemic condition may help in reversing the sialadenosis.

### **Traumatic: Mucocele**

**Aetiology-**They is caused due to rupture of a salivary gland duct mostly due to trauma resulting in spillage of mucin into the surrounding tissues. Clinical features: Clinically a mucocele appear as bluish thin walled lesion which is fluctuant, and the most common site of occurrence is on the lower lip. Ranula: is a special type of mucocele which grows in the floor of the mouth, usually unilateral and is called due to its similar appearance to enlarged abdomen region of a frog. Treatment- in case of superficial recurrent or deep mucoceles, surgical intervention is indicated while large ranulas are treated by marsupialization. A study by Wilcox *et al*<sup>[6]</sup> recommends intra lesional corticosteroids administration before surgery.

**Nicotinic stomatitis:** Aetiology-The long standing habits of tobacco and or alcohol/hot liquid consumption. Clinical feature: Exhibits whitened areas of the hard palate due to hyperkeratosis caused by the thermal irritation. This irritation also causes inflammation and dilatation of the duct openings of the minor salivary glands of the palate manifesting as red patches or spots on a white background<sup>[1]</sup>. Treatment- discontinuation of the habits reverses the condition back to normal.

### **Autoimmune: Sarcoidosis**

**Aetiology-**is an autoimmune chronic granulomatous inflammatory condition which causes destruction of the tissue by T lymphocytic, mononuclear phagocytic infiltration and granuloma formation<sup>[6]</sup>. The parotid salivary glands are affected in 10%-30% of cases. Clinical feature: The patient presents with a hard, bilateral enlargement of the parotid gland usually asymptomatic in nature. Sarcoidosis of parotid glands along with uveitis and facial nerve paralysis is termed as Heerfordt's syndrome or uveo parotid fever<sup>[35]</sup>. The patient may complain of dry mouth and minor salivary gland biopsy confirms the diagnosis. Treatment- palliative treatment primarily relieving of the symptoms of salivary component of sarcoidosis is advised.

Corticosteroid or with Chloroquine has been recommended. Immunosuppressive and immune modulatory medications are administered in patients who do not respond the corticosteroids.

**Sjogrens syndrome:** Aetiology-is an autoimmune disorder associated with HLA-DR3 AND HLA-B8. The disease was described by Henric Sjogren in 1933. Clinical feature: The primary Sjogren syndrome/sicca complex exhibit dry eyes and mouth. The secondary Sjogren syndrome develops SLE, polyarteritis nodosa, polymyositis, rheumatoid arthritis and in scleroderma.

This condition is most commonly seen in women over 40 years with male: female in the ratio of 1: 10.

Sjogrens syndrome case definition<sup>[6,34]</sup> requires at least 2 out of the following 3 criteria as mentioned in Table 2. Laboratory findings: Anti salivary duct antibodies, anti-nuclear antibodies, rheumatoid factor increased ESR, Lip biopsy-lymphocytes around salivary glands. The other tests are Schirmer test, Rose Bengal dye test, Sialography and sialochemistry<sup>[6]</sup>. Treatment- to limit the harmful effects of the disease especially the ocular and oral conditions, symptomatic relief of administration of artificial tears, saliva substitutes, fluoride applications and oral hygiene measures are suggested<sup>[6,34]</sup>.

**Mikulicz's disease:** Aetiology-Mikulicz's disease of unknown aetiology was first reported by Johann von Mikulicz-Radecki in 1888. However, it has been demonstrated that autoimmune, viral, and genetic factors may contribute to the pathogenesis of the disease. Clinical feature: Patients suffering from Mikulicz's disease present with asymptomatic, bilateral swelling of the parotid, and submandibular salivary glands along with lacrimal glands. This disease closely resembles Sjogren's syndrome. However the lacrimal and salivary secretion depletion is very minimal in Mikulicz's disease. Histologically the disease resembles Sjogren's syndrome, but lacks the characteristic anti-SS-A and anti-SS-B antibodies of Sjogren's syndrome. Studies have found increased levels of IgG4 antibodies in the serum of patients with Mikulicz's disease. Treatment- Mikulicz's disease is very much responsive for steroid therapy particularly to<sup>[35]</sup> methylprednisolone.

### **Neurological**

Frey's syndrome also known as Auriculo temporal syndrome which is characterized by sweating in the pre auricular and temporal areas after gustatory stimulation.

**Aetiology-**the condition most commonly caused due to faulty regeneration of sympathetic and parasympathetic nerve fibres which were injured during parotid tumor surgery or ramus resection. Clinical feature: Post-surgery the parasympathetic fibres start innervating the sweat glands and vasculature of the skin around the parotid area. The symptoms usually appear within few minutes of the start of mastication or during stimulation of saliva and

**Table 2 American College of Rheumatology Classification Criteria for Sjögren's Syndrome: Sjögren's syndrome case definition requires at least 2 out of the following 3**

Positive serum anti-SSA and/or anti-SSB or (positive rheumatoid factor and ANA $\geq$ 1:320)
Ocular staining score $\geq$ 3
Presence of focal lymphocytic sialadenitis with focus score $\geq$ 1 focus/4 mm <sup>2</sup> in labial salivary gland biopsies

may remain up to 30 min after discontinuing mastication. The diagnosis of the syndrome can be confirmed by starch iodine test<sup>[36]</sup>. Treatment- Reassurance to the patient is advocated in most of the cases. Intra cutaneous injection of botulin toxin is found to be effective in severe condition and Tympanotomy<sup>[23]</sup> may be the treatment of choice with severe symptoms.

### Degenerative

Sialolithiasis-is a condition of unknown aetiology. However, there could be several coexisting causes leading to the salivary stone formation. Some of these cofactors may be related to disturbed pH of saliva, abnormalities in the sphincter mechanism related to salivary duct opening and abnormal calcium metabolism<sup>[5,6]</sup>. Clinical Feature: This condition most often will not produce any signs and symptoms. Rarely, it may cause complete ductal obstruction, pain and swelling of the salivary glands. Treatment- Large salivary stone are managed by extracorporeal or intracorporeal lithotripsy<sup>[6,17]</sup> procedure.

### Non inflammatory non neoplastic

Sialadenosis is a non-infectious, non-inflammatory gland enlargement usually affecting the parotid bilaterally. This condition is most often seen in women causing salivary hypo salivation which can occur due to systemic disorders<sup>[6,12]</sup>.

### Vascular

Necrotizing sialometaplasia: Aetiology-The probable cause could be due to vascular infarction of the salivary gland lobules and is often mistaken for oral cancer<sup>[37]</sup>. Vascular compression is caused by a necrotic myocutaneous reconstruction of the flap used in palatal surgeries and embolization from carotid endarterectomies, Berger's disease, Raynaud's phenomenon. Predisposing factors are dental injections, ill-fitting denture, traumatic injury, previous surgery and upper respiratory tract infections. Clinical feature: appears as a non-neoplastic lesion that usually arises from a minor salivary gland in the lips, posterior part of the palate, and retro molar regions. Treatment: The condition is self-limiting and the healing of the lesion normally takes about 6-8 wk.

### Neoplastic

**Benign:** Pleomorphic Adenoma, Papillary Cystadenoma Lymphomatosum (warthins tumor), Basal Cell Adenomas, Oncocytoma, Canalicular Adenoma, Myo-

epithelioma, Sebaceous Adenoma, Ductal Papilloma.

**Malignant:** Adenoid Cystic Carcinoma, Hyalinising Clear Cell Carcinoma, Mucoepidermoid Carcinoma, Acinic Cell Carcinoma, Adeno carcinoma, Pleomorphic Adenoma, Lymphoma<sup>[5,6,12]</sup>.

### Oral diagnostic approaches to the patients with salivary gland disorders:

(1) Imaging of salivary glands: Salivary gland is one of the main soft tissue structures in the maxillofacial area. Imaging is useful in identifying the masses of salivary glands and also in differentiating them from the masses/pathologies of adjacent cervical spaces, especially para pharyngeal, masticator, submental spaces and mandibular lesions. Conventional radiography has a very limited role in the diagnosis of salivary gland pathology which includes plain radiography. It aids in identifying mainly salivary stones and calcifications. Gland plain radiography like in postero anterior skull projection with cheeks blown out to delineate the parotid duct and submandibular gland radiography includes lateral oblique radiograph with mouth wide open; and (2) Sialography was used as the sole imaging technique before the advent of advanced imaging techniques which include ultrasonography, elastography, computed tomography, scintigraphy, and magnetic resonance imaging. Sialography, an imaging technique of salivary gland, uses contrast medium to delineate the ductal system of salivary glands. Due to use of contrast medium this technique is not suitable and is contraindicated in acute conditions of salivary glands<sup>[38]</sup>. However sialography is found to be useful in assessment of salivary gland dysfunction secondary to obstructive disorders of the gland<sup>[39]</sup>.

Studies have suggested other various diagnostic methods-magnetic resonance (MR) sialography is a non-invasive technique useful in evaluating the hypo functioning of salivary glands. Sialo endoscopy assist in detecting ductal anomalies that may not be<sup>[40]</sup> possible to detect by means of either traditional or new imaging techniques.

Sialography, Sialoendoscopy, and MR Sialography are indicated for evaluation of the ductal system of the salivary glands.

Ultrasonography, computed tomography, magnetic resonance imaging is helpful in assessment of the parenchyma of the salivary glands<sup>[41]</sup>. However; all these diagnostic aids have their own limitations in the diagnosis of salivary gland lesions.

**Ultrasonography:** Ultrasound examination of salivary glands with a high resolution transducer is found to be a highly sensitive, a non-invasive method for salivary gland evaluation<sup>[42]</sup>. It is a cost effective imaging tool which displays high definition images useful in evaluating the superficial structures particularly the peripheral areas of the affected salivary gland. High frequency linear probes of 7.5-12 MHz are used in imaging of salivary glands<sup>[43]</sup>. In acute conditions such as acute radiation



induced sialadenitis, the gland appears swollen and show anechoic appearance on ultrasonography<sup>[44]</sup>. In a recent clinical study ultrasonography was found useful in diagnosing lymph node and salivary gland enlargement in submandibular region and suggested that it also helps in identifying the salivary glandular tissue in accessory salivary gland and salivary calculi<sup>[45]</sup>.

**Shock-wave lithotripsy:** Shock-wave lithotripsy is a non-invasive diagnostic tool suggested for the management of sialolithiasis. Iro *et al*<sup>[46]</sup> in 1989 introduced the application of extracorporeal shock-wave lithotripsy (ESWL) in the management of salivary gland. Sialolithotripsy helps in removing salivary stones into smaller particles and thereby removal by flushing action is possible from the salivary duct system or after salivation induced by citric acid or other sialogogues. The shock-waves are generated extracorporeally by using Piezoelectric and electromagnetic techniques or intra-corporeally using electro-hydraulic, pneumatic or laser endoscopic devices<sup>[46]</sup>.

**Sonoelastography:** Elastography is an ultrasonography technique which measures the tissue elasticity *in vivo*. This imaging technique measures the elasticity of the glandular parenchyma and is useful in evaluating the hypo function of saliva especially in post radiation hypo function of salivary glands<sup>[41]</sup>.

**Computed tomography:** Computed tomography (CT) scans of the salivary glands are useful in delineate the extent of the lesion and its relation to adjacent structures<sup>[47]</sup>. Multi detector CT scans help in characterizing tumours of salivary glands like Warthin tumor which demonstrates peak enhancement of signals after administration of contrast agents which is not found in other tumors of salivary glands. However CT scans perform poorly in characterizing the histopathologic nature of the tumors. CT scans help in differentiating the benign and malignant neoplasms of salivary glands. The irregular tumor margin and surrounding tissue infiltration is the characteristic feature of malignancy<sup>[48]</sup>. However studies have found overlap of CT scan characteristics between malignant and benign lesions. Apart from tumor identification CT scan also aids to view dystrophic calcifications in salivary glands.

**CT sialography:** Interpretation of sialography findings depend on the imaging technique used to acquire sialography images. Traditionally plain radiographs were used for assessment of salivary glands after injection of the contrast medium. Introduction of CT and MRI scans in maxillofacial imaging have shifted the focus from plain radiography to these advanced imaging techniques. However CT sialography may have limited applications due to the accessibility and cost factors. Moreover the prolonged image acquisition time of CT scans may jeopardize the viewing of CT contrast medium uptake<sup>[49]</sup>; (3) Special imaging; cone beam computed tomography (CBCT): some of the

limitations of CT sialography have been addressed by use of CBCT technology with sialography. A study reported the usefulness of CBCT in demonstrating the secondary structures of submandibular salivary glands in comparison with plain radiography coupled with sialography. The same study reported that the effective dose from CBCT scans were comparable to that of plain radiography when a smaller field of view (FOV) was used<sup>[50]</sup>.

Magnetic imaging resonance (MRI) scans are useful in assessment of salivary glands. The wide variety of soft tissue signals differences and multi planar image acquisition have made MRI an effective imaging modality for assessment of salivary gland tumors. This imaging modality is helpful in assessment of tumors affecting the deep lobes of parotid glands, skull base invasion of the tumours of salivary glands, evaluation of recurrent pleomorphic adenomas and much more<sup>[51]</sup>. Also high resolution MRI scans delineate the intra parotid course of facial nerve which is an important landmark for surgeons operating on parotid glands<sup>[52]</sup>.

Magnetic resonance sialography-Major limitations of conventional sialography include use of iodine based contrast agents and inability of the contrast agent in overcoming the strictures within the ductal system of the salivary gland which in turn prevent the visualization. These limitations can be overcome by switching on to MR sialography which uses patients own saliva as a contrast medium. MR sialography also demonstrates the actual ductal diameter due to non-use of contrast agents<sup>[53]</sup>.

Scintigraphy-Salivary gland scintigraphy uses Tc-99m pertechnetate which helps in assessment of salivary gland dysfunction in disorders like Sjogrens syndrome. This technique is valuable in assessment of xerostomia<sup>[54]</sup>.

The minimally invasive techniques for preserving the glandular tissue which are currently being used in the management of obstructive salivary disease are sialoendoscopy, shockwave lithotripsy, interventional radiology, endoscopically video-assisted trans-oral and surgical retrieval of stones, and botulinum toxin therapy. Three dimensional reconstruction imaging (MR sialographic) and MR virtual endoscopy have recently been suggested for salivary gland ducts studies on par with their applications in medical field<sup>[55]</sup>.

**Emerging imaging based diagnostics:** Positron emission tomography (PET) scan: A PET scan focuses for areas of high cellular activity suggesting a sign of cancer growth. It also helps to diagnosed cancer, and to assess its spread to lymph nodes or any other parts of the body. This test requires an injection of a very small quantity of radioactive substance usually a type of sugar known as FDG, which will be excreted by the body later in a day. As cancer cells growth is faster in the body, they absorb more of the radioactive sugar. After about an hour, the patient is moved onto a table and made to lie for about 30 min. Meanwhile a special camera

captures a picture of areas of radioactivity in provide helpful information about whole body. It is also possible to take a PET and CT scan at the same time (PET/CT scan). This enables the doctor compare areas of higher radioactivity on the PET scan with the more detailed picture of that particular area on the CT scan<sup>[56]</sup>; (4) Sialochemistry and Sialometry: Sialochemistry deals with chemical analysis of saliva whereas Sialometry is concerned with measuring salivary flow rates and these two measurements of saliva helps in assessment of functioning of salivary glands. The normal volume of the saliva produced by both the major and minor salivary glands constitutes around 600 to 1000 mL per day<sup>[57]</sup>. This volume varies in different individuals and it may alter in different systemic conditions.

Sialometry can be in relation to whole saliva or gland specific saliva. Whole saliva is a mixture of salivary gland secretions, non salivary secretions including serum transudates, gingival crevicular fluid, food debris and oral microbes<sup>[58]</sup>. Most often clinicians assess the salivary gland functions through collection of whole saliva. This method is easy to perform and does not require any special equipment. However, whole saliva analysis is of limited value due to its low sensitivity in detecting gland specific dysfunction and gland specific changes in salivary chemical composition<sup>[59]</sup>; and (5) Salivary gland biopsy or fine needle aspiration (FNA) helps to determine whether the tumor is benign or malignant. In some cases this type of biopsy can help a clinician to avoid unnecessary surgery. Incisional biopsy; is a type of biopsy sometimes preferred if the FNA biopsy does not get a large enough sample to examine. For salivary gland tumors these types of biopsies are not done often. Surgery can both provide enough of a sample for a diagnosis and treat the tumor at the same time<sup>[6,17]</sup>.

#### **WHO classification of salivary glands neoplasm is listed in Table 1**

Salivary gland neoplasm-Salivary gland cancers include tumors of different patho histologic characteristics and biological behaviour. The most prevalent salivary gland tumors<sup>[6,60-62]</sup> are: (1) Benign Condition: Pleomorphic Adenoma, Papillary Cystadenoma Lymphomatosum (Warthins Tumor), Basal Cell Adenomas, Oncocytoma; and (2) Malignant tumors: Muco Epidermoid Carcinoma, Adenoid Cystic Carcinoma. Salivary gland neoplasms according to study report represent less than 3% of all tumors.

**Prevalence:** The tumors can arise in about 80% in parotid gland, 15% in submandibular gland and 5% in the sublingual and minor salivary gland. 65% of submandibular, 50% of minor salivary gland and 20% of sublingual gland tumors are benign<sup>[6,12,60]</sup>. Aetiology: of the salivary gland neoplasm is not known. However, certain environmental factors and abnormalities are implicated. Environmental factors such as radiation,

viruses, extensive use of tobacco and their products, molecular changes and genetic factors are considered as the causative factors. Clinical features: Subjects with benign tumor of parotid gland present with a unilateral, asymptomatic swelling of the involved gland and rarely suffer from pain, difficulty in swallowing and extrusion of fluid from the ears. The benign tumor of other types of salivary glands also present as asymptomatic mass of the affected gland without compromising the functions of the individual.

Malignant tumor of the salivary glands may also present as asymptomatic mass and in advanced stages may cause pain and mucosal/skin ulceration. One third of patients with parotid gland malignancy most often present with facial nerve paralysis<sup>[60]</sup>. The signs of malignancy in a previous benign tumor of parotid gland can be a sudden increase in the size of the mass, with facial nerve paralysis and shows ulceration of the skin overlying the parotid mass<sup>[61]</sup>.

**Pleomorphic adenoma:** this tumor has many names- Mixed tumor, Endothelioma, etc. which was termed by Willis. In 90% of the cases the tumors affects the parotid gland, most often present in lower pole of superficial lobe of the gland. It occurs more frequently in females than in males between 4-6 decade with average of 43 years. Clinical features: The lesion presents as small, painless quiescent nodules which slowly begin to increase in size, sometimes showing intermittent growth. Surgical excision is the treatment of choice. Treatment: Based on factors like the high recurrence rate, the patient's age, and extensiveness of resection, XRT may be a useful therapy for this type of tumor.

**Papillary cystadenoma lymphomatosum (warthins tumor):** is the most common tumor in salivary glands first recognised by Albrecht in 1910 and later in 1929 it was described by Warthins. Clinical features: The tumor occurs mainly in parotid, seen over 60 years of age with the sex prediction is male to female 5:1 ratio. Clinically seen bilateral in 6%-12% of patients as painless lesion unless it is secondarily affected<sup>[6,12]</sup>. Treatment is mostly by surgical excision.

**Basal cell adenomas: Clinical features:** a benign salivary gland adenoma constitute to about 1%-2% of the salivary adenomas occurring mostly in the parotid gland and upper lip of the minor salivary gland. The other types of fewer occurrences of benign salivary adenomas are Canalicular Adenoma, Myo Epithelioma, Ductal Papilloma, and Sebaceous Adenomas. Oncocytoma is another benign tumor particularly affecting the parotid bilaterally seen in both men and women<sup>[6,61-63]</sup>. Treatment is by conservative surgical excision.

Muco epidermoid carcinoma is the most common malignant tumor of the salivary gland mostly affecting the parotid gland and these accounts for 5% of salivary

gland tumor. Clinical features: This tumor also affects minor salivary gland in 15% of these cases. They are seen in the age group of 40-50 years with female predilection. The tumor is classified as low grade or high grade depending on the ratio of epidermal cells to mucous cells. In this type of tumor the most common cytogenic abnormality is the recurrent translocation between chromosomes 11 and 19 to form CRTCI-MAML2 fusion protein<sup>[34,61]</sup>. Treatment is the surgical excision of the tumor with post-operative radiotherapy<sup>[61]</sup>.

Adenoid cystic carcinoma accounts for 30% of tumors in minor salivary glands and 6% affecting the parotid gland. Clinical features: It occurs in the middle and older individuals. The tumor has the ability to infiltrate the nervous tissue and spread along the nerve pathways. Biomarkers of epithelial to mesenchymal transition (EMT) such as Snail and Slug appear to be helpful in the diagnosis of adenoid cystic carcinoma<sup>[62,64-68]</sup>.

Treatment is the radical surgical excision followed by Photon beam radiotherapy has shown to be effective.

Adenocarcinoma is the tumor which takes its origin from epithelium of the salivary duct<sup>[62]</sup>. This group of salivary gland tumors includes specific lesions, like polymorphous low grade adenocarcinoma, salivary duct carcinoma, Cribriform adenoma carcinoma, *etc.* These tumors present a painful swelling of the affected gland and are very rare in occurrence. Management of these tumors depends on the histologic type of the tumors.

Cribriform adenocarcinoma of the tongue and minor salivary glands (CATMSG) is a low grade salivary gland tumor affecting the minor salivary glands of the oral cavity. This tumor was earlier described by Michal *et al*<sup>[64]</sup> in 1999 under the name Cribriform Adenocarcinoma of the tongue. In later years studies suggested its origin to be renamed and considered as Cribriform Adenocarcinoma of minor salivary glands a distinct neoplasm<sup>[64]</sup>.

Hyalinizing clear cell carcinoma (HCCC) is a rare, unique low grade tumor affecting minor salivary gland. Milchgrub *et al*<sup>[65]</sup> in 1994 first described this tumor which exhibited nests, cords, trabeculae and eosinophilic cells in a hyalinised stroma. Clinical features: It primarily arises in the oral cavity but has been described at all salivary gland and seromucous gland sites. Dardick extensively studied under electron microscope, and after re-examination the features of HCCC it was confirmed that it is a squamous lesion<sup>[65]</sup>. Treatment: the various salivary gland tumors exhibit different histo biological features. In benign tumors no other treatment is usually needed. But when the lesion spreads beyond, treatment of malignant salivary neoplasms depends on the appropriate diagnosis, histologic findings, the clinical stage/condition at presentation and the more recent is the considerations of genetic factor<sup>[66,67]</sup>. At present the treatment approach is towards conservative elective surgical procedures, combined with the application of postoperative irradiation and chemotherapy<sup>[6,17,48,60]</sup>. A clinician should have a

thorough knowledge of the subject, also be aware of their recent advancements, and work with the group of associated specialists in the management of salivary gland disorders. By following the required, appropriate, systematic diagnostic procedures it helps the clinician to establish a definitive diagnosis and finally assesses the potential for treatment.

### **Metastatic malignant salivary gland neoplasms:**

Studies suggests that polymorphous low grade adenocarcinoma, adenoid cystic carcinoma and muco epidermoid carcinoma of the salivary glands<sup>[67]</sup> are found to have increased metastatic potential. Adenoid cystic carcinoma<sup>[68]</sup> has been found to metastasize to lungs, bones, skeletal muscles and skin.

### **Advances in radiotherapy for head and neck cancer sparing the salivary glands**

Intensity modulated radiotherapy (IMRT) for head and neck cancer has partial parotid sparing effect which reduces the intensity of post radiotherapy xerostomia<sup>[66]</sup>.

Exposure of salivary glands to Ionizing radiation cause damage to the secretory apparatus of the glands causing xerostomia which could be avoided by the use of any one of the presently available<sup>[67]</sup> techniques: (1) Shielding of one or more salivary glands from radiation- During radiotherapy for the tumors of parotid gland and areas outside the oral cavity, radio protecting shield can be used to protect the major salivary glands. Shielding may not be feasible in radiotherapy for midline lesions, cancer of oropharynx and larynx due to the position of the cancer and the alignment of the radiotherapy port. Use of conformational dose delivery techniques- The 3 dimensional imaging techniques like CT scans provide for accurate and precise delivery of radiation to the affected tissues with no or minimal damage to the surrounding normal structures. These radiotherapy techniques helps in minimizing the radiation induced xerostomia; (2) Stimulation of acinar cells prior to Radiotherapy- Administration of salivary stimulants like Pilocarpine before each radiotherapy session is found to reduce the complication of diminished salivary flow. However in radiation dose above 50 Gy this beneficial effect is reduced; (3) Use of salivary sparing agents during radiotherapy- Use of agents like Amifostine and heat shock proteins during radiotherapy for head and neck cancer helps in protecting the salivary glands against radiation induced damage; (4) Transplantation of the salivary gland away from the radiation field- A few studies have reported the beneficial effects of transplanting the major salivary gland away from the radiation field with maintenance of the ductal connection; and (5) Advanced methods like gene therapy for repairing the damaged acinar cells, injecting the stored pre radiotherapy salivary cells after the completion of radiotherapy, inducing the hematopoietic stem cells to differentiate into salivary acinar cells and thereby replacing the damaged cells

and fabricate artificial salivary tissues from donor tissues and introducing them in place of damaged glands using tissue engineering techniques help in restoring the functions of salivary glands and reduce the complications of reduced salivary flow<sup>[68-75]</sup>.

### **Emerging salivary diagnostics: Molecular and protein markers of oral diseases**

In the oral cavity the presence of multifarious microbial flora exhibits more than many hundreds of microbial species which have been identified so far. Advance microbial research has thrown open to much more new insights and saliva has become the major source to a library of information, and the biomarkers represent the disease and health status of the oral cavity<sup>[69-72]</sup>.

Saliva is a fluid that can be easily collected and contains locally and systemically derived markers of oral disease<sup>[68]</sup>. The term "salivaomics" was coined in 2008 to reflect the rapid development of knowledge about the various "omics" constituents of saliva. Salivaomics includes five diagnostic alphabets proteins, mRNAs, miRNAs, metabolic compounds, and microbes offers substantial advantages because disease states may be accompanied by detectable changes in one, but not all, dimensions<sup>[69]</sup>. Human salivary proteome analysis is important for understanding oral health and disease pathogenesis.

Metabolomics is the global assessment and validation of endogenous small-molecule metabolites within a biologic system that has gained increasing popularity and significance in life sciences<sup>[70]</sup>. Analysis of these key metabolites in body fluids has become an important role to monitor the state of biological organisms and is a widely used diagnostic tool for disease. Metabolomics provides potential advantages that classical diagnostic approaches do not, based on the discovery of clinically relevant biomarkers that are affected by the disease<sup>[71-80]</sup>.

Increase in the incidence of oral cancer has prompted research in salivary biomarkers for oral cancer. More than 100 different salivary biomarkers for oral cancer have been identified. A review on salivary biomarkers for oral cancer categorized this vast variety of salivary biomarkers under different groups which include: (1) Non-organic compound biomarkers, *e.g.*, sodium, calcium, magnesium; (2) Peptide or protein biomarkers, *e.g.*, P53 autoantibody, alpha amylase, *etc.*; (3) DNA, RNA and microRNA biomarkers, *e.g.*, P53 gene codon 63, IL 8, miR-125a, *etc.*; (4) Metabolomic biomarkers, *e.g.*, Valine, lactic acid, *etc.*; and (5) Miscellaneous biomarkers, *e.g.*, Telomerase activity<sup>[63,81-95]</sup>.

Salivary biomarkers are also used for assessment of caries risk. DNA based methods like DNA hybridization, mono clonal antibody (MAb) technique, 16S rRNA/ rDNA, gene cloning and genomic sequencing or T-RFLP methods of analysis help in identification and cariogenic microbial taxonomy using saliva without the need for culture methods<sup>[62,73,77,80]</sup>.

PCR based identification techniques allow for accurate measurement of cariogenic microbiota. Salivary diagnostics suggests a new diagnostic tool for the detection and quantification of oral pathogens directly from its liquid state without the need for isolation of bacterial cells. In children low salivary levels of alpha defensins HNP1-3 may represent biological factor that contributes to caries susceptibility while salivary IgA antibody responses to streptococci mutants can be observed in early childhood<sup>[73]</sup>.

Salivary epithelial cells are found to secrete proteins into blood stream which has led to research on the duocrine function of salivary glands. This function of salivary epithelial cells is being researched as a potential target site for *in situ* gene transfer producing proteins for treating several systemic disorders<sup>[74,82]</sup>.

Saliva, the fluid bathing the oral cavity, is one of the important secretions in the human body. One of the main functions of saliva is digestion of complex carbohydrates and lipids. Technological advancements in the field of diagnostics have opened new avenues to understand the other important and far reaching functions of saliva. The constituents of saliva, also known as biomarkers, act as an index for underlying systemic disease ranging from infections to malignancies.

Salivary glands are surrounded by a rich network of vasculature allowing the biomarker constituents of blood to enter salivary acinus and finally into the salivary secretions. Biomarker is defined as an objectively measured and evaluated indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention.

Biomarkers can be in the form of proteins, carbohydrates, lipids or microorganisms. Change in the constitution of these biological molecules may reflect the status of underlying disease processes and can aid in diagnosis, management, evaluating the prognosis and monitoring the outcome of the condition<sup>[75]</sup>. Biomarkers in saliva have the potential to be used for screening purposes in epidemiological studies.

Matias I, Gatta-Cherifi B, in their study were able to quantify endocannabinoids in human saliva as potential and useful biomarker of obesity<sup>[76,96]</sup>. Two major forms of Ghrelin (GAH) a recently identified peptide hormone in saliva shows their decrease levels in salivary samples in obese type 2 diabetic patients.

The levels of mRNAs regulating the metabolism of endocannabinoids, N-acyl ethanolamines and of cannabinoid type 1 [CB (1)] receptor, were assessed in human salivary glands. The study helps in further understanding of the physiopathological mechanisms leading to type 2 diabetes and obesity.

There are numerous investigative tools to identify and quantify the type and load of microbes in the oral cavity. Most of these tools are based on microbial culture methods for identifying disease specific pathogens. Biomolecular microarray based diagnostics (quantitative 16S rRNA gene sequencing, terminal restriction



fragment length polymorphism analysis, etc.) are advancements over the conventional culture methods. These methods, when combined with microbial culture techniques, help in enhancing the chances of accurate identification of pathogens<sup>[77]</sup>. Salivary fluid can also be used for detection of systemic infections. Saliva based enzyme-linked immunosorbent assay (ELISA) has shown promising results in detection of HIV pathogens with 99.3% sensitivity and 99.8% specificity. However positive test results are to be confirmed with western blot analysis. Other systemic infections which can be detected by salivary analysis include hepatitis A, B, C infections, malaria, Ebola, Dengue, CMV, EBV<sup>[77,92,93,97]</sup> and human herpes virus (HHV) infections. These infections are identified by assessing the viral load, viral antibodies and viral antigens in saliva. These diagnostic parameters are found to correlate well with their corresponding levels in serum. Leptin, is a cytokine identified in human saliva play a protective role in bacterial *P. gingivalis* infection<sup>[9,86]</sup> induced inflammatory responses. Another salivary component Ghrelin is found to have a counteracting effect on *P. gingivalis* induced impairment of mucin synthesis which plays a role in periodontal infections<sup>[61]</sup>.

Molecular analysis of saliva employing next generation sequencing and human microbe identification micro array techniques have enabled the clinician to identify and characterize a large number of oral microbiota in diseases including Crohn's disease, pancreatic cancer, oral cancer and obesity. In children suffering from Crohn's disease, there is an overall decrease in diversity of oral microorganisms as compared to healthy children. Studies employing the advance microarray techniques report suggests overall significant reduction in *Neisseria elongate* and *Streptococcus mitis* species count in the saliva of patients with pancreatic cancer as compared to normal subjects<sup>[61,75]</sup>.

**Future research direction:** Advances in the management of salivary gland tumours studies stress the need towards molecular targeted therapy of the unusual subpopulation of tumorigenic cancer cells which could arrest the recurrence and metastasis of the tumor. In this direction the cancer stem cell research needs to be further explored in the salivary gland tumors<sup>[78,98,99]</sup>.

Recently a non-invasive, academic prototype chair side cancer diagnostic kit (GC America Inc.) has been devised by Wong DT for the early detection of cancer<sup>[79]</sup>. Newer field like Proteomics helps in the analysis of the salivary proteins which is extensively used in identification of a specific protein biomarker in saliva for diseases including AIDS, oral cancer, diabetes, periodontal disease and mammary gland carcinoma. The transudate of oral mucosa contains secretory immunoglobulin IgG, IgM and IgA, which serve as a valuable source for immunodiagnostic-based procedures. Using Point-of-care salivary diagnostic screening tests kit<sup>[79,92]</sup> it is possible to detect viruses in viral infectious diseases such as human papillomavirus (HPV), HCV and HIV.

Advanced Molecular Salivary tests for caries susceptibility may further aids in motivation and patient's

education, evidence based dentistry and also in determining effectiveness of anti-caries therapy or caries-control measures including community based services and caries vaccine<sup>[73,79]</sup>. Further advancements are now being focused at "Omic technologies", which include genomics, proteomics, transcriptomics, and metabolomics have already set their mark in life science research studies<sup>[69,77,79]</sup>. These emerging technologies have shown to offer highly sensitive, specific, quick and affordable diagnostic test kits in future. Local drug delivery system is another interesting area with the advent of Nano medicine being used in pharmaceuticals industry and biomedical engineering field have shown promising results in future therapeutics. In cancer therapeutics, Nano particles, such as, semiconductor quantum dots, biodegradable micelles, iron oxide nano-crystals<sup>[78,81,82,94]</sup>, are linked with bio targeting ligands, to aim at specific sites in malignant tumors, helpful in cancer therapeutics. Endothelin-1 is one of the probable salivary biomarkers for oral cancer has been reported<sup>[63,82,95]</sup> for early cancer detection. Dependability of saliva for early diagnosis of dengue disease especially useful in dengue endemic countries is awaited<sup>[96]</sup>. Salivary ghrelin plays an important protective role in chronic periodontitis and needs further research<sup>[86,97,98]</sup>. Salivaomics, the future of saliva-based techniques for early diagnosis of dental diseases, is promising. However, further long term studies are needed before these newer methods are adapted to routine clinical practice.

**Conclusion:** Saliva reflects the physiologic state of the body. Salivary gland diseases may be inflammatory, non-inflammatory, non-neoplastic or neoplastic lesions. Only when a definitive diagnosis is established, treatment depends upon the lesion size, cause, severity, extent and other clinical considerations of the disease. However, a thorough knowledge of the subject including their recent advancements together with a team of associated medical and dental specialists, it is possible to detect the diseases of salivary glands in their early stage and manage them more efficiently. Salivaomics, the future of saliva-based techniques for early diagnosis of dental diseases is promising. Saliva being readily available can be used as a diagnostic tool to help the clinicians for early detection of oral diseases like caries, periodontal disease, oral cancer, salivary gland disorders and non-oral diseases by adapting the advance non-invasive technique and technologies.

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## Diagnostic imaging: Morphological and eruptive disturbances in the permanent teeth

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imaging, including periapical, occlusal, panoramic, or cephalometric radiographs are essential in localization and management of morphological and eruptive disorders. However, due to their inherent limitations such as insufficient precision because of unusual projection errors and lack of information about spatial relationships, these methods are considered unreliable. Thus, the use of newer image acquisition techniques that allow comprehensive three dimensional imaging and visualization of dental abnormalities is highly recommended for making a confirmatory diagnosis. The significance of accurate endodontic, surgical and orthodontic treatment planning in dental abnormalities cannot be overstated as it pertains to critical anatomic landmarks such as proximity to adjacent teeth or the mandibular canal. The precise information on spatial relationships provided by multiplanar imaging helps the dental surgeon to establish more accurate diagnosis, management strategies and also increases the patient safety. This review highlights the use of high-end diagnostic imaging modalities in diagnosis of the various morphologic and eruptive dental abnormalities.

**Key words:** Three-dimensional imaging; Spiral computed tomography; Magnetic resonance imaging; Eruptive malformations; Morphological disturbances; Conebeam computed tomography

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### Abstract

This paper reviewed the literature on newer three-dimensional imaging techniques and their applications in diagnosis and treatment planning of various dental anomalies. Developmental anomalies can occur during any of the developmental stages and are manifested clinically after the tooth is fully formed. These dental anomalies may involve a single tooth, a group of teeth, or the entire dentition. Two-dimensional diagnostic

**Core tip:** The advent of cone beam computed tomography, Spiral Computerized Tomography and Magnetic resonance imaging in the field of dental radiology has greatly facilitated access to the internal morphology of soft tissue and dental hard tissue structures. These techniques are beneficial in viewing spatial relationship of the suspected anomalous tooth and surrounding structures. Multiplanar imaging resolves the ambiguity of conventional two-dimensional radiographs by allowing the rotation of images at arbitrary angles without image magnifications and distortions.

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## INTRODUCTION

Dental anomalies are expressed as morphological and eruption disorders. Morphological dental abnormalities occur due to disturbances during odontogenesis and it includes abnormality in number (supernumerary teeth), abnormality of tooth shape and size (dens in dente, dilaceration, fusion, root dwarfing)<sup>[1]</sup>. Eruption disturbances are mainly divided as disturbances related to time (premature eruption, delayed eruption or impactions) and disturbances related to position (ectopic eruption and transpositions).

A number of factors are responsible for eruptive and morphological dental abnormalities including genetic and congenital anomalies, metabolic disturbances, post operative complications of head and neck radiation therapy, use of chemotherapeutic agents, traumatic injuries to the primary dentition affecting the permanent tooth formation, etc<sup>[1,2]</sup>. The embryologic tooth development of teeth starts around one and half month of intrauterine life and is characterized by distinct odontogenic stages including initiation, proliferation, histodifferentiation, morphodifferentiation, apposition, and calcification. Each stage has its own significance and disturbance at any stage may result into the development of an anomaly. The development of primary dentition occurs in a protected prenatal environment and duration of deciduous teeth development is small, therefore, they are less prone to dental abnormalities than the permanent teeth.

Radiographic method is considered to be advantageous for the preoperative determination of position and nature of these dental anomalies. Conventional plain film radiographic methods such as periapical, occlusal, panoramic, or cephalometric radiographs are a de-facto standard for diagnosis and treatment planning. However, due to their inherent limitations such as insufficient precision because of unusual projection errors and lack of information about spatial relationships, these methods are considered unreliable<sup>[3,4]</sup>. Earlier, computed tomography (CT) has been used widely in maxillofacial imaging to provide detailed 3-dimensional (3D) information. It forms an integral part in diagnosis of oral and maxillofacial regions as it facilitates access to the internal morphology of dentofacial structures. Its benefits of viewing spatial relationship of the anomalous tooth with surrounding structure by the rotation of images at arbitrary angles and absence of image magnification and distortions are well recognized and widely accepted in the literature. It is considered as more desirable morphometric tool than conventional

plain film radiography<sup>[5-7]</sup>. However, it has certain limitations reducing its diagnostic reliability in dentistry including relatively low between-slice accuracy, no interslice gaps, artifacts, edge gradient effects and high radiation dose<sup>[8]</sup>. Recently, a series of cone beam computed tomography (CBCT) scans for three dimensional imaging of dentomaxillofacial region have been developed<sup>[8-13]</sup>. The aim of the study is to present a systematic review of the literature on the diagnostic imaging of the morphological and eruptive disturbances in the permanent teeth.

## DIAGNOSTIC IMAGING TECHNIQUES FOR ASSESSMENT OF ERUPTIVE AND MORPHOLOGICAL DENTAL ANOMALIES

CBCT is relatively newer image acquisition techniques that allow comprehensive multiplanar imaging and visualization of dental abnormalities in which resolution is measured in voxels<sup>[13,14]</sup>. It uses cone-shaped X-ray beam centered on a two-dimensional (2D) detector. The source-detector system performs one rotation around the object producing a series of 2D images. The 3D images are obtained by reformatting the 2D data in volume using a modification of the original cone-beam algorithm developed by Feldkamp *et al*<sup>[15]</sup> in 1984. CBCT scanners for the dentofacial region were originally developed in the late 1990s independently by Arai *et al*<sup>[16]</sup> in Japan and Mozzo *et al*<sup>[17]</sup> in Italy. CBCT has little projection effect and no magnification errors because X-ray beams are orthogonal, resulting in undistorted 1:1 measurements. It provides information for the entire craniofacial region<sup>[18,19]</sup> (Table 1).

## IMPACTED TEETH

Impaction is defined as eruption failure of a tooth to its normal site in occlusion during its normal growth period because of malposition, lack of space, abnormal habit or mechanical obstruction in its eruption trajectory. The precise localization and diagnosis of an impacted tooth is required for proper surgical access and treatment planning. Nakajima *et al*<sup>[20]</sup> demonstrated the importance of CBCT image acquisition technique in cases of delayed eruption of the maxillary left second premolars and severe impaction of a maxillary second bicuspid. CT images provided more accurate information for orthodontic diagnosis and management strategies than conventional radiographic images such as precise observation of tooth morphology, root condition, and superimposition of bone.

### 3D imaging in impacted permanent incisors

Traumatic injuries to primary dentition cause eruptive malformations in underlying permanent tooth germs as they are in a close contact with their primary predecessors<sup>[21]</sup>. It may hinder the eruption pathway of the permanent tooth germ leading to delayed or failure of

**Table 1** Role of conebeam computed tomography for assessment of eruptive and morphological disturbances

Ref.	Year	Eruptive or morphological disturbances	Tooth involved
Nakajima <i>et al</i> <sup>[20]</sup>	2005	Impaction	Maxillary second bicuspid
Walker <i>et al</i> <sup>[12]</sup>	2005	Impaction	Canine
Siraci <i>et al</i> <sup>[45]</sup>	2006	Talon cusp	Facial and lingual surfaces of a supernumerary primary tooth
Maverna <i>et al</i> <sup>[34]</sup>	2007	Impaction	Maxillary canine
Andrade <i>et al</i> <sup>[49]</sup>	2007	Root dilaceration	Maxillary right central incisor
Liu <i>et al</i> <sup>[14]</sup>	2007	Supernumerary teeth	Complete dentition
Liu <i>et al</i> <sup>[32]</sup>	2008	Impaction	Maxillary canines
Haney <i>et al</i> <sup>[18]</sup>	2010	Impaction	Maxillary canine
Patel <i>et al</i> <sup>[59]</sup>	2010	Dens invaginatus	Mandibular lateral incisor
Song <i>et al</i> <sup>[73]</sup>	2010	Fusion	Right maxillary first molar and supernumerary tooth
Gurge <i>et al</i> <sup>[24]</sup>	2011	Impaction	Upper lateral incisor
Alqerban <i>et al</i> <sup>[33]</sup>	2011	Impaction	Maxillary canine
Kaneko <i>et al</i> <sup>[60]</sup>	2011	Dens invaginatus	Maxillary lateral incisor
Narayana <i>et al</i> <sup>[61]</sup>	2012	Dens invaginatus	Maxillary right lateral incisor
Vier-Pelisser <i>et al</i> <sup>[62]</sup>	2012	Dens invaginatus	Maxillary left lateral incisor
Kfir <i>et al</i> <sup>[63]</sup>	2013	Dens invaginatus	Right maxillary central incisor
Kato <sup>[64]</sup>	2013	Dens invaginatus	Maxillary lateral incisor
Cantin <i>et al</i> <sup>[65]</sup>	2013	Impaction	Mesiodens
Oenning <i>et al</i> <sup>[30]</sup>	2014	Impaction	Third molar
Mahesh <i>et al</i> <sup>[50]</sup>	2014	Root dilaceration	Permanent maxillary right central incisor

eruption<sup>[22]</sup>. The effect on the underlying tooth bud is related to its stage of odontogenesis, type and direction of impact<sup>[23]</sup>.

Gurge *et al*<sup>[24]</sup> carried out CBCT imaging for comprehensive multiplanar evaluation, exact localization and conservative management of non erupted permanent upper lateral incisor with a previous history of a trauma through the primary predecessor in a 9-year-old patient. They highlighted the need for CBCT image acquisition techniques in the cases of impacted teeth where 3D visualization is necessary.

### Impacted 3rd molars

Third molars are the most frequently impacted teeth. The dental literature has revealed these teeth are usually associated with pericoronitis, cheek biting, cysts, odontogenic tumors, and external root resorption of proximal teeth<sup>[25-29]</sup>. CBCT has proven to be an efficient method for evaluation of spatial relationship in different planes before deciding on management of impacted third molars.

Oenning *et al*<sup>[30]</sup> assessed external root resorption of second permanent molars associated with impacted third molars by conventional radiography and CBCT imaging. They observed significantly higher number of cases of ERR with CBCT imaging technique and highly recommended its use in cases of impaction specially mesioangular or horizontal impactions.

### Impacted canines

Maxillary canines are the 2<sup>nd</sup> most commonly impacted teeth. Earlier tube shift technique was used to reveal the position of unerupted canine but the exact extent of displacement cannot be determined. CBCT imaging is beneficial in providing the accurate labial/palatal position and angulation of the impacted canine<sup>[3,31]</sup>.

Walker *et al*<sup>[12]</sup> assessed the spatial relationship of impacted canines with adjacent structures and root resorption of incisor with the aid of 3D images produced from NewTom QR-DVT 9000. 3D volumetric imaging of impacted canines depicted the size of the follicle, inclination of the long axis of the tooth, relative buccal and palatal positions, bone covering the tooth, 3D proximity and resorption of roots of proximal teeth, local anatomic considerations and stage of dental development.

Liu *et al*<sup>[32]</sup> determined the position of 210 impacted maxillary canines and resorption of adjacent incisors with CBCT images. The angular and linear measurements depicted the spatial variations of the impacted canines which provided the picture for three dimensional relationships of the impactions relative to the adjacent dental arch.

Haney *et al*<sup>[18]</sup> compared differences in the diagnosis and treatment planning of impacted maxillary canines with traditional 2D imaging techniques and 3D CBCT volumetric images. The results yielded that the clinicians' confidence in the accuracy of diagnosis and treatment plan was statistically greater for CBCT images ( $P < 0.001$ ).

Alqerban *et al*<sup>[33]</sup> compared two CBCT systems vs traditional 2D imaging for assessing the location of impacted maxillary canine and identification of root resorption and observed that CBCT was more sensitive than panoramic radiography.

Maverna *et al*<sup>[34]</sup> evaluated different radiographs for the localization of impacted maxillary canines [orthopantomography (OPT), laterolateral and postero-anteriorteleradiography, parallax method, laterolateral, occlusal radiography, computerized axial tomography, cone beam CT]. They concluded that CBCT provided elements which escaped during traditional radiographic analysis and

is therefore indicated in case of impacted teeth or cranio-facial structural anomalies.

## ECTOPIC ERUPTIONS

Transposition is a rare type of ectopic eruption where a permanent tooth erupts in the position normally occupied by another permanent tooth<sup>[35-39]</sup>. Transposition are more frequently observed in upper arch (68.5%-76%) than in lower arch<sup>[39-42]</sup>. Maxillary canine and the first premolars are most commonly transposed<sup>[40]</sup>. The ultimate success of the treatment plan is based upon accurate assessment and precise localization of the transposed teeth. Ericson and Kurol<sup>[43]</sup> reported that, in a sample of Swedish children, conventional periapical radiography successfully localized only 80% of ectopic canines. Rest 20% required tomography for exact localization especially in cases with overlapping lateral incisor (Table 1).

## TALON CUSP

Talon cusp is an unusual morphological dental anomaly that is most commonly seen in the form of an accessory cusp-like structure projecting from the lingual or facial surface of anterior teeth<sup>[44]</sup>. A talon cusp is morphologically well-delineated. The appearance of projection is conical and resembles an eagle's talon. Talon cusp may occur in both primary and permanent dentitions. It can occur in maxillary or mandibular anterior teeth. It is seen in both sexes<sup>[45]</sup>.

Siraci *et al.*<sup>[46]</sup> demonstrated unusual presentation of a talon cusp, occurring on both the facial and lingual surfaces of a supernumerary primary tooth. Existence of pulpal extensions was investigated using cone beam X-ray CT. It revealed distinct existence of pulpal extensions within the facial and palatal talon cusps. According to Mader and Kellogg<sup>[47]</sup>, it was very difficult to distinguish the existence of a pulpal extension, which was confirmed in this case. Other two radiographs were taken from different angles but the interpretation of accessory pulp horns was uncertain which necessitated the utilization of a cone-beam CT for a correct diagnosis.

## ROOT DILACERATION

Dilaceration is a developmental anomaly which occurs as a result of an abrupt change in the axial inclination between the crown and the root of a tooth. But the criteria in the literature for recognizing root dilaceration vary. Two possible causes of dilacerations are trauma and developmental disturbances. It has also been proposed that it might be associated with some developmental syndromes. Dilaceration is seen in both the permanent and deciduous dentitions, and it is more commonly found in posterior teeth and in the maxilla. Periapical radiographs are commonly used to diagnose the presence of root dilacerations<sup>[48]</sup>.

Andrade *et al.*<sup>[49]</sup> evaluated tooth displacement and

root dilaceration after trauma to primary predecessor by CT. The tomograms were analyzed using a dental computed tomography software program in order to evaluate the root formation of the upper right permanent central incisor and its position in the anterior alveolar process.

Mahesh *et al.*<sup>[50]</sup> described the use of CBCT for the 10-year-old patient with the complaint of non-eruption of the permanent maxillary right central and lateral incisors. A cone-beam CT scan was performed to assess the extent of dilaceration, if any, and to aid in the creation of a suitable treatment plan. It revealed palatal displacement of the crown and a gradual curvature in the apical 1/3<sup>rd</sup> of the root of right central incisor.

## SUPERNUMERARY TEETH

Supernumerary teeth are a relatively frequent disorder of odontogenesis characterized by an excess number of teeth. It can be found in any region of the dental arch both in the primary and permanent dentition. Associated complications are failure of adjacent teeth to erupt, displacement and crowding of the adjacent teeth, abnormal diastema, root resorption.

Liu *et al.*<sup>[14]</sup> used CBCT for evaluation of 626 supernumerary teeth in 487 patients. The ability of CBCT to visualize dental and skeletal structures relative to supernumerary teeth was also evaluated. A new system was proposed to classify the complex spatial location of supernumeraries in the maxillary anterior arch based on evaluation with CBCT. Type I, type II, and type VI were located palatal to the neighboring incisors in a variant craniocaudal position. Type III and type IV were seen within the dental arch, oriented normally, inverted, or in cross section. Type V was the supernumerary teeth located labially and superior to the incisor root and is rarest in occurrence. This classification system may yield an accurate picture for the 3D relationship of the supernumeraries relative to the adjacent dental structures, which is important during surgical or orthodontic evaluation. CBCT imaging yields accurate 3D pictures of local dental and bony structures, which is helpful for pretreatment evaluation of supernumerary teeth.

Supernumerary premolars are a rare anomaly in the maxillofacial complex. Its rarity and complex characteristics often makes it difficult to treat. CBCT plays an important role in assessment of both the location and the typing of supernumerary teeth<sup>[14,51,52]</sup>. Thus, CBCT is crucial for exact localization which assists in proper treatment planning, and for the surgical approach in cases of multiple supernumerary teeth<sup>[53]</sup>. The benefits of CBCT imaging being low radiation dose and accurate diagnosis of the complex pathology in case of supernumerary teeth<sup>[54]</sup>. Odontomas are odontogenic tumours, resulting from epithelial growth and differentiated mesenchymal cells, clinically asymptomatic, and often associated with changes to the eruption of the permanent dentition. In recent years,



CBCT has been used in the diagnosis and treatment planning of this condition<sup>[55]</sup>.

## DENS INVAGINATUS

Dens invaginatus (DI) is a dental developmental anomaly that results from invagination of the enamel organ into the dental papilla prior to the mineralization phase<sup>[56]</sup>. The cavity that forms in the case of dens invaginatus may serve as an external route of communication with the pulp or periapical tissues through the foramen caecum. The complexity of the internal anatomy in the case of dens invaginatus creates clinical challenges. Conventional periapical radiographs provide limited information regarding the anatomical configuration. The 3D imaging (CBCT) helps in identifying the morphology of the individual dens so that appropriate treatment planning and treatment options can be selected<sup>[57,58]</sup>.

Patel *et al.*<sup>[59]</sup> reported the use of CBCT in the assessment of chronic periradicular periodontitis associated with an infected invagination in an immature mandibular lateral incisor tooth. A CBCT scan revealed that there was no communication between the invagination and the main root canal. Endodontic treatment was carried out on the invagination. It was observed that the true nature of dens invaginatus cannot be estimated from conventional radiographs accurately. Cone beam computed tomography is a useful diagnostic tool in the management of dens invaginatus.

Kaneko *et al.*<sup>[60]</sup> described the use of CBCT to diagnose Oehlers' type III dens invaginatus in a maxillary lateral incisor. The CBCT scans demonstrated inaccessible and unfilled canal and invagination areas because of complex internal morphology. It was characterized by C-shaped cross-sectional canal configuration with constrictions at different points in different root levels and a prominent intraradicular cavity that was communicated with the enamel-lined invagination and opened into the apical periodontium. It was however judged that further endodontic treatment of the same was not feasible. CBCT helped in the diagnosis thus decision of avoiding further intervention was made that could have been difficult to negotiate.

Narayana *et al.*<sup>[61]</sup> used CBCT to aid in the diagnosis and treatment-planning phase in 11-year-old male who reported for the treatment of maxillary right lateral incisor. 3D imaging helped in identifying the morphology of the individual dens which further guided the selection of the treatment provided. The morphology of the dens invaginatus was identified, and a periapical radiolucent area was detected that was not visible on a standard periapical radiograph.

Vier-Pelisser *et al.*<sup>[62]</sup> presented the case of a maxillary left lateral incisor with Oehlers' type III dens invaginatus in which CBCT was used as an adjunctive resource in the diagnosis and in the planning and 2-year follow-up of the nonsurgical/surgical treatment. The CBCT scans revealed that the periapical radiolucency was significantly larger than seen radiographically and

the increased thickness of the buccal cortical plate was also seen.

Kfir *et al.*<sup>[63]</sup> investigated the use of 3D plastic models, printed CBCT data, for accurate diagnosis and conservative treatment of a complex case of dens invaginatus. The CBCT scan provided with the information about the true nature of invagination and its relationship to the main canal. It was useful for demonstrating how the invagination had compressed the pulp space of the main canal at different levels which led to irregular main canal with a cross-section resembling a thin crescent encircling the invagination. It was also seen that there was no communication between the invagination and the pulp space.

Kato<sup>[64]</sup> described a case of surgical and non-surgical endodontic therapy for a maxillary lateral incisor with type III dens invaginatus with necrotic pulp and an associated large periradicular lesion. CBCT was used for three-dimensional observation of the morphological details of this area. It was observed that even complicated cases of dens invaginatus can be diagnosed and treated using non-surgical root canal management with the help of CBCT.

Dens invaginatus can also be associated with other abnormalities such as dysmorphic mesiodens. Though this condition can be detected by chance on the conventional radiography, the three-dimensional nature and the exact morphological patterns of DI can be determined by CBCT. Cantin *et al.*<sup>[65]</sup> presented a morphological study of impacted mesiodens in a 9-year-old girl in whom the three coronal invaginations were detected only by CBCT.

The presence of double dens invaginatus is extremely rare. Understanding the type, extension, and complex morphology of dens invaginatus is essential for the proper treatment planning. Advanced imaging techniques, such as CBCT are very helpful in diagnosis of these complex anatomic variations as they give the 3 dimensional images unlike the conventional radiographic methods<sup>[66]</sup>.

## FUSION

Fusion also known as synodontia or false germination; occurs due to the union of 2 or more separately developing tooth germs at the dentinal level, presenting a single large tooth during odontogenesis, when the mineralization of crown is yet mineralized<sup>[67]</sup>. The prevalence of tooth fusion is estimated to be 0.5%–2.5% in primary dentition<sup>[68]</sup>, whereas it is lower in permanent dentition. When fusion takes place between a normal tooth and a supernumerary tooth, the fused teeth shows an anomalous broad crown<sup>[69]</sup>. The pulp chambers and root canals can be joined or separated, depending on the stage of development when fusion took place<sup>[70]</sup>. Radiographic examination of fused teeth is important for management of endodontic problems. But the conventional intraoral periapical views produced only a 2D image which resulted in the superimposition

**Table 2** Role of spiral computerized tomography in diagnosis of morphological disturbances of teeth

Ref.	Morphological disturbance	Tooth involved
Gopikrishna <i>et al</i> <sup>[79]</sup>	Unusual morphology of a single root and a single canal	Maxillary first molar
Ballal <i>et al</i> <sup>[77]</sup>	Fusion	Mandibular second molar with a paramolar
Metgud <i>et al</i> <sup>[78]</sup>	Single conical non bifurcated posterior root forms, taurodontism, dens invaginatus, labial lobes of the canines, pyramidal cusps of the premolars, dens evaginatus of the molar crowns, and localized reduction in tooth size	Entire dentition

of structures<sup>[71]</sup>. Nowadays a new diagnostic tool, CBCT, is being used in endodontics. Matherne *et al*<sup>[72]</sup> reported that CBCT imaging is useful in identifying root canal systems.

Song *et al*<sup>[73]</sup> discussed the endodontic management of a supernumerary tooth fused with a right maxillary first molar. They used CBCT for proper imaging of the same. Proper diagnosis and treatment planning can be done with the use of CBCT that further ensures predictable and successful results.

Ferreira-Junior *et al*<sup>[74]</sup> reported a case of fusion between an impacted third molar and a supernumerary tooth. The surgical intervention was carried out, with the objective of eliminating the dental elements. Proximity to the mandibular ramus made the final diagnosis difficult with panoramic radiography. Thus, CBCT was used to determinate the final diagnosis and also to help in the further surgical planning. It was observed that cone-beam computed tomography resulted in precise 3D information which was not possible with conventional radiography (Table 2).

Recently, a new CT technique, *i.e.*, spiral computed tomography (SCT) also called volume acquisition CT, has been developed which has a significant advantage. It uses simultaneous patient translation through the X-ray source with continuous rotation of the source-detector assembly<sup>[75]</sup>. SCT acquires raw projection data with a spiral-sampling locus in a relatively short period<sup>[76]</sup>. The data can be viewed as conventional transaxial images without any additional scanning time. This technique makes reconstruction of overlapping structures at arbitrary intervals possible. Thus the ability to resolve small subjects is increased.

The unique arrangement of the gantry and rotating X-ray source assembly reduces scan times. With standard incremental CT, small objects can be missed or their detection compromised if the patient's degree of inspiration and expiration varies from scan to scan. Moreover, multiplanar and 3D image reconstructions of structures from standard incremental CT data are degraded by motion-induced misregistration artifacts<sup>[77]</sup>.

Ballal *et al*<sup>[77]</sup> reported a rare case of successful endodontic management of unilateral fused mandibular second molar with a paramolar. The rarity and complexity of the entity makes it difficult to diagnose and treat. The use of diagnostic imaging modalities such as spiral SCT helps in forming a confirmatory diagnosis and treatment plan.

Metgud *et al*<sup>[78]</sup> reported a unique case with a

unusual combination of morphological dental anomalies, including single conical non bifurcated posterior root forms, taurodontism, dens invaginatus, labial lobes of the canines, pyramidal cusps of the premolars, dens evaginatus of the molar crowns, and localized reduction in tooth size involving the entire dentition. It was not related with any other apparent systemic complication. The accurate assessment of the presence of single conical non bifurcated posterior root forms was done with the help of spiral computerized tomography.

Gopikrishna *et al*<sup>[79]</sup> reported a maxillary first molar with an unusual morphology of a single root and a single canal. An accurate assessment of this unusual morphology was made with the help of a Spiral computed tomography which was then endodontically managed.

Both case reports highlighted the use of high-end diagnostic imaging modalities such as spiral computerized tomography in diagnosis of the various morphologic abnormalities (Table 3).

3D imaging techniques are being utilized in dentistry beyond maxillofacial surgical planning. Dental magnetic resonance imaging (MRI) is technique that adds a third dimension to treatment planning other than on CT and digital volume tomography.

MRI, is quite new in the field of dental radiology. The technique does not use ionizing radiation and is safe when no contraindications are present such as (cardiac pacemakers, implanted cardiac defibrillators, aneurysm clips, neurostimulators, metallic foreign bodies in the eyes, *etc.*). It has no limitations in the frequency of examinations. MRI is based on the nuclear magnetic resonance phenomenon, which takes place when nuclei of certain atoms (usually hydrogen in medicine) are placed in a strong static magnetic field and absorb energy of an alternating magnetic field of a specific, resonant frequency. The use of spatially varying magnetic fields makes it possible to spatially encode the nuclei and perform tomographic imaging.

The signal measured on MRI usually originates from soft tissues and liquids in the human body. The teeth and jawbone appear black in images taken by MRI due to low water content and short relaxation constants of hydrogen atoms. The dental pulp, jawbone marrow, mandibular canal containing the mandibular artery and vein and the alveolar nerve, saliva, gingiva, facial soft tissues, tongue, and palate produce a signal on clinical MRI. But there is no measurable signal from dental enamel, dentin, cortical bone, and air. The structures that do not produce any sign can also be measured indirectly from the contrast

**Table 3** Magnetic Resonance Imaging in diagnosis of eruptive and morphological dental anomalies of permanent teeth

Ref.	Morphological disturbance	Tooth involved
Tymofiyeva <i>et al</i> <sup>[81]</sup>	Impaction	Entire dentition
Tymofiyeva <i>et al</i> <sup>[83]</sup>	Mesiodens, gemination, dilacerations, transmigration, transposition	Entire dentition

with adjacent signal-emitting structures.

MRI enables 3D measurement of the mandible because of the contrast between the cortical bone and the surrounding soft tissue<sup>[80]</sup>. Impacted teeth can be visualized and their positions in all 3 dimensions can be assessed. As there is difference in contrast between the teeth and the surrounding tissue, such as the gingiva, tongue, cheek, saliva, and jaw bone marrow<sup>[81]</sup>. The most significant advantage of dental MRI is the complete absence of ionizing radiation when compared to other 3D imaging techniques.

Tymofiyeva *et al*<sup>[81]</sup> discussed economic aspects and technical properties of MRI compared with cone-beam CT in diagnosing impacted teeth. Gaudino *et al*<sup>[82]</sup> reported that MRI shows a comparable accuracy and better visibility in the detection of teeth and periodontal anatomy compared with cone-beam CT.

Tymofiyeva *et al*<sup>[83]</sup> assessed the feasibility of MRI of dental abnormalities in 16 patients (mean age, 10.8 years). The selected patients included 3 with a mesiodens, 9 with supernumerary teeth other than a mesiodens, 1 with gemination, 1 with dilacerations, 1 with transmigration, and 1 with transposition. MRI was found to be a suitable imaging modality for the diagnosis of dental abnormalities in children and for orthodontic treatment and surgical planning. MRI had various advantages when compared with conventional radiographic methods such as 3 dimensionality and complete elimination of ionizing radiation, which is relevant for repeated examinations in children.

## CONCLUSION

In conclusion, the results of this review showed that 3D imaging techniques are crucial for exact localization and provides precise three dimensional information on spatial relationships by depicting the size of the follicle, inclination of the long axis of the tooth, relative buccal and palatal positions, bone covering the tooth, proximity and resorption of roots of proximal teeth, local anatomic considerations and stage of dental development. Thus, the use of newer image acquisition techniques such as Cone Beam Computed Tomography, Spiral Computerized Tomography and Magnetic Resonance Imaging are advocated for final diagnosis and precise treatment planning of eruptive and morphological dental anomalies.

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## Klippel-feil: A syndrome in the occipital-cervical spine field and its dentofacial manifestations

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vertebrae and deviations in the craniofacial profile in non-syndromic patients with severe malocclusion. To our knowledge, no previous studies have described the craniofacial profile including the cranial base of KFS patients on lateral cephalograms. Therefore KFS and its craniofacial and dental manifestations were described according to existing literature and additionally the craniofacial profile and cranial base was analysed on lateral cephalograms of two patients with KFS. According to the literature the dental manifestations of KFS-patients included oligodontia, overjet, cross bite, open bite and deep bite. The craniofacial profile was clinically described as reduced lower facial height, midfacial hypoplasia, and mandibular prognathia. The analyses of the two lateral cephalograms showed increased mandibular inclination, increased vertical jaw-relationship, increased jaw angle and maxillary retrognathia. The cranial base was normal in both cases. The sagittal jaw relationship and mandibular prognathia varied between the two cases. The literature review and the analyses of the two lateral cephalograms have shown that deviations in the occipital and cervical spine field as KFS were associated with deviations in the teeth and craniofacial profile.

**Key words:** Occipital and cervical spine field; Klippel-Feil syndrome; Notochord; Embryology; Cervical column morphology; Malocclusion

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### Abstract

Klippel-Feil syndrome (KFS) is defined by congenital cervical vertebral spine fusion and is seen with a wide spectrum of dental manifestations and craniofacial profiles. Previous studies on lateral cephalograms have documented an association between fusion of the cervical

**Core tip:** Klippel-Feil syndrome (KFS) is defined by congenital cervical vertebral spine fusion and is seen with a wide spectrum of dental manifestations and craniofacial profiles. According to the literature dental manifestations of KFS-patients included oligodontia, horizontal maxillary overjet, cross bite, open bite and deep bite. The craniofacial profile was clinically described as reduced lower facial height, midfacial hypoplasia, and mandibular prognathia. Furthermore, two cases showed

increased mandibular inclination, increased vertical jaw-relationship, increased jaw angle and maxillary retrognathia. The literature review and case analyses showed that deviations in the occipital and cervical spine field as KFS were associated with dentofacial deviations.

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## INTRODUCTION

Spranger *et al.*<sup>[1]</sup> define syndromes accordingly: "A syndrome is a pattern of multiple anomalies thought to be pathogenically related and not known to represent a single sequence or a polytopic field defect". "Sequence" is defined as "A pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor" and polytopic field defect is defined as "A pattern of anomalies derived from the disturbance of a single developmental field"<sup>[1]</sup>. Dorland's Illustrated Medical Dictionary defines syndromes as: "A set of symptoms that occur together; the sum of signs of any morbid state; a symptom complex. In genetics, a pattern of multiple malformations thought to be pathogenically related"<sup>[2]</sup>.

In Gorlin's Syndromes of the Head and Neck<sup>[3]</sup> states that: "Congenital malformations of the head and neck are common and most resolve spontaneously within the first few days of postnatal life". In some cases these "congenital malformations" turns out to be a part of a syndrome.

There are many different syndromes of the head- and neck-region and these syndromes are characterized by various clinical manifestations<sup>[3]</sup>. The manifestations can be specific for one particular syndrome, but different syndromes can have common manifestations<sup>[3]</sup>. Clinical manifestations can be revealed as skeletal deviations, soft-tissue-deviations or a combination of both<sup>[3]</sup>.

Klippel-Feil syndrome (KFS) is a syndrome of the head- and neck-region. The syndrome has originally been described in the 16<sup>th</sup> Century, but was not named until 1912 by Hennekam *et al.*<sup>[3]</sup>. KFS is defined by faulty segmentation of two or more cervical vertebrae<sup>[3]</sup> resulting in the occurrence of fusion of two or more cervical vertebrae on head film radiographs as lateral cephalograms. KFS is characterized by a triad of clinical symptoms such as short neck, limitation of head movement, and low posterior hairline. Furthermore, there are many associated anomalies in the craniofacial field in patients with KFS<sup>[3]</sup>.

KFS is located in the occipital and cervical spine developmental field. The occipital and cervical spine field consists of structures of common embryological origin

initiated by notochordal induction of the sclerotome formation in the somites, which develop into the cervical spine and the osseous structures in the occipital region<sup>[4-9]</sup>. The developmental field is funnel-shaped and limited anteriorly by the vertebral bodies, the basilar part of the occipital bone, and the postsphenoid bone. Posteriorly, the developmental field is limited by the cartilaginous part of the occipital bone and the vertebral arches<sup>[5,6]</sup>.

A series of recent studies of non-syndromic patients with severe skeletal malocclusion traits have described the occurrence of cervical vertebral column fusion anomalies and analyzed the association between fusion anomalies and the craniofacial profile on lateral cephalograms<sup>[10-13]</sup>. These studies have documented significant associations between fusion and a large cranial base angle, between fusion and retrognathia of the jaws, and between fusion and inclination of the jaws. These findings indicate an association between fusion of the cervical vertebral column and the craniofacial profile including the cranial base in non-syndromic patients with severe skeletal malocclusion traits<sup>[10-14]</sup>.

To our knowledge no previous studies have described the craniofacial profile including the cranial base of KFS patients on lateral cephalograms.

Therefore, the aim of the present study was to describe KFS and its craniofacial and dental manifestations according to previous literature. Additionally, the aim was to describe the craniofacial profile including the cranial base on lateral cephalograms of two patients with KFS.

## RESEARCH

A literature review was performed in order to describe KFS and the dentofacial manifestation. Furthermore, lateral cephalograms of two patients with KFS with no other known symptoms (one boy, 8 years old and one girl, 15 years old; Figures 1 and 2) were included in the study. The two KFS patients comprise all KFS patients with no other known symptoms from Professor Sven Kreiborg's archive, Department of Odontology, Copenhagen University. The craniofacial profile including the cranial base were measured by points and lines according to Solow and Tallgren<sup>[9]</sup>; illustrated in Figure 3. The landmarks used in the present study were marked on acetate sheets fixed to the radiograph. The variables were measured using a protractor and are shown in Table 1. The variables were compared to normal values of the craniofacial profile according to Björk *et al.*<sup>[15]</sup> (Table 1). As the present study was a literature review and description of two lateral cephalograms no statistical analyses have been applied.

## LITERATURE REVIEW

### Definition, prevalence and diagnosis

KFS is a rare, congenital, skeletal malformation. It is defined by failure of normal segmentation of any two of the seven cervical vertebrae<sup>[16,17]</sup>. KFS may



Figure 1 Lateral cephalogram of an 8-year-old boy with Klippel-Feil syndrome with no other symptoms.



Figure 2 Lateral cephalogram of a 15-year-old girl with Klippel-Feil syndrome with no other symptoms.

include fusion caudally of the cervical region. However, fusion in the lower spine, in the absence of cervical vertebral fusion, is not classified as KFS<sup>[18]</sup>. Generally, the second and the third vertebrae (C2-3)<sup>[18-20]</sup> and the fifth and sixth vertebrae (C5-6)<sup>[19]</sup> interspaces are most commonly fused. The C2-3 interspace fusion is thought to be an autosomal dominant inheritance, while C5-6 interspace fusion is considered to be autosomal recessive<sup>[19]</sup>.

The absence of population screening studies has made it impossible to define the exact incidence and prevalence of KFS, but it has been estimated that it occurs in approximately 1:40,000-42,000 births<sup>[21,22]</sup>. Other studies have suggested, that KFS has an incidence of up to 0.5% of live births<sup>[18]</sup>. The incidence was none significantly slightly higher in females<sup>[19,21,22]</sup>.

Although affected patients have cervical anomalies at birth, KFS is usually diagnosed at a later age<sup>[22]</sup>. It has been suggested that the fusion process in KFS patients is not fully present at birth and could be ongoing until skeletal maturity<sup>[20]</sup>. The disorder is often discovered incidentally when radiographs have been taken for other reasons<sup>[22]</sup>. The prognosis for most individuals diagnosed with KFS is good if the disorder is diagnosed early. But diagnostics of KFS is often complicated because the presence of cervical fusion

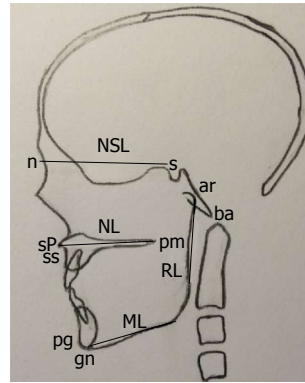


Figure 3 Illustration of reference points and lines according to Solow and Tallgreen<sup>[9]</sup>, 1976 on lateral cephalogram. NSL: Nasion-Sella line; NL: Nasal line; ML: Mandibular line; RL: Ramus line.

cannot be determined in children younger than 8 years due to the development and ossification of the cervical vertebrae<sup>[17,22]</sup>.

Occipitalization is also seen in KFS<sup>[20]</sup>, and patients with atlantoaxial fusions are often diagnosed with KFS at younger ages than patients with more caudal fusions<sup>[22]</sup>.

### **Etiology, pathogenesis and classification**

KFS is both affected by genetic and environmental factors and is morphologically and etiologically heterogeneous<sup>[3,23]</sup>. The heterogeneity of patients with KFS has made the diagnosis and classification difficult and has complicated elucidation of the genetic etiology of the syndrome<sup>[22]</sup>. Mutations in Pax1 have been found in patients with KFS, but the significance remains uncertain<sup>[3]</sup>.

The earliest classification of KFS, by Feil, was based only on the anatomic distribution of the fused segments. Patients with KFS were assigned to one of three types<sup>[19]</sup>: Type I applied to patients with extensive cervical and upper thoracic fusion. Type II defined patients with one or two cervical interspace fusions and are often associated with hemivertebrae and occipitoatlantal fusion. Type III classified individuals with both cervical and lower thoracic or lumbar fusion<sup>[19]</sup>.

Whereas Feil's classification was based on the extent of vertebral fusion, a classification made by Clarke *et al.*<sup>[18]</sup> focused on the etiology and genetic origins of the syndrome. Clarke *et al.*<sup>[18]</sup> used three families, all affected with KFS, as a model for a new and comprehensive classification consisting of four different classes of KFS (KF1-4). Their study showed that an association exists between the position of the most rostral fusion, mode of inheritance, and some specific KFS associated anomalies<sup>[18]</sup>.

### **Craniofacial and dental symptoms**

Fusion of the cervical vertebrae can be symptomatic or asymptomatic. Some studies have found that up to 68% of KFS patients reported symptoms related to their syndrome<sup>[20]</sup>. The classic triad of KFS included low



**Table 1** Measurements of the craniofacial profile in two Klippel-Feil syndrome patients (case I and II) and normal values

	Boy 8 yr (Figure 1) Case I	Girl 15 yr (Figure 2) Case II	Normal values according to Björk <i>et al.</i> <sup>[15]</sup>
Sagittal dimensions			
s-n-ss	78.5°	76°	82° (SD 3.5°)
s-n-pg	75°	86°	80° (SD 3.5°)
ss-n-pg	3.5°	-10°	2° (SD 2.5°)
Vertical dimensions			
NSL/NL	9.5°	8°	8° (SD 3°)
NSL/ML	39.5°	37°	33° (SD 6°)
NL/ML	30°	29°	25° (SD 6°)
Cranial base			
n-s-ba	132°	134°	131° (SD 4.5°)
Jaw angle			
ML/RL	142°	131°	126° (SD 6°)

Normal values according to Björk *et al.*<sup>[15]</sup>. SD: Standard deviations; NSL: Nasion-sella line; NL: Nasal line; ML: Mandibular line; RL: Ramus line.

posterior hairline, short neck, and limitation of the neck movement<sup>[17,19]</sup>. However, the triad is present in only 50% of the patients<sup>[16,19,22]</sup>. Several other anomalies have been associated with KFS in varying degrees<sup>[18]</sup>. The anomalies included both systemic manifestations and craniofacial manifestations<sup>[24]</sup>.

The most common manifestations in the craniofacial field are cleft palate<sup>[19,24]</sup>, bifid uvula, and facial asymmetry<sup>[24]</sup>. Less frequently reported is the incidence of craniosynostosis and facial appearance. Facial appearance includes: reduced lower facial height, midfacial hypoplasia, mandibular malformation, and hypoplasia<sup>[19,24]</sup> and mandibular prognathia<sup>[25]</sup>.

Moreover, KFS-patients show jaw anomalies, *e.g.*, multiple jaw cysts, abnormal bony masses, duplication of the rami of the mandibular, and pseudoankylosis of the TMJ<sup>[24]</sup>. The documentation of the manifestations was based on clinical examinations and visual assessment of lateral cephalograms without any linear or angular measurements reported to describe the craniofacial profile.

The described dental manifestations included: oligodontia<sup>[17,24,26]</sup>, horizontal maxillary overjet, cross bite, anterior open bite<sup>[24]</sup>, and deep bite<sup>[17]</sup>. A case report has shown persistent primary teeth due to late eruption of the permanent dentition. Furthermore, the report showed velopharyngeal insufficiency causing difficulty in chewing and talking<sup>[17]</sup>.

It has not been determined whether the craniofacial and dental findings were of random association or if they were truly related by any malformation mechanism of KFS<sup>[17]</sup>.

## ANALYSIS OF THE TWO CASES

The results of the analyses of the craniofacial profile on lateral cephalograms and the normal values according

to Björk *et al.*<sup>[15]</sup> are shown in Table 1.

Regarding the vertical dimensions of the craniofacial profile the KFS patients showed an increased mandibular inclination (NSL/ML), increased vertical jaw-relationship (NL/ML) and an increased jaw angle (ML/RL) compared to normal values (Table 1, Figures 1 and 2). In the sagittal plane the two cases showed retrognathia of the maxilla (s-n-ss) compared to the normal values whereas the prognathia of the mandible (s-n-pg) was larger in case II and smaller in case I. Furthermore, the sagittal jaw relationship (ss-n-pg) was larger in case I and smaller in case II compared to normal values (Table 1, Figures 1 and 2). The inclination of the maxilla (NSL/NL) and the cranial base angle (n-s-ba) was comparable to normal values.

## DISCUSSION

KFS is a rare, congenital malformation defined by faulty segmentation of two or more cervical vertebrae<sup>[3]</sup>. Therefore, KFS is located in the occipital and cervical spine field<sup>[4-9]</sup>. The syndrome is morphologically and etiologically heterogeneous and within the group of KFS patients several anomalies have been reported<sup>[22]</sup>. In the literature the dental manifestations in KFS-patients were reported as oligodontia, horizontal maxillary overjet, cross bite, anterior open bite, and deep bite<sup>[24]</sup>. The craniofacial profile was clinically described as reduced lower face height, midface hypoplasia, and mandibular prognathia<sup>[24]</sup>.

When comparing the clinical reports in the literature on the craniofacial profile with the two cases analyzed on lateral cephalograms in the present study some similarities are evident. The midface hypoplasia is described in the literature<sup>[24]</sup> and is also found in the two cases as retrognathia of the maxilla. Only in one case (case II) was mandibular prognathia seen in agreement with the clinical reports in the literature<sup>[24]</sup>. The increased inclination of the mandible, the increased vertical jaw-relationship, and the increased jaw angle indicating an increased lower face height in both cases in the present study was in disagreement with previous clinical reports in the literature<sup>[24]</sup>. The agreement and disagreements between the literature and the cases in the present study may reflect the morphologically and etiologically heterogeneous within the group of KFS patients<sup>[22]</sup> which complicates the understanding of this developmental syndrome<sup>[18]</sup>.

Recently, a series of studies have shown significant associations between fusion of the cervical vertebrae and retrognathia of the jaws, between fusion and inclination of the jaws, and between fusion and a large cranial base angle in non-syndromic patients with severe skeletal malocclusion traits<sup>[10-12,14]</sup>. The measurements of the two KFS-cases showed both similar but also deviant patterns compared to those documented in the non-syndromic patients. Retrognathia of the maxilla was in agreement with previous findings in non-syndromic

patients with fusion of the cervical vertebrae as well as inclination of the mandible<sup>[10-12,14]</sup>. On the other hand, retrognathia of the mandible was only seen in one case (case I) whereas mandibular prognathia was found in case II. Surprisingly, none of the cases showed a large cranial base angle, which was expected according to the literature<sup>[10-12,14]</sup>.

An explanation for the association between the cervical spine and the craniofacial profile including the cranial base found in KFS and non-syndromic patients with fusion of the cervical vertebrae could be the notochord in the early embryogenesis<sup>[4]</sup>. The notochord develops in the human germ disc and determines the development of the cervical vertebrae, especially the vertebral bodies and the basilar part of the occipital bone in the cranial base (the posterior part of the cranial base angle)<sup>[4-9]</sup>. The para-axial mesoderm forming the vertebral arches and the remaining parts of the occipital bone are also formed from notochordal inductions<sup>[4-9]</sup>. The notochord is, by direct or indirect signaling, responsible for the formation of the structures in the occipital and cervical spine field in the early embryogenesis<sup>[4,5]</sup>. Therefore, a deviation in the development of the notochord may influence the surrounding bone tissue in the spine as well as in the posterior part of the cranial base to which the jaws are attached<sup>[10-14,27]</sup>. Furthermore, the jaws, including the condylar cartilage, develop from tissue that derives from the neural crest. The neural crest cells migrate to the craniofacial area before the notochord is surrounded by bone tissue and disappears<sup>[4]</sup>. In the first branchial arch, the neural crest cells migrate from the neural crest towards the mandible, followed by the cells to the maxilla, and lastly by the cells to the nasofrontal region<sup>[4]</sup> before the notochord is surrounded by bone tissue<sup>[28]</sup>. Therefore, it is understandable that a disturbance in the amount of migrating maxillary and mandibular cells or timing of the migration of the maxillary and mandibular cells may influence both the sagittal development (retrognathia of the jaws) and vertical development (inclination of the jaws)<sup>[11-13]</sup>. How the migration of the neural crest cells are influenced by signals from the notochord is still unclear, but signaling during early embryogenesis between the notochord, para-axial mesoderm, the neural tube, and the neural crest, as described above, is believed to be important for the associations between malformation of the craniofacial structures and the cervical vertebrae<sup>[14,27]</sup>.

The associations found in KFS and in non-syndromic patients with severe malocclusion traits between fusion of the cervical vertebrae and deviations in the craniofacial profile may lead to considerations regarding etiology and classification of KFS.

## CONCLUSION

KFS is defined by congenital vertebral fusion of the cervical spine and is seen with a wide spectrum of dental manifestations and craniofacial profile. According to

the literature the dental manifestations of KFS-patients include oligodontia, horizontal maxillary overjet, cross bite, open bite and deep bite. The craniofacial profile is clinically described as reduced lower facial height, midfacial hypoplasia, and mandibular prognathia.

The analyses of the two lateral cephalograms showed increased mandibular inclination, increased vertical jaw-relationship, increased jaw angle and maxillary retrognathia. The cranial base was normal in both cases. The sagittal jaw relationship and mandibular prognathia varied between the two cases.

The literature review and the analyses of the two lateral cephalograms have shown that deviations in the occipital and cervical spine field as KFS were associated with deviations in the teeth and craniofacial profile.

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## Treatment of mouth and jaw diseases with intralesional steroid injection

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joint. This technique is used also for a number of mouth and jaw lesions. Localized langerhans cell histiocytosis, central giant cell granuloma, oral submucous fibrosis, oral lichen planus, lichen sclerosus of the oral mucosa, lymphatic malformations and orofacial granulomatosis can be considered among these diseases. The purpose of this review is to investigate the effects of intralesional steroid injections in the treatment of oral diseases.

**Key words:** Intralesional injections; Steroids; Langerhans Cell histiocytosis; Giant cell granuloma; Oral submucous fibrosis; Oral lichen planus; Orofacial granulomatosis

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**Core tip:** Intralesional steroid injections are often used in the lesion occurred in oral and maxillofacial region in recent years. Especially in large lesions, it can be applied as an alternative or adjunct to surgical procedures. It is an effective treatment method, because, without the need for major surgical procedures and providing patient comfort.

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### Abstract

Many lesions of the oral region are treated with surgical methods such as curettage and resection. Chemotherapy and radiation therapy with or without surgical intervention can be used as an adjunct in some cases. Intralesional steroid injection is a conservative procedure which is already used in various regions of the body and

### INTRODUCTION

Corticosteroids are one of the most widely used drugs due to their anti-inflammatory, anti-allergic and immunosuppressive effects. Today they are used as systemic, topical, intra-articular and intralesional in the clinic. They were first used systemically in a patient with severe rheumatoid arthritis in 1948 by Hench *et al*<sup>[1]</sup>.



Consequently a further 15 patients were successfully treated. In 1950, their discovery of the effect of cortisone brought Hench, Edward and Reichstein the Nobel Prize in Medicine and Physiology<sup>[2]</sup>. Beneficial effects of intra-articular corticosteroid (hydrocortisone acetate) injection was first published in 1951<sup>[3]</sup>. In 1956, prednisolone was introduced by Rothermich and Phillips<sup>[4]</sup> as an satisfactory and more potent alternative for intra-articular injections. Boland and Liddle<sup>[5]</sup> compared methylprednisolone with prednisolone and found them equally effective. Triamcinolone acetonide was applied in the treatment of dermatoses by Robinson<sup>[6]</sup> in 1958. Later, triamcinolone hexacetonide was reported to be a potent synthetic corticosteroid for intra-articular usage<sup>[7]</sup>. In the 1970s, corticosteroids were administered in intra-osseous lesions such as bone cysts<sup>[8-10]</sup>. Intralesional steroid injection (ISI) has been performed in both of bone and mucosal lesions of oral and maxillofacial region since 1980. Currently, this method is widely accepted as an alternative or aid to surgical treatment especially in large reactive lesions.

In this review, we review the hard and soft tissue lesions of oral region that can be treated with intralesional steroid injections. Under the each disease's title, we also discuss the action mechanism of steroids.

## DISEASES THAT CAN BE TREATED WITH ISI

### **Bone lesions**

Localized langerhans cell histiocytosis (eosinophilic granuloma) and central giant cell granuloma.

### **Soft tissue lesions**

Soft tissue lesions include oral submucous fibrosis; oral lichen planus; oral lichen sclerosis; lymphatic malformations; and orofacial granulomatosis.

## LOCALIZED LANGERHANS CELL HISTIOCYTOSIS (EOSINOPHILIC GRANULOMA)

Langerhans' cell histiocytosis (LCH), formerly known as histiocytosis-X, is a disease characterized by cell proliferation exhibiting phenotypic characteristics of Langerhans cells<sup>[11]</sup>. There are three clinical forms of the disease: Letterer-Siwe disease, Hand-Schüller-Christian syndrome and Localized Langerhans Cell Histiocytosis (LLCH) or eosinophilic granuloma<sup>[12]</sup>.

Letterer-Siwe disease is an acute disseminated form of LCH and characterized by hepatosplenomegaly, lymphadenopathy, anemia, skin rash, and bone lesions with dissemination. It usually affects young children and follows an acute or sub-acute course.

Chronic disseminated form of the LCH is called Hand-Schüller-Christian syndrome and it is usually associated

with a triad of exophthalmos, diabetes insipidus and punched-out bone lesions. This form of the disease typically affects the patients in the second and third decades or older age<sup>[13]</sup>.

LLCH, a localized disease. It accounts for 60%-70% of LCH cases and it can be found as solitary or multifocal bone defects. While mandible, skull and ribs are most often affected in children, long bones and vertebrae are more frequently involved in adults. The disease peaks in the first three decades and males are affected twice as females<sup>[14]</sup>. Possible symptoms are swelling, pain and tenderness over the lesion's site. General malaise, fever, headache, toothache, bleeding, loose teeth and sensory disturbances may accompany as well. It is also possible not to see any symptoms<sup>[15]</sup>. The lesions appear as radiolucent areas with well-demarcated borders in radiographic views. Pathologic fractures may arise due to resorption of the overlying cortical bone<sup>[16]</sup>. Treatment options of LLCH include resection or curettage, chemotherapy, radiotherapy or a combination of them<sup>[17]</sup>. Spontaneous healing has been reported, too<sup>[18]</sup>.

### **Treatment of the LLCH with ISI**

Currently there is not a clear treatment protocol for the ISI in the LLCH. Previously a few studies have been reported. In 1980, Cohen *et al*<sup>[19]</sup> first employed this technique in eosinophilic granulomas of the bones. While they did a single dose of methylprednisolone directly into the lesions in various parts of the body, in mandibular lesions they did a second injection. Jones *et al*<sup>[16]</sup> applied single intralesional dose of 165 mg methylprednisolone to a mandibular LCH and reported complete resolution of the lesion after 8 mo. Others<sup>[20]</sup> have described a case with multifocal LCHs in the mandible, who failed to respond to radiotherapy and systemic therapy with prednisone and etoposide. On a weekly basis, the authors injected 2 mL of 25 mg/mL triamcinolone into the lesion for six times. Complete remission was reached by the 15 mo. Putters *et al*<sup>[21]</sup> treated three LLCH cases of the mandible in a one-stage procedure. They performed intralesional injections of 80, 40, and 80 mg of methylprednisolone succinate, respectively. The lesions showed radiologically and clinically complete remission after 6 mo. In another case<sup>[22]</sup>, 200 mg of intralesional methylprednisolone injection was used in a mandibular lesion and complete resolution had been achieved after 17 mo. Esen *et al*<sup>[23]</sup> reported a case of LLCH of the mandible, which also caused a non-displaced pathologic fracture. They started repeated ISIs and the fracture line disappeared within 14 mo without using any reduction or fixation methods. By the end of the 36-mo follow-up, the lesion was entirely healed. In a later paper<sup>[24]</sup>, two patients were treated in one-stage procedures with intralesional methylprednisolone injections. The lesions healed clinically and radiologically 35 and 15 mo after treatment.

### Action mechanism of steroids

Many questions remain to be clarified to understand the therapeutic effects of corticosteroids in LLCH. It is unknown whether they suppress T lymphocytes, the Langerhans cells, eosinophils or stimulate osteogenesis. It has been suggested<sup>[8,25]</sup> that corticosteroid microcrystals can break the connective tissue of the cystic wall and allow secondary osteogenic repair or IL-1 is inhibited by steroids. Even though these hypotheses may explain the improvement in bone cysts, it does not apply to LLCH, because there is no membrane covering the lesion.

As evident from the literature, ISI is a successful method in cases of LLCH. It is an effective treatment method, because, without the need for major surgical procedures and providing patient comfort.

## CENTRAL GIANT CELL GRANULOMA

The central giant cell granuloma (CGCG) was first described by Jaffe<sup>[26]</sup> in 1953. CGCG occurs almost solely within the jaws and it is a benign proliferation of fibroblasts and multinucleated giant cells. It typically presents as a solitary radiolucent lesion of the mandible or maxilla. The lesions occur twice as often in the mandible than in the maxilla. It is predominantly found in young adults before the age 30 with a female preponderance<sup>[27]</sup>. Based on its clinical behavior, CGCG has been classified as non-aggressive and aggressive lesion. Non-aggressive lesions tend to grow slowly and do not perforate the cortical bone. Recurrence usually is not seen after treatment. Aggressive lesions are characterized by rapid growth, pain, expansion or perforation of the cortical bone, root resorption, and a high recurrence tendency<sup>[28]</sup>. The traditional treatment of CGCG is curettage or resection depending on the lesion's behavior, size, location, and radiographic appearance. Non-surgical treatment methods are systemic administration of calcitonin, intralesional injection of corticosteroids and administration of  $\alpha$ -interferon<sup>[29-32]</sup>.

### Treatment of the CGCG with ISI

The treatment of CGCG with corticosteroids was first reported by Jacoway *et al*<sup>[33]</sup> in 1988. They suggested is a 50/50 mixture of 2% lidocaine with 1:100000 epinephrine and triamcinolone acetonide (TA) to inject 2 mL/1 cm of lesion as seen on a panoramic radiography and to repeat this six times at weekly intervals. Later, Terry and Jacoway<sup>[34]</sup> presented four patients treated with steroids in 1994. A weekly done ISI during six weeks resulted in a complete resolution in three patients, while one patient needed additional surgery. Kermer *et al*<sup>[35]</sup> published another case of CGCG treated with corticosteroids in the same year. Rajeevan and Soumithran<sup>[36]</sup> reported that intralesional triamcinolone acetonide was administered to a 17-year-old girl who had CGCG in 1998. They indicated that almost healing the lesion of the left mandible was observed after the

sixth month. In 2000, Khafif *et al*<sup>[37]</sup> applied the same protocol to a 36-year-old female patient who had a CGCG of maxilla and they reported that a complete remission was seen after two years. Kurtz *et al*<sup>[38]</sup> also used ISI to a 10-year-old CGCG patient in 2001. They reported that the proper healing was seen after 5 years. In 2002, Carlos *et al*<sup>[39]</sup> added four new cases to the literature. They reported that the lesions showed clinically and radiologically recovery approximately 6-7 years after treatment except for one case in which partial remission was observed. Abdo *et al*<sup>[40]</sup> reported that a recurrent CGCG in a 14-year-old girl in the anterior region of the mandible was treated successfully by ISI in 2005. Sezer *et al*<sup>[41]</sup> also reported that an 11-year-old boy with a CGCG is successfully treated with intralesional corticosteroid injections after 3 years follow-up in the same year. Comert *et al*<sup>[42]</sup> preferred to use prednisolone in their patient who had CGCG of the maxilla. They reported that a partial recovery was achieved and a limited surgery could be performed. Wendt *et al*<sup>[43]</sup> employed ISI for a maxillary CGCG with a 1:1 triamcinolone acetonide (10 mg/mL) and 0.5% bupivacaine. The solution was injected into the lesion for a period of 11 wk. After 6-years follow-up, the treatment was found to be successful clinically and radiographically. Mohanty and Jhamb<sup>[44]</sup> performed same protocol and reported that two patients were successfully treated with triamcinolone acetonide injections. Nogueira *et al*<sup>[45]</sup> contributed to literature with 21 new cases in 2010 using ISI with triamcinolone hexacetonide. Two patients did not responded to the treatment and surgical resection was needed; a moderate improvement noted in four patients (curettage in two patients) and 15 of the cases showed good response (curettage in one patient). Shirani *et al*<sup>[46]</sup> performed ISI in an aggressive and extensive case and they could not get the answer to the treatment. Ferretti *et al*<sup>[47]</sup> applied the same protocol to 16-year-old female patient who had CGCG and they reported that a complete remission was seen after 4 years follow up. Rachmiel *et al*<sup>[48]</sup> performed combination therapy consisting of ISI, calcitonin nasal spray and curettage in a 24-year-old female patient and found that no recurrence after 5-year follow-up. da Silva *et al*<sup>[49]</sup> treated a 36-year-old male with a CGCG crossing the midline of mandible with ISI combined with alendronate sodium for the control of systemic bone resorption. They reported that no recurrence or side effects at the end of four years. Finally, Fonseca *et al*<sup>[50]</sup> reported that intralesional triamcinolone acetonide was administered to a 15-year-old boy who had CGCG. They indicated that partial resolution of the lesion was observed after the sixth month.

### Action mechanism of steroids

There are several theories about the action mechanism of ISI in the CGCG. Osteoclasts achieve bone resorption by secreting lysosomal proteases. These agents mediate the process by creating an extracellular medium. It

has been showed<sup>[51,52]</sup> that 17 $\beta$ -estradiol (E2) could directly inhibit osteoclastic bone resorption. Moreover, at concentrations effective for inhibiting bone resorption, E2 could also induces osteoclast apoptosis.

On the basis of the aforementioned experimental evidence the mechanism of corticosteroids in the treatment of these lesions is suggested as inhibition of the extracellular production of lysosomal proteases and steroidal apoptotic action on osteoclast-like cells. These two mechanisms could cause cessation of bone resorption<sup>[39]</sup>.

According to literature, ISI is an effective method in patients with CGCG. However, it is not always possible to obtain a positive response to the treatment in the multilobular or aggressive lesions. Hence, in such cases, it is necessary to apply surgical or combined treatment methods. In addition, serum calcium, phosphorus and parathyroid hormone levels should be examined on suspicion of hyperparathyroidism after definitive diagnosis result of the incisional biopsy. It should be noted that the images of brown tumor and CGCG can't be distinguished histologically. And before starting the ISIs, possible diabetes mellitus and the presence of peptic ulcers or any infection should be questioned.

## ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis (OSF) is a chronic disease of the oral mucosa. It affects the pharynx, oral cavity, upper third of the esophagus and it is characterized by inflammation and a progressive fibrosis of sub-epithelial tissues<sup>[53]</sup>. Connective tissue fibers of the lamina propria and deeper parts change, which in turn lead to mucosal stiffness and limitation in mouth opening<sup>[54]</sup>. OSF is considered as high-risk precancerous disease<sup>[53-55]</sup>. Several factors contributing to OSF include general nutritional or vitamin deficiencies and hypersensitivity to various dietary constituents. The primary factor appears to be chewing of the areca (betel) nut. Genetic factors are thought to be involved in the etiology. It has been reported that a polymorphism of the promoter region of the matrix metalloproteinase 3 gene is common in OSF and may contribute to development of the disease<sup>[27]</sup>. The potential morbidities of OSF are restriction of mouth opening, difficulty with swallowing, mastication, speech, and a burning sensation as well. It has a mortality potential because of the possibility of transformation into squamous cell carcinoma<sup>[55]</sup>. Both nonsurgical and surgical treatment options have been suggested. Nonsurgical options are ISIs, hyaluronidase and interferon gamma. Surgery primarily targets to improve the mouth opening and comprises the excision of the fibrous bands, skin grafts and splitting of the temporalis tendon.

### Treatment of the OSF with ISI

Treatment is generally intended to increase the mouth opening and to decrease the burning sensation. For

early-stage submucous fibrosis cases, the results are better with non-surgical methods. In intralesional applications, the triamcinolone acetonide is the most preferred agent but different substances are also applied such as salvianolic acid B (SA-B) and lycopene. As far as we know, Gupta and Sharma<sup>[56]</sup> were the first who successfully treated the OSF with local injections of chymotrypsin, hyaluronidase, and dexamethasone. Later, sub-mucosal steroid injection and hyaluronidase or topical vitamin A, topical steroid application and oral iron preparations were applied by Borle and Borle<sup>[57]</sup> in 326 patients with oral submucous fibrosis. Khanna *et al.*<sup>[58]</sup> presented 100 patients in their clinical study in which the author implemented intralesional injection of triamcinolone acetonide in patients with very early and early-stage of OSF cases while they performed surgical intervention in advanced cases. Satisfactory results were reported in long-term follow up. Kumar *et al.*<sup>[59]</sup> applied the lycopene and lycopene combined with ISI of betamethasone in OSF patients. They reported that positive clinical response was obtained in both study groups when compared with placebo. Singh *et al.*<sup>[60]</sup> compared the efficacy of hydrocortisone acetate and hyaluronidase at weekly interval vs triamcinolone acetonide and hyaluronidase at 15 d interval. They notified no significant differences in symptom or sign scores and any histopathological improvement between the groups. The authors conclude that treatment regimen of triamcinolone acetonide and hyaluronidase was more convenient to the patients because of less number of visits required and of cost efficiency. No side effects were seen<sup>[60]</sup>. Rao<sup>[61]</sup> treated the patients with OSF using alpha lipoic acid in addition to the ISI of betamethasone and hyaluronidase. He reported that the alpha lipoic acid group exhibited better relief of symptoms as compared to the controls and he concluded that the use of an antioxidant, alpha lipoic acid, along with conventional therapy of ISI is effective in the management of OSF. Jiang *et al.*<sup>[55]</sup> investigated that the effectiveness of triamcinolone acetonide and (SA-B) intralesional combined injection in the treatment of oral submucous fibrosis (OSF) and they concluded that the triamcinolone acetonide + SA-B intralesional injections improved mouth open and burning sensation in these OSF patients. Shetty *et al.*<sup>[62]</sup> examined the efficacy of spirulina as an antioxidant adjuvant to corticosteroid injection in management of oral submucous fibrosis. They treated the OSF patients in a group with spirulina+ betamethasone and placebo capsules + betamethasone in other group. They reported that the mouth opening and burning sensation was found to be statistically very highly significant in favor of the spirulina group.

Some complications can be seen after the procedure in the OSF cases. Chen *et al.*<sup>[63]</sup> observed facial candida albicans cellulitis in a diabetes mellitus patient with oral submucous fibrosis after ISI treatment. Therefore, it should be noted that some complications can arise due

to the predisposing factors such as immunodeficiency (HIV), immune-suppression (systemic treatments with corticosteroids), chronic illness, obesity, diabetes, malnutrition, vitamin deficiency, alcohol misuse, tobacco smoking and intravenous drugs abuse.

### Action mechanism of steroids

According to the hypothesis of Tsai *et al*<sup>[64]</sup>, some alkaloids (arecoline, arecaidine) inhibit fibroblast phagocytosis and this contributes for the development of OSF. ISIs could cause an enhancement of fibroblast collagen phagocytosis. Juxta-epithelial inflammatory cell infiltration and then progressive hyalinization of the lamina propria and deeper connective tissues are associated with early OSF<sup>[55,65,66]</sup>. Use of ISI have been directed to chronic juxta-epithelial inflammation<sup>[55-57,60]</sup>. The steroids can prevent or suppress inflammatory reactions, so they fight with fibrosis by decreasing fibroblastic proliferation and collagen deposition<sup>[55,65,66]</sup>. Therefore, it can be more successful when the steroid injections administered in the early stages of the disease. According to the literature, triamcinolone acetonide or betamethasone appears to be a suitable choice.

## ORAL LICHEN PLANUS

Oral lichen planus (OLP) is a chronic mucocutaneous disease of unknown cause, with oral lesions occurring most commonly in women over 30 years of age. Incidence of OLP is between 0.2% and 2% in the population. Different types of OLP have been described as reticular, plaque form, erosive, atrophic, or bullous. Intraorally, the buccal mucosa, tongue and the gingiva are commonly involved although other sites may be rarely affected. Oral mucosal lesions present alone or with concomitant skin lesions. The most common type is the reticular form which is characterized by numerous interlacing white keratotic lines or striae that produce an annular or lacy pattern<sup>[27,67]</sup>. The plaque form of OLP tends to resemble leukoplakia clinically but has a multifocal distribution. In the erosive form, the central area of the lesion is ulcerated. A fibrinous plaque or pseudomembrane covers the ulcer. The erythematous or atrophic type appears as red patches with very fine white striae. It may be seen in conjunction with reticular or erosive variants. Patients complain of pain, burning, sensitivity and generalized discomfort in particularly erosive and atrophic types<sup>[27,67]</sup>. The risk of malignant transformation varies between 0.4% and 5% over periods of observation from 0.5 to 20 years<sup>[68]</sup>. A few studies have reported that the malignant potential of OLP and hepatitis C virus infection apparently increased the risk for oral squamous cell carcinoma<sup>[69-71]</sup>. Patients with reticular and other asymptomatic OLP lesions usually require no active treatment but symptomatic lesions may also need treatment. Nonsurgical treatments are systemic drug therapy, topical corticosteroids-calcineurin

inhibitors - retinoids, injection of steroids and ultraviolet irradiation. The other methods are surgery, laser therapy and cryosurgery<sup>[67]</sup>.

### Treatment of the OLP with ISI

According to literature, intra- and sublesional treatment of OLP with triamcinolone acetonide was reported by Sleeper<sup>[72]</sup> for the first time in 1967. The author reported that after 72 h, examination of the lesions showed 45% to 50% involution with corresponding relief of symptoms. In three cases the entire lesion disappeared in two weeks. In the other four cases with larger lesions, approximately 10% to 15% of the lesion remained, but the patients were completely symptom free. In 1974, Randell and Cohen<sup>[73]</sup> applied dexamethasone in patients with OLP and they reported successful results. Then Zegarelli<sup>[74,75]</sup> performed ISI with triamcinolone acetonide and methylprednisolone in patients with erosive or ulcerative OLP. Xia *et al*<sup>[76]</sup> studied with 45 patients with clinical and histologically confirmed ulcerative OLP. Each participant received 0.5 mL intralesional triamcinolone acetonide injection (40 mg/mL) on one side and other side was left as control. The treated areas gave rapid relief of signs and symptoms, while the control areas showed minimal decrease. Thirty-eight (84.4%) patients demonstrated complete response in ulceration size. No complications were noted with triamcinolone acetonide injections. They concluded that intralesional triamcinolone acetonide injection in ulcerative OLP is effective and safe in achieving lesion and pain regression. Xiong *et al*<sup>[77]</sup> compared the intralesional polysaccharide nucleic acid fraction of bacillus Calmette-Guerin (BCG-PSN) and triamcinolone acetonide in patients with erosive OLP. They randomly assigned 56 OLP patients receive either intralesional injection of 0.5 mL BCG-PSN every other day ( $n = 31$ ) or 10 mg triamcinolone acetonide (a positive-controlled group,  $n = 25$ ) every week for 2 wk. After the cessation of treatment, patients were followed up for 3 mo. After 2-wk treatment, 27 of 31 BCG-PSN-treated patients (87.1%) and 22 of 25 TA-treated patients (88.0%) healed. There were no statistical differences between the two groups in erosive areas and pain scores. They concluded that topical intralesional BCG-PSN injection is as effective as triamcinolone acetonide for erosive OLP. Lee *et al*<sup>[78]</sup> investigated intralesional injection vs mouth rinse of triamcinolone acetonide in 40 patients with OLP in terms of pain and burning sensation. They concluded that the efficacies of both treatments were similar. The rate of adverse effects was significantly lower for intralesional injection of triamcinolone acetonide than mouth rinse of TA. In another clinical study, intralesional triamcinolone acetonide plus oral prednisolone was applied by Kuo *et al*<sup>[79]</sup> in 50 patients with erosive OLP. They reported that although the patients showed complete response in 90% of cases after three weeks, recurrence of erosive or ulcerative lesion was observed after 3-24 (mean 12) mo of follow-up in all of these cases. Liu *et al*<sup>[80]</sup> analyzed



the efficacy and safety of intralesional betamethasone in the treatment of erosive OLP. They implemented intralesional betamethasone 1.4 mg to the experimental group and 8 mg intralesional triamcinolone acetonide to the control group once a week for two weeks in 61 patients with erosive OLP. They found that 93.1% of participants were healed after two intralesional injections of 1.4 mg betamethasone, and 66.7% of participants were healed after two intralesional injections of 8 mg triamcinolone acetonide and authors concluded that intralesional betamethasone was a more effective way to treat erosive OLP.

According to the literature, triamcinolone acetonide is the most preferable agent as intralesional injection in patients with OLP. Recently, betamethasone seems to be also effective. General usage of triamcinolone acetonide is to dilute 10 to 20 mg in 0.5 mL saline or 2% lidocaine, then to inject into the lesion once 1 wk for 2 times<sup>[81]</sup>. Injections are administered into the connective tissue below the erosive lesion from the adjacent normal mucosa. The treatment is absolutely required in patients with erosive and erythematous types due to the daily life is affected by pain and burning sensation. Generally, patient comfort is provided and the lesions disappeared within one to two weeks after ISI. However, recurrence of the lesions may occur on the long-term follow-up. Disadvantages include mucosal atrophy, difficulty to deposit sufficient quantities into gingival lesions and painful injection<sup>[82]</sup>.

### Action mechanism of steroids

While the etiology of OLP is not clear, it has been suggested that it could be caused by a immune response with an inflammatory cell population composed of T lymphocytes<sup>[83,84]</sup>. When the steroids are injected directly into the connective tissue below the lesions, they can suppress T cells and show a strong anti-inflammatory and immunosuppressive effect<sup>[80]</sup>.

## OTHER DISEASES

Other oral diseases treated with ISI are very limited in the literature. Azevedo *et al.*<sup>[85]</sup> used intralesional injection of triamcinolone acetonide in patients with oral lichen sclerosis. The authors reported that the patients showed improvement and elasticity of oral tissues enhanced. Luo and Gun<sup>[86]</sup> found that intralesional injection of pingyangmycin with triamcinolone acetonide was more effective than pingyangmycin alone for management of lymphatic malformations in oral and maxillofacial region. Anjomshoa *et al.*<sup>[87]</sup> performed intralesional injections of triamcinolone acetonide in a patient with follicular lymphoid hyperplasia. In addition, they reported that complete resolution of the lesion was obtained at 7-mo follow-up. Another disease in which ISI could be effective is orofacial granulomatosis (OFG). It is an uncommon disease, usually presents as recurrent or persistent swelling of the soft tissues

in the orofacial region, predominantly on lips, causing significant cosmetic and functional problems<sup>[88,89]</sup>. The reason of this disease is unknown. OFG may also be part of the triad of Melkersson-Rosenthal syndrome (MRS) and some consider it a monosymptomatic form of MRS<sup>[90,91]</sup>. Sakuntabhai *et al.*<sup>[92]</sup> used high-volume intralesional triamcinolone acetonide injections (3 to 10 mL of 10 mg/mL) and they reported that intralesional triamcinolone injections reduced lip swelling. However, Mignogna *et al.*<sup>[91]</sup> performed small volume, high concentrate, delayed release, intralesional injection of triamcinolone acetonide in patients with OFG. They reported that all patients remained without recurrences or with cosmetically acceptable slight lip enlargement for a mean time of 19 mo and this method was very affective and it did not require nerve blockage. The same researchers investigated the long-term outcome in patients treated with intralesional triamcinolone acetonide injections and reported that complete clinical remission were obtained in all patients for a mean time of  $56.3 \pm 18.2$  mo<sup>[93]</sup>. Several other clinical studies have reported that injections of intralesional steroids are clinically successful method in patients with OFG<sup>[88,89,94]</sup>.

Exogenous corticosteroids are usually classified based on their relative glucocorticoid and mineralocorticoid potency as well as duration of their effects. The most potent glucocorticoids are also the most potent suppressors of the hypothalamic pituitary adrenal axis. While short-acting steroids (e.g., Cortisol) are effective for less than 12 h, intermediate-acting steroids (Prednisone, Prednisolone, Methylprednisolone and Triamcinolone) can stay active for 12-36 h and long-acting steroids (Betamethasone, Dexamethasone and Flumethasone) are effective for more than 36 h<sup>[95]</sup>. Most prominent properties of corticosteroids are their anti-inflammatory, anti-allergic and analgesic effects. Glucocorticoids help keeping normal vascular permeability and stabilize lysosomal and cellular membranes. On the other hand, in acute inflammation, they decrease vascular permeability and inhibit the migration of polymorphonuclear lymphocytes into tissues. They also induce apoptosis in normal lymphoid cells; inhibit the clonal expansion of T and B lymphocytes; and reduce the eosinophils, basophils, and monocytes in the circulation. Glucocorticoids have different effects on neutrophils. They hinder margination of neutrophils and increase the release of mature neutrophils from the bone marrow.

However, they may also decelerate wound healing<sup>[95]</sup>. Long-term use of corticosteroids can cause osteoporosis, hypertension, electrolyte imbalance, hyperglycemia, delayed wound healing, and a tendency for infections. There are some contraindications for steroids such as history of allergy, peptic ulcer, Cushing syndrome, uncontrolled diabetes, renal failure, anticoagulation usage, fungal diseases and varicella zoster infection<sup>[96]</sup>. Although intralesional injection can be performed easily, several precautions should be taken during the

processing. The injection must always be made using sterile procedures and anatomy of the area should be known. Adjacent nerves should be kept away and intravenous injections should be avoided because of the possibility of systemic effects such as adrenal suppression<sup>[96]</sup>.

## CONCLUSION

ISI is one of the most preferable non-surgical methods for the treatment of mucosal or bone reactive lesions occurred in oral and maxillofacial region. The accumulating evidence suggests that ISI is well tolerated by patients, the likelihood of postoperative complications is less than those of other methods and patient complaints diminish rapidly. Especially in large lesions, it can be applied as an alternative or adjunct to surgical procedures. This method is also minimally invasive and relatively inexpensive.

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## Oral graft *vs* host disease: An immune system disorder in hematopoietic cell transplantation

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National Institutes of Health in 2005 by Working Group on Diagnosis and Staging Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD (cGVHD) established 2 principal categories of oral GVHD, acute and chronic. The oral mucosa may be the first site of manifestation of the disease. Clinical diagnosis needs to be confirmed by a biopsy of oral mucosa and minor salivary glands. Microscopic results have played a major role in the diagnosis and management of acute and chronic oral GVHD. Development of second malignancies is the greatest risk of oral cGVHD patients, mostly regarding squamous cell carcinoma. The focus of oral GVHD therapy is to improve symptoms and maintain oral function. The aim of this review article is to update the information on the oral GVHD in its clinical, microscopic features and their complications.

**Key words:** Stem cell transplantation; Graft *vs* host disease; Mouth mucosa; Diagnosis; Oral; Salivary glands

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**Core tip:** Graft *vs* host disease (GVHD) patients are susceptible to recurrent and deadly infections due to immune system harm. Chemotherapy treatment may cause a range of complications, such as neuropathic pain resulting from vincristine adverse effects, overgrowth of gingival due to cyclosporine and effects on bones and teeth growth and development during childhood and youth. Oral GVHD patients must have follow-ups due to risks of oral infections, bleeding, and cancerous developments.

### Abstract

Graft *vs* host disease (GVHD) is a complication of patients who are treated by hematopoietic cell transplantation.

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## INTRODUCTION

Graft vs host disease (GVHD) is a complication of patients who are treated by Hematopoietic Cell Transplantation (HCT). GVHD has immunoregulatory characteristics when donor T cells react against histocompatibility antigens of the host. National Institutes of Health (NIH) in 2005<sup>[1]</sup> by Working Group on Diagnosis and Staging Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD (cGVHD) established 2 principal categories of GVHD, acute and chronic, and each of the categories has 2 subcategories. The acute stage occurs with the absence of diagnostic or distinctive features of chronic GVHD. This stage also involves (1) classic acute GVHD that occurs within 100 d after transplantation; and (2) persistent, recurrent, or late acute GVHD (features of acute GVHD that occur beyond 100 d, often during withdrawal of immune suppression). The wide category is chronic GVHD, which involves (1) classic chronic GVHD (without features or characteristics of acute GVHD); and (2) an overlap syndrome, in which diagnostic or distinctive features of chronic GVHD and acute GVHD appear together<sup>[1,2]</sup>.

Both forms, acute and chronic, may affect oral cavities and be highly morbid. Skin rash, mucosal ulcerations, elevated liver enzymes, and diarrhea indicate the acute form. Sjögren's syndrome, scleroderma, thickening and lichenoid lesions of the skin and mucosa, xerostomia, mucositis, and dysphagia indicate the chronic form<sup>[3,4]</sup>.

GVHD patients are susceptible to recurrent and deadly infections due to immune system harm. Chemotherapy treatment may cause a range of complications, such as neuropathic pain resulting from vincristine adverse effects, overgrowth of gingival due to cyclosporine, and effects on bones and teeth growth and development during childhood and youth. Oral GVHD patients must have follow-ups due to risks of oral infections, bleeding, and cancerous developments.

## INCIDENCE OF ORAL GVHD

Ion *et al.*<sup>[5]</sup> in a retrospective study characterized a cohort of patients treated with HCT over 15 years (total 2578 patients). The study found that only 21 patients had developed acute GVHD (aGVHD), but 5 demonstrated only oral manifestations. Acute GVHD occurred in a median time of 22 d (8 to 154 d), and oral aGVHD occurred in a median time of 35 d (11 to 159 d). Oral features included an erythema and ulcerations of buccal mucosa (19 of 21; 90%), tongue (18 of 21; 86%; dorsum in 8), labial mucosa (16 of 21; 76%), palatal mucosa (15 of 21; 71%; hard palate in 7), and floor of mouth (7 of 21; 33%). Eight cases (38%) presented lip ulceration and crusting<sup>[5]</sup>.

Some risk factors were tissue incompatibility (HLA

and "minor" non-HLA antigens) between donor and recipient, advanced donor's age and patient's age, and the intensity of the conditioning therapy used for HCT preparations<sup>[6]</sup>.

Chronic GVHD occurs more frequently (40% to 70%) in allogeneic bone marrow transplantation patients (allo-BMT), but is not necessarily related to a prior history of aGVHD manifestations<sup>[7]</sup>. Risk factors for cGVHD were related to donor, graft, and transplant-related older patient age, history of aGVHD, genders of donor and patient, certain underlying diagnoses (*e.g.*, chronic myelogenous leukemia or aplastic anemia), the use of mismatched or unrelated donors, infusion of donor lymphocytes, use of peripheral blood stem cells instead of bone marrow, and lack of T-cell depletion<sup>[6]</sup>.

## CLINICAL FEATURES

The oral mucosa may be the first site of the manifestation of the disease, which suggests that other organs should be investigated<sup>[8]</sup>. The signs and symptoms are divided by direct and indirect effects of cGVHD. The direct signs and symptoms are distributed in the areas<sup>[9,10]</sup>: (1) Mucosa - Lichenoid striation, plaque, papule, erythema, ulceration, atrophic glossitis (Figure 1); (2) Salivary glands - Dryness, mucocele (multiple); (3) Musculoskeletal - Limitation of mouth opening, limited tongue mobility; (4) Taste buds - Taste alteration; and (5) Gingiva - Desquamative gingivitis, lichenoid.

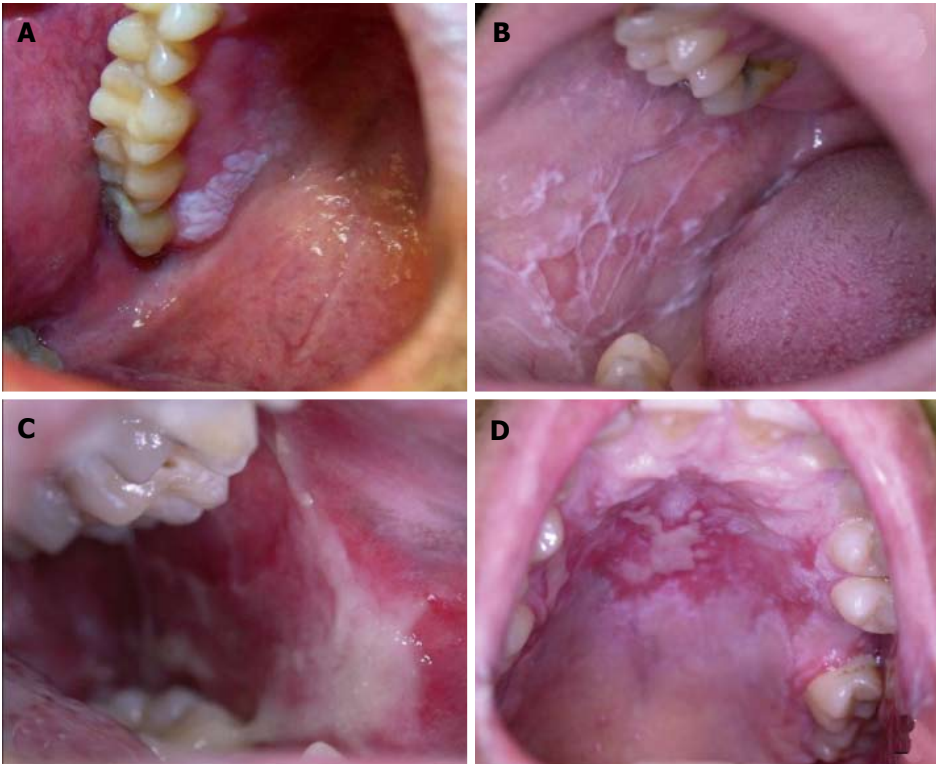
The indirect effects are dental decay, loss of attachment of periodontium, osteonecrosis of the jaw, candidiasis, and malignant transformation of oral mucosa and salivary glands<sup>[9,10]</sup>.

The NIH Consensus Development Project defined 4 different types of manifestations of oral cGVHD that should be used to assess the severity of oral cGVHD (Figure 2). In the 0- to 15-point system, clinical evidences are assessed globally to reflect the severity and extent of oral involvement<sup>[11]</sup>.

Clinical diagnosis needs to be confirmed by a biopsy of oral mucosa and minor salivary glands. The criteria for obtaining these specimens are an incisional biopsy of a nonulcerated site to include underlying gland lobules<sup>[12]</sup> (5 to 10 lobules is recommended) and the site of preference as the lower lip mucosa, which is the clinical manifestation in this area of the mouth. The orientation regarding characteristics of the biopsy and the sequence of observation for microscopic structures facilitate the process of the histological diagnosis<sup>[13]</sup>.

## MICROSCOPIC FEATURES

Chronic GVHD is a multifactorial disease with clinical and histopathologic features that can often confuse the pathologist. Horn *et al.*<sup>[14]</sup> published the first study about the significance of oral mucosa and salivary glands after allogeneic HCT. It was based on the lichen planus-like lesions in association with xerostomia in



**Figure 1** Clinical features of oral chronic graft vs host disease. A: Plaque; B: Lichenoid striation; C: Papule ulceration; D: Erythema ulceration.

Mouth	Mucosal change		No evidence of cGVHD		Mild		Moderate		Severe	
	Erythema	None	0		Mild erythema or moderate erythema (< 25%)	1	Moderate ( $\geq$ 25%) or severe erythema (< 25%)	2	Severe erythema ( $\geq$ 25%)	3
	Lichenoid	None	0		Hyperkeratotic changes (< 25%)	1	Hyperkeratotic changes (25%-50%)	2	Hyperkeratotic changes (> 50%)	3
	Ulcers	None	0		None	0	Ulcers involving ( $\leq$ 20%)	3	Severe ulcerations (> 20%)	6
	Mucocoeles <sup>1</sup>	None	0		1-5 mucocoeles	1	6-10 scattered mucocoeles	2	Over 10 mucocoeles	3
						<sup>1</sup> Mucocales scored for lower labial and soft palate only		Total score for all mucosal changes		

**Figure 2** NIH's oral chronic graft vs host disease clinical scoring instrument. Adapt from Treister *et al*<sup>[37]</sup>.

59 transplanted patients<sup>[14]</sup>. The study established that the histopathological criteria for oral GVHD should include both oral mucosa and salivary glands features (Table 1)<sup>[14]</sup>. The histopathological features of oral cGVHD in epithelium and lamina propria included basal vacuolization, exocytosis, and interstitial inflammation (Figure 3). Salivary glands features included mild to severe destruction of ducts and acini (Figure 4)<sup>[14]</sup>.

Histopathology has played a major role in the diagnosis and management of acute and chronic GVHD<sup>[12]</sup>. However, histological observations of cGVHD lesions are not specific. The changes may vary, depending on time between HCT and biopsy, biopsy size, number of serial sections, presence of ulceration area, insufficient depth, and the coexistence of other inflammatory processes at the site<sup>[15]</sup>. Histopathological changes can be more apparent after 60 d post-HCT and may be represented by nonspecific inflammation that leads to false-negative GHVD diagnosis<sup>[12,16]</sup>. Therefore, the NIH consensus of the

Working Group highlighted the importance of considering the clinical features, such as lichen planus-like lesions and xerostomia, to define the diagnosis of oral cGVHD<sup>[12]</sup>.

The NIH consensus presented the minimal criteria necessary to diagnose GVHD (whether acute or chronic) and the diagnostic features for chronic GVHD in each involved organ system (Tables 2 and 3). The minimal histological criteria for oral cGVHD follows basic criteria; this includes localized or generalized epithelial changes comprising lichenoid-like inflammation, exocytosis, apoptosis, the presence of intralobular, periductal lymphocytes with or without plasma cells, and exocytosis of lymphocytes into intralobular ducts and acini<sup>[13]</sup>. Apoptotic bodies in both epithelium and salivary glands can be seen in oral cGVHD<sup>[12]</sup>.

The most frequent microscopic features in the epithelium include acanthosis, lymphocyte exocytosis, and the thickening of basal lamina. In the lamina propria, the most frequent features include interstitial



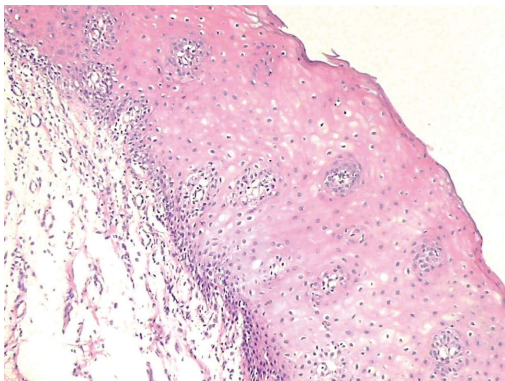
**Table 1** Histological grading of oral mucosa and salivary glands according to Horn *et al*<sup>[14]</sup>

Grade	Definition
Grade I	Mucosa: Vacuolization of basal cells, moderate lymphocytic infiltrate, moderate epithelial exocytosis Salivary glands: Mild interstitial inflammation
Grade II	Mucosa: Epithelial cells with basal vacuolization and dyskeratotic, necrotic keratinocytes with satellitosis, moderate to heavy lymphocytic infiltrate in the submucosa and moderate epithelial exocytosis Salivary glands: Mild acinar destruction, ductal dilation, squamous metaplasia, mucous pooling, mild fibrosis, duct cell proliferation, periductal lymphocytic infiltrate
Grade III	Mucosa: Focal cleavage between the epithelium and connective tissue, intense lymphocytic infiltrate in the connective tissue, dyskeratotic epithelial cells, lymphocyte exocytosis Salivary glands: Marked interstitial lymphocytic infiltrate. Diffuse destruction of ducts and acini
Grade IV	Mucosa: Separation of epithelium and the connective tissue Salivary glands: Nearly complete loss of acini, dilated ducts, interstitial fibrosis with or without inflammation

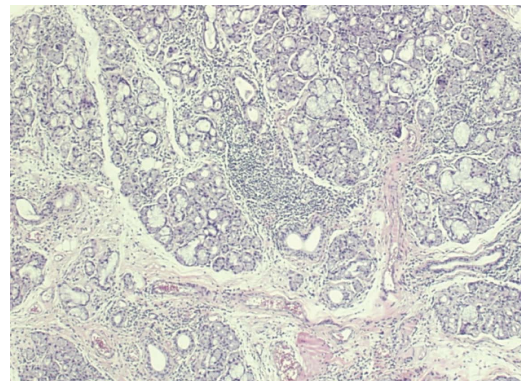
**Table 2** Minimal criteria for diagnosis of oral chronic graft *vs* host disease and categories

Category	Definition
Not GVHD	No evidence for GVHD
Possible GVHD	Evidence of GVHD but other possible explanations ( <i>e.g.</i> , Clinical features that suggest or favor a drug reaction)
Consistent with GVHD	Clear evidence of GVHD with mitigating factors ( <i>e.g.</i> , Unequivocal evidence of CMV yet abundant apoptotic epithelial changes that are not associated with CMV- infected cells by immunostaining)
GVHD	Unequivocal evidence of GVHD and no further comment necessary ( <i>e.g.</i> , Inflammation may be minimal despite extensive destruction of the targeted epithelia)

Adapt from Shulman *et al*<sup>[12]</sup>. GVHD: Graft *vs* host disease; CMV: Cytomegalovirus.



**Figure 3** Epithelium and lamina propria showing basal vacuolization, exocytosis and interstitial inflammation.



**Figure 4** Salivary glands features included mild to severe destruction of ducts and acini.

lymphocytes infiltration. In minor salivary glands, they include periductal fibrosis and inflammatory infiltrate both in acini and periductal sites. Salivary glands analysis must be done carefully because they can be affected, even before the development of mucosal injury. Major salivary glands can reflect the same features of inflammatory infiltration and fibrosis<sup>[17]</sup>.

Horn's criteria<sup>[14]</sup> and the NIH Consensus<sup>[12]</sup> are different in objectives and subjective features (Tables 1-3). In fact, any correlation between clinical and histopathological severity of oral GVHD leads to a nonsynchronous understanding of the epithelium and salivary gland disease. The absence of clinical and histopathological correlation does not diminish the importance of histological analysis of cGVHD. A comparison of the NIH Consensus<sup>[12]</sup> and the

Horn criteria<sup>[14]</sup> for histopathological diagnosis of cGVHD shows that they are related in a certain way. This suggests that the use of the NIH Consensus<sup>[12]</sup> for oral mucosa and salivary glands may be better to characterize the extent of cGVHD<sup>[13]</sup>. Moreover, a differential diagnosis is possible with infectious lesions and drug reactions<sup>[13,18,19]</sup>.

## COMPLICATIONS OF THE ORAL CGVHD

Viral, fungal, and bacterial infections of the oral mucosa are frequently superimposed in patients with cGVHD. Mainly due to the dryness and immunosuppression<sup>[9]</sup>.

Related to fungal infections acute pseudomembranous candidiasis is the most frequent presentation<sup>[20]</sup>, but all clinical forms: erythematous, pseudomembranous,



**Table 3** Shulman *et al.*<sup>[12]</sup> chronic graft-vs-host disease histologic classification of oral mucosa and salivary glands, according to National Institutes of Health Consensus

Epithelium	Epithelial thickness (normal, atrophic, hyperkeratosis and acanthosis), presence of vacuolization, apoptosis, spongiosis, atypical keratinocytes, exocytosis of lymphocytes, presence of other inflammatory cells and thickening of basal lamina
Lamina propria	Predominant cell type in the inflammatory infiltrate and their distribution in relation to the salivary duct and epithelium
Salivary glands	Lymphocytes within the duct, periductal mixed infiltrate, presence of lymphocytes within the acini, apoptosis in the ducts and acini, periductal fibrosis, acinar cell degeneration, interstitial fibrosis, duct ectasia and loss of polarity of epithelial cells of the duct

hyperplastic, and angular cheilitis can be seen at some point in the course of the disease. To prevent and treat candidiasis nystatin and chlorhexidine mouth washes may be prescribed<sup>[20,21]</sup>. When multiple areas of the mouth are affected and there are risk of invasive candidiasis, the systemic fluconazole is indicated.

When patients with oral cGVHD are thrombocytopenic, there is a risk for bleeding mouth, gums and also primarily associated with ulcers of the mucosa<sup>[22]</sup>. In these cases, careful and effective oral hygiene in biofilm reduction are important.

## SECOND MALIGNANCIES AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

The biggest concern regarding late complications, with patients who underwent HCT, is the development of second malignancies. These patients have a higher risk of developing hematological malignancies, lymphoproliferative disease, and solid tumors (lung, esophagus, skin, oral mucosa, colon, melanoma, glioblastoma, sarcoma, and other organs), owing to various risk factors, including total body irradiation, chemotherapy, and cGVHD<sup>[23,24]</sup>.

Besides the cellular mechanisms that link to chronic inflammation of GVHD with malignant transformation of the affected sites, there are other possible mechanisms of malignant transformation that are related to the prolonged use of immunosuppressive therapy, performed for the treatment of chronic GVHD. Such suppression can facilitate infections with oncogenic viruses, such as Human Papilloma virus or Epstein-Barr virus, which would normally be controlled by the immune system<sup>[23,25,26]</sup>. In young patients with cGVHD reached the peak of development of oral squamous cell carcinoma (SCC) occurs 8 to 9 years after HCT<sup>[24]</sup>.

Studies that evaluated the risk of cancer in patients after HCT showed an increased risk of developing secondary malignancies in comparison to the general population<sup>[25,27,28]</sup>. It is noteworthy that in patients with Fanconi anemia, the risk of developing a second tumor is even higher<sup>[29,30]</sup> being observed an increased risk of 10 to 15 times, a difference that may be related to chromosomal instability and deficiency in the repair process of the disease<sup>[26]</sup>. Chronic GVHD is associated with risks of developing oral SCC<sup>[26,28,31]</sup>.

In a retrospective study, Atsuta *et al.*<sup>[28]</sup> evaluated 17,545 patients who underwent HCT. The researchers

concluded that in recipients of allogeneic HCT (myeloablative conditioning), extensive-type chronic GVHD was an important risk factor for the development of secondary solid cancers (RR = 1.9,  $P < 0.001$ ); it was an independent risk factor for cancers in the oral cavity/pharynx and esophagus. In a cohort study, Majhail *et al.*<sup>[32]</sup> evaluated 4318 patients who underwent HCT (Acute Myeloid Leukemia 1742, Chronic Myeloid Leukemia 2576) and found that out of cancer patients, 72% had a diagnosis of cGVHD. In this study, cGVHD was the only significant risk factor associated with oral cavity cancer. Chen *et al.*<sup>[33]</sup> evaluated 170 patients who underwent allogeneic HCT over twenty years with a median follow-up of 14.1 years (range 5.1-23.3 years). Eight (4.7%) patients developed secondary carcinoma: 5 developed squamous cell carcinomas in the oral cavity, 1 in the esophagus, 1 ovarian adenocarcinoma, and 1 breast. In this group, 7 patients (87.5%) were subjected to treatment for cGVHD with a median time post-transplant diagnosis of 10 years. Patients who had cGVHD after HCT were at risk of developing secondary carcinomas (RR = 15.374; 95%CI: 2.168-59.875). In this study, before the development of oral squamous cell carcinoma, all 5 patients had signs and symptoms of recurrent oral ulcers, warts, and white lesions in the regions of developing cancer. It is important to note that HPV was not associated with carcinogenesis in these patients with oral SCC.

While oral cancer is represented mostly by squamous cell carcinoma and very aggressive-type behavior, it is important to emphasize that this particular type represents about 50% of all solid tumors in patients who undergo HCT<sup>[23,25,31-36]</sup>. Abdelsayed *et al.*<sup>[34]</sup> mentioned that oral cancer in patients with GVHD might have more aggressive biologic potential with a higher tendency for recurrence and the development of new lesions. Mawardi *et al.*<sup>[37]</sup> evaluated 26 post-HCT patients who had developed verrucous hyperplastic hyperplasia (12%), dysplasia (19%), and invasive carcinoma (69%). Twenty-four patients (96%) had cGVHD, and of these patients, 96% (23/24) presented oral features.

Due to the increased amount of patients who survive HCT and remain free of the original disease, attention should be paid to the presence of potentially cancerous lesions or tumors that already exist. Studies reported that after HCT, patients had an increased risk of developing secondary tumors in comparison to the general population<sup>[25,27]</sup>. Therefore, there is concern about the early detection of a second primary

tumor in these patients. Currently, the consensus on screening guidelines and long-term follow-ups of HCT complications is that oral mucosa and dental status should be examined during the annual examination of patients with GVHD and every 6 mo for patients with Fanconi's anemia<sup>[23,29,38]</sup>.

## TREATMENT

Oral cGVHD management focuses on ameliorating symptoms, maintaining oral function, and restoring mucosal integrity by treating symptomatic oral abnormalities and ulcerative lesions<sup>[9]</sup>.

The first-line therapy for cGVHD in other areas beside oral mucosa, involves systemic corticosteroids. When the oral cavity is the only site involved, the topical management of oral cGVHD may be indicated<sup>[10]</sup>. Therapy is indicated based on corticosteroid with presentations on solutions<sup>[10]</sup> such as Dexamethasone, Budesonide, Prednisolone, Triamcinolone, and Betamethasone<sup>[37]</sup>. The corticosteroids with presentation gel, creams, and ointments are Fluocinonide, Clobetasol, Betamethasone, and Triamcinolone. The nonsteroidal immunosuppressive solution and ointment is Tacrolimus<sup>[10]</sup>.

## CONCLUSION

GVHD is a common sequela of patients who are treated by HCT. Diagnosing oral complications and manifestations of GVHD disease is fundamental for dental management during medical therapy.

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## Oral lichenoid lesion: A review of the literature

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to the dental materials, drugs, and on graft-*vs*-host disease (GVHD). OLL to dental material happen when restorative materials, most commonly amalgam, are in direct contact with the mucosa in sensitized individuals. Medications that produce OLL are oral hypoglycemic agents, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory agents. GVHD is a complication in bone marrow transplantation and OLL is a common lesion observed in this disease especially in chronic GVHD. The clinical and histological aspects of OLL are similar to oral lichen planus and turn it difficult to make a differential diagnosis. The purpose of this paper is review about OLL related to the dental materials, drug use and GVHD.

**Key words:** Oral lichenoid lesion; Lichenoid contact reaction; Lichenoid drug reaction; Lichenoid related to graft-*vs*-host disease

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**Core tip:** There are various oral manifestations like oral lichen planus. These lesions are related to local or systemic factors and are important in oral diagnosis and patient's management. Considering the increased of number of these lesion in current moment, we investigated previous publications and aim to present a literature review.

Grossmann S de MC, de Oliveira C de NA, Souto GR, Góes C, Mesquita RA. Oral lichenoid lesion: A review of the literature. *World J Stomatol* 2015; 4(2): 103-107 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v4/i2/103.htm> DOI: <http://dx.doi.org/10.5321/wjs.v4.i2.103>

### Abstract

The oral lichenoid lesion (OLL) is response that occurs on the oral mucosa. The OLL include allergic response

### INTRODUCTION

Oral lichenoid lesion (OLL) is a chronic inflammatory lesion of the oral mucosa that occurs as an allergic



response to dental materials, to use of certain medications, in patients with graft-vs-host disease (GVHD), in patients with systemic diseases, *e.g.*, chronic hepatitis C<sup>[1]</sup> and patients vaccinated against hepatitis B<sup>[2]</sup>. Various terminologies have been used to describe this condition, as oral lichenoid lesions, oral lichenoid reaction, oral lichenoid tissue reaction, lichenoid contact stomatitis or lichen-planus-like lesions, due the similar clinical and histological aspects of OLL and oral lichen planus<sup>[3]</sup>.

The OLL is a frequent condition, with prevalence 2.4% in general population<sup>[4]</sup>. These lesions occurs generally in oral mucosa of adults<sup>[5]</sup>, mostly in women with average age of 53 years old<sup>[6]</sup>. The lesions are mostly present in the buccal mucosa, lateral border of the tongue and oral mucosa of the lips, when associated with composite restorations. It is generally limited size and unilateral. This find can be important to distinguish OLL from the oral lichen planus (OLP) lesions, which occurred commonly bilateral in oral mucosa<sup>[2,3,6,7]</sup>.

Clinically the lesions showed as white striations, plaques, erythema, ulcers or blisters, asymptomatic. The patients can complain of sensitivity to spicy foods or burning sensation. Histologically, observed a hyperkeratinization, liquefaction degeneration of the basal cell layer and band-like layer of lymphocytic infiltrate in the connective tissue<sup>[2,6-9]</sup>. OLP, OLL and GVHD could not be histopathologically discriminated<sup>[10,11]</sup>, however some authors investigate possible histopathological aspects among the lesions<sup>[12]</sup>. Moreover, the clinical and histological aspects are not useful to distinguish OLL from OLP<sup>[13,14]</sup>. Some authors showed that the level of salivary IgA and IgG in OLP and OLL patients is higher than healthy controls, but they cannot be used as differential diagnosis of both alterations<sup>[15]</sup>.

The purpose of this paper is review about OLL associated with dental materials, with medication use, with systemic diseases, in patients vaccinated against hepatitis B and in patients with GVHD. The methodology was a search of the literature, from 1966 through December 2014, about OLL related to the dental materials, drug use, GVHD listed on PubMed. The search was conducted in both English and Portuguese, and the keywords used were "oral lichenoid lesion", "oral lichenoid lesion and dental materials", "oral lichenoid lesion and drug" and "oral lichenoid lesion and GVHD". Additional studies were found in the reference lists of the selected articles.

## ORAL LICHENOID LESION TO THE DENTAL MATERIALS

Resin-based composite, gold and the amalgam and its components can cause hypersensitivity reactions on the oral mucosa<sup>[6,13,16-19]</sup>. According to Lygre *et al.*<sup>[20]</sup> the principal cause of OLL was associated with adverse reaction to dental materials, being amalgam fillings as responsible for 84% of the cases. The OLL associated

with amalgam restorations can be observed in about 2% of population<sup>[7,20-22]</sup>. Although uncommon, the composite resin also can be associated with OLL<sup>[23]</sup>.

The induction of OLL to the dental materials is probably the long-term. The contact of oral mucosa with dental material develops hypersensitivity reaction over a period of days and the clinical manifestations may present many years after initial contact with the dental material<sup>[7]</sup>. In case of the amalgam, reaction can occur the release of corrosion products from the restoration surface, and may result in lymphocyte activation and induction of a cell-mediated autoimmune response directed at basal keratinocytes<sup>[13]</sup>. The cell mediated type IV hypersensitivity response of amalgam restoration can result in immune-mediated damage of the basal keratinocytes<sup>[7,17,21,22]</sup>. In most cases of OLL the hypersensitivity is the mercury, however other components of amalgam fillings as copper, tin or zinc can be associated with the reaction<sup>[6,16,18]</sup>. Some authors suggested that this reaction occurs in susceptible individuals for long time of exposure<sup>[21,13]</sup>, since OLR does not develop in all individuals with amalgam alloys in contact with oral mucosa. However, the levels of IL-6 and IL-8 in saliva of patients underwent to amalgam filling replacement showed significant reduction<sup>[8]</sup>.

Although the use of patch test for OLL to dental material is controversial, showing limited value<sup>[16,24,25]</sup>, Thornhill *et al.*<sup>[13]</sup> showed that the combination of a positive patch test and the presence of oral lesions together to amalgam restoration were an important predictor of lesion improvement. An interesting observation made by these authors was that the desquamative gingivitis clinical aspect was not observed in any of the patch test positive patients or patients with a strong clinical association between the lesions and their fillings. Moreover, these patients did not demonstrated history of skin lesions.

Conflicted points related to skin patch test can be described: amalgam components to use in the test; distinguish sensitivity from irritant responses; how long the material should remain in contact with the skin; and the value of skin patch testing in identifying true oral lichenoid lesions. Furthermore, there is debate about the validity of extrapolating skin reactions to mucosal responses<sup>[17]</sup>. Nevertheless, the patch test may be helpful to determinate an alternative material to use when replacing amalgam<sup>[17,25]</sup>.

The final diagnosis of OLL to dental material is confirmed by clinical and histological aspects associated with the resolution of the lesions after replacement of the restoration<sup>[6,16]</sup>. Most of the OLR associated to amalgam disappear in 3 to 15 mo after that the restoration was changed<sup>[6,8,13,17,18,24]</sup>.

The study by Thornhill *et al.*<sup>[14]</sup> confirmed the difficulty of histological distinction between OLL and OLP, showing that five oral pathologists were able to differentiate both conditions in just one-third of the cases. According to the authors, some features may be present in OLL and absent in OLP: an inflammatory infiltrate located

**Table 1 Medications related to the induce oral lichenoid lesion described in literature**

Type of medication	Example
Antibiotics and chemotherapeutic agents	Penicillin, tetracycline, streptomycin, pyrazinamide, sulfadoxin, ketoconazole, pyrimethamine, demeclocycline
Antidiabetic agents	Chlorpropamide, tolbutamide
Antiepileptic agents	Carbamazepine
Antihypertensive agents	Methyldopa, labetalol, propranolol, captopril
Antimalarials	Chloroquine, quinacrine
Antimaniac drugs	Lithium salts
Antiplatelet agent	Clopidogrel
Antirheumatic agents	Gold Salts
Antiulcer medication	Bismuth
Benzodiazepines	Lorazepam
Nonsteroidal anti-inflammatory drugs	Salicylates, indometacin, fenelofenac, isoxicam, piroxicam

Adapt from Guijarro Guijarro and López Sánchez<sup>[27]</sup>.

deep to superficial infiltrate in some or all areas; focal perivascular infiltrate; plasma cells and neutrophils in the connective tissue. Juneja *et al*<sup>[3]</sup> found increased epithelial thickness in OLL compared to OLP, probably due to the release of inflammatory mediators from the cellular infiltrate, inducing the proliferation of basal keratinocytes. However, the number of mast cells, neutrophils and macrophages is significantly higher in OLP than in OLL, besides a continuous thin, linear band of basement membrane and numerous strands extending into the irregularity connective tissue. Thus, these parameters can be considered useful to differential diagnosis between OLP and OLL<sup>[3]</sup>. However, it is necessary to emphasize the importance of excluding the presence of *Candida* infection, which it is common in association with OLLs<sup>[26]</sup>, principally in areas of ulceration since in both of them may result in accumulations of neutrophils and plasma cells<sup>[14]</sup>.

## ORAL LICHENOID LESION TO THE DRUG

Drugs are identified as inducers of oral lichenoid lesion (OLL-d), principally associated with prolongation use of the drugs<sup>[17]</sup>. When a drug is suspected to cause the OLL-d, the change of them should be considered<sup>[21]</sup>. In contrast to cutaneous lichenoid lesion to the drugs, the OLL-d is uncommon<sup>[17]</sup>. The Table 1 presented drugs that can induce OLL-d<sup>[27]</sup>.

The final diagnosis of OLL-d is difficult, and the readministration of the medication can help to establish if the oral lesions are drug-induced, though this can be dangerous for the patient<sup>[17,28]</sup>. Generally the lesion disappears after suspension of the drug<sup>[3,17,28]</sup>. However, the complete resolution of the lesion can hold out several months.

In some cases, the medication is potentially indispensable to survival of the patients; thus its suspension or replace is not possible<sup>[17,28]</sup>. In these cases, the lesions must be treated conventionally as OLP. According some authors the patients with OLL-d related with drugs to cardiovascular diseases, have reported to decrease unstimulated whole saliva secretion<sup>[29]</sup>, suggesting the

hyposatiation as a trigger to OLL-d in these patients<sup>[19]</sup>.

Other medications have been related to OLL-d and OLP<sup>[1]</sup>. It has been extensively demonstrated that IFN may induce or worsen immunological diseases. With the advent of pegylated IFN- $\alpha$ , a causal link among the treatment of chronic hepatitis C with combination of pegylated IFN plus ribavirin and several autoimmune events have been suggested. The development or exacerbation of OLP has also been reported after the introduction of IFN- $\alpha$  to treat hepatitis C<sup>[2,3,9,28,30-32]</sup>, and also contribute to the development of new lesions as OLL. It is quite plausible that IFN- $\alpha$  may induce or worsen previous lesions due to its interference with the cytokine cascade<sup>[31]</sup>. Grossmann *et al*<sup>[33]</sup> described three cases of exacerbation of OLP during the treatment of chronic hepatitis C with pegylated IFN plus ribavirin. However, it is difficult establish if the lesions were exacerbation of previous lesions of OLP or new lesions of OLL-d.

McCartan and Lamey<sup>[30]</sup> investigated the use of a lichen planus-specific antigen as a marker to distinguish idiopathic OLP from OLL-d and demonstrate that it is not a useful marker.

## ORAL LICHENOID LESION ON GVHD

GVHD is a very frequent complication of allogeneic bone marrow transplantation (BMT), and it is associated with morbidity and mortality. It is characterized by dermatological, gastrointestinal and hepatic lesions<sup>[31,34,35]</sup>.

GVHD occurs when the donor immune system recognizes the host tissue as foreign and attacks its cellular constituents. Donor's T-lymphocytes reacts against recipient of antigens<sup>[17,31,32,34-36]</sup>. Three conditions can be observed in patients with GVHD<sup>[37]</sup>: the graft must contain immunologically competent cells; the recipient must express tissue antigens that are sufficiently different from those of the donor; or the recipient must be incapable of rejecting the graft because of either tolerance, lack of recognition, or immunosuppression.

There are acute and chronic GVHD: acute GVHD (aGVHD) occurs within the first hundred days after

transplant, while chronic GVHD (cGVHD) in more than 100 d after BMT<sup>[17,34,31,35]</sup>, and systemic organs and oral mucosa are involved<sup>[17]</sup>.

The aGVHD presents as painful desquamative and ulcerative lesions in oral cavity. Clinical manifestations of cGVHD appear very similar to those of autoimmune connective tissue diseases: white papular eruptions or reticular lesions with areas of erythema, erosion, or ulceration. Generally are symmetrically distributed and the areas of involvement include the tongue, buccal and labial mucosa<sup>[31,32,35-36]</sup>. It is commonly seen to arise or worsen after an infectious insult or when immunosuppression is reduced<sup>[17,31]</sup>, and they can influence quality of life of patients<sup>[36]</sup>.

Erythema, mucosal atrophy, and lichenoid changes are common oral findings in patients with cGVHD, with lichenoid reactions having the highest positive predictive value<sup>[31]</sup>. According to a study of Nakamura *et al.*<sup>[35]</sup>, OLL were the only clinical sign that had a statistically significant relationship to the diagnosis of cGVHD<sup>[25]</sup>. Clinically the OLL on cGVHD appears as lacy white striations similar to the striae of Wickham in the OLP<sup>[31]</sup>. Histologically these reactions consist of a degeneration of the basal cell layer and lymphocytic infiltration in the sub-mucosa. In some cases intracellular edema of epithelial cells can be observed<sup>[35]</sup>.

The OLL can be controlled when treating the systemic GVHD with immunosuppressive therapy. If the oral lesions persist or represent an isolated feature of GVHD, the management with potent topical corticosteroids is generally indicated<sup>[32]</sup>. Some medications used for the treatment of OLL associated with GVHD are diphenhydramine with kaolin and pectin or clobetasol gargles, topic fluocinonide, oral prednisone (20 to 50 mg/d) or thalidomide (50 to 200 mg/d)<sup>[34]</sup>.

## CONCLUSION

In summary, the OLL are a group of intriguing lesion principally when investigates their causal relationship. Moreover, determinate the differential diagnosis of OLL and OLP is important, considering that the different management of this lesions. Thus, epidemiological and laboratorial investigations including a larger number of patients are warranted to elucidate important aspects of OLL until obscures.

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## Effects of different root canal preparation methods on root fracture resistance: A systematic review of the literature

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**Data sharing:** Technical appendix and dataset available from the corresponding author at [wangqing@sdu.edu.cn](mailto:wangqing@sdu.edu.cn). Participants gave informed consent for data sharing.

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and 11 kinds of Chinese or English dentistry journals. Retrieval time on Internet was in all years and hand retrieval time was from January 2013 to October 2013. The literatures were selected through reading abstracts and full texts by two reviewers independently and Revman 5 software was used to analyze the literature.

**RESULTS:** Six articles met the inclusion criteria. According to Meta-analysis of tooth root bending properties, total standardized mean difference (SMD) was 0.63 (95%CI: -0.24-1.50,  $P > 0.05$ ). That indicated there was no statistically significant between the two groups. Subgroup analysis was carried out. SMD were 2.22 (95%CI: 0.23-4.20,  $P < 0.05$ ) and -0.61 (95%CI: -1.05- -0.17,  $P < 0.05$ ) when the premolar teeth with a single canal or the mesiobuccal roots of molars were used as the materials for tests to compare the effects of different root canal preparation methods on root fracture resistance. That only indicated that there were statistically significant in two subgroups.

**CONCLUSION:** *In vitro* experiments, the effects on the fracture resistance of root had no statistical difference with Ni-Ti rotary instruments and stainless steel hand instruments in root canal preparation.

**Key words:** Root canal therapy; Root canal preparation; Root fracture; Meta-analysis

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### Abstract

**AIM:** To study the root fracture resistance after root canal preparation with Ni-Ti rotary instruments and stainless hand instruments by means of meta-analysis.

**METHODS:** Literature was researched in CNKI and CBMDisc, PubMed, CALIS, Proquest, Web of Science

**Core tip:** There were different opinions on the effect of root fracture resistance using nickel-titanium rotary instrument. The present study carried out Meta-analysis on the references related to the influences on root fracture resistance of two different root canal preparation methods. The result can provide evidence for clinical therapy. The present study confirms that the effects of root canal preparation by Ni-Ti rotary instruments or manual stainless steel instruments on root fracture

resistance are not statistically significant. These two preparation methods are both safe and effective if dentin is not excessively cut under normal chewing conditions.

Li XG, Wang Q. Effects of different root canal preparation methods on root fracture resistance: A systematic review of the literature. *World J Stomatol* 2015; 4(2): 108-114 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v4/i2/108.htm> DOI: <http://dx.doi.org/10.5321/wjs.v4.i2.108>

## INTRODUCTION

So far, root canal therapy is the most thorough and perfect method for endodontic and periapical disease, and root canal preparation is the key procedure for root canal therapy. However, more and more studies showed that the teeth after root canal therapy may have an inclination towards longitudinal fissure in tooth root<sup>[1,2]</sup>. Sclerotic tissues of teeth lost nutrients due to removing endodontium in root canal preparation, and dentin became dehydrated and embrittled<sup>[3]</sup>. The studies demonstrated that there was a close relationship between tooth resistance and root canal cavity size, lumen wall thickness and cavity shape. Wilcow *et al*<sup>[4]</sup> studied 34 maxillary anterior teeth *in vitro* and indicated that subclinical crack was detected in almost 30% of the tooth roots under the same burden on root canal wall when the root canals were enlarged to 20%-30% of the diameters of the root canals. When the root canals were enlarged to 40% of the diameters of the root canals, longitudinal fissure in tooth roots were detected. Sathorn *et al*<sup>[5]</sup> prepared root canals and enlarged the middle diameter of root canals progressively in ten mandibular incisors *in vitro*. The results of finite element analysis showed that the root fracture resistance successively decreased for the root canals with diameters at 0.5, 1.0, 1.5 and 2.0 mm<sup>[5]</sup>. There was a close correlation between the degree of root canal preparation and tooth resistance. The larger cavity size lead to the less tooth resistance. Thus, the remaining dentine thickness was an important factor affecting root fracture resistance of teeth.

Nickel-titanium rotary instruments have an excellent shaping ability due to ideal remotion ability and flexibility, which ensures a perfect root canal preparation combined with crown-down technique<sup>[6]</sup>. Therefore, nickel-titanium rotary instruments have become the main instrument for root canal preparation. However, there were different opinions on the effect of root fracture resistance using nickel-titanium rotary instruments. The present study carried out meta-analysis on the references related to the influence on root fracture resistance of two different root canal preparation methods. The result can provide evidence for clinical therapy.

**Table 1 PubMed search strategy**

No.	Search history	Limits	Results
I	(Root canal therapy or root canal preparation) and root fracture	Human Chinese or English All years	1014
II	(Nickel-titanium rotary instrument or manual stainless steel instrument) and root fracture	Human Chinese or English All years	27
III	(Hand instruments or rotary instruments) and root fracture	Human Chinese or English All years	32
Total			1073

## MATERIALS AND METHODS

### Literature retrieval

Using three groups of research terms: "(root canal therapy or root canal preparation) and root fracture", "(nickel-titanium rotary instrument or manual stainless steel instrument) and root fracture", "(hand instruments or rotary instruments) and root fracture". The published literature were assessed in CNKI, CBMdisc, China Academic Library and Information System (CALIS), PubMed (Table 1), Proquest, Web of Science and in 11 Chinese or English dentistry journals by hand. Retrieval time on Internet was in all years and hand retrieval time was from January 2013 to October 2013. The literature was selected through reading abstracts and full texts.

### Literature inclusion and exclusion

**Literature inclusion criteria:** Literature inclusion criteria were made according to Meta rules and then the literature were selected for second time. Literature inclusion criteria were: (1) All experiments were randomized controlled trials and the tested teeth were randomly divided into hand instruments preparation group and nickel-titanium rotary instrument preparation group; (2) The teeth *in vitro* were selected as materials. There were no significant defect and abnormal shape. In every included experiments, the differences in lengths of teeth, buccolingual diameters, mesiodistal dimensions and root tip curvatures should not be statistically significant; (3) Root canal preparation method was the only variable in every experiment; (4) Teeth were similarly handled before testing. Step-back technique was used to prepare root canal in hand instruments group, and crown-down technique was used in nickel-titanium rotary instrument group; (5) The universal loading machine of general international standards was used for the instrument for tests, and 1 mm/min was used as the loading rate; (6) The pressure values when root fracture appeared were recorded; and (7) All data were analyzed by statistic software.

### Research data

There were six publications meeting the inclusion

**Table 2** The information statistics of included literature

Ref.	Dental notation	Hand preparation numbers	Hand preparation mean	Hand preparation SD	Ni-Ti preparation numbers	Ni-Ti preparation mean	Ni-Ti preparation SD	Ni-Ti instruments taper
Lan <i>et al</i> <sup>[7]</sup> I	Molar	13	10.2	4.4	13	15.7	9.1	0.06
Lan <i>et al</i> <sup>[7]</sup> II	Molar	13	10.2	4.4	13	13.2	6.1	0.08
Ren <i>et al</i> <sup>[8]</sup>	Pre-molar	10	308	8.69	10	228	10.19	0.06
Sathorn <i>et al</i> <sup>[9]</sup>	Incisor	25	113.5	20.2	25	114.9	37.1	0.04
Shi <sup>[10]</sup> I	Pre-molar	8	459.5	163.4	8	436.75	146.58	0.02
Shi <sup>[10]</sup> II	Pre-molar	8	459.5	163.4	8	474.25	101.44	0.04
Shi <sup>[10]</sup> III	Pre-molar	8	459.5	163.4	8	431.38	90.67	0.06
Singla <i>et al</i> <sup>[11]</sup>	Pre-molar	10	482.78	19.33	10	399.07	13.279	0.12
Zare Jahromi <i>et al</i> <sup>[12]</sup>	Molar	16	50.33	19.1	16	63.1	25.46	0.06

criteria<sup>[7-12]</sup>. In Lam *et al*<sup>[7]</sup> study, there were two experimental groups in different Ni-Ti rotary instruments taper. So there were two randomized controlled trials among two experimental groups and a control group. They were marked as Lam I and Lam II in Table 2. In Shi<sup>[10]</sup> study, three experimental groups B1, B2 and B3 and a control group A took root canal preparation method as the only variable. So there were three randomized controlled trials among them. They were marked as Shi I, Shi II and Shi III in Table 2. There were four groups in Singla *et al*<sup>[11]</sup> study, but only one randomized controlled trials between hand instruments group and Protaper rotary instruments group fit inclusion criterias<sup>[11]</sup>.

Essential characteristics of all groups were showed in Table 2.

### Meta analysis of inclusive literature

Revman 5 software was used for meta-analysis. Since the measuring units for the included references were not consistent, so standardized mean difference (SMD) analysis was carried out and represented by 95%CI.  $\chi^2$  test was carried out to test the heterogeneity among the references. Randomized effect model and fixed effect model were performed respectively in meta analysis when there was statistic significance heterogeneity or not ( $P < 0.05$ ,  $I^2 > 50\%$  or  $P > 0.05$ ,  $I^2 < 50\%$ ). Then the forest map was plotted.

### Statistical analysis

This document certifies that the statistics in the above manuscript was reviewed and edited by the subject experts (Professional statistician and PhD-level American expert) at 4UPUB to ensure the statistics method, spelling, grammar, and word flow adhere to the standards of professional and academic journals.

## RESULTS

### Meta analysis of the included literature

In six included literature, nine groups of clinical trials,

there was statistical heterogeneity ( $P < 0.05$ ,  $I^2 > 50\%$ ), so the random effect model of meta analysis was used. The results were showed in Figure 1.

SMD in Figure 1 was 0.63. This indicated that the teeth prepared by manual stainless steel instruments had more root fracture resistance. But the effect quantity was no statistically significant (95%CI: -0.24-1.50,  $P > 0.05$ ).

Subgroup analysis was carried out according to the difference of the tooth positions in each experiment: (1) The premolar teeth with a single canal were used to compare the effects of different root canal preparation methods on root fracture resistance, and the results were shown in Figure 2. The figure indicated that this subgroup of references had statistical heterogeneity ( $P < 0.05$ ,  $I^2 > 50\%$ ). Thus the SMD analysis under the random effect model was used. SMD was 2.22 (95%CI: 0.23-4.20,  $P < 0.05$ ), indicating that the preparation by using Ni-Ti rotary instruments was liable to cause root canal fracture; and (2) The mesiobuccal roots of molars were used to compare the effects of different root canal preparation methods on root fracture resistance, and the results were shown in Figure 3.

The figure mentioned above indicated that this subgroup of references had no statistical heterogeneity ( $P > 0.05$ ,  $I^2 = 0$ ). Thus the SMD analysis under the fixed effect model was used. SMD was -0.61 (95%CI: -1.05- -0.17,  $P < 0.05$ ), indicating that the preparation by using manual stainless steel instruments was liable to cause root canal fracture.

### Heterogeneity analysis

As shown in Figure 1, there was statistical heterogeneity among seven included references ( $P < 0.05$ ,  $I^2 > 50\%$ ). By reading literature, significant heterogeneity was found in the references of Ren *et al*<sup>[8]</sup> and Singla *et al*<sup>[11]</sup>, and heterogeneity analysis should be carried out.

The pressure loading direction utilized in the reference of Ren *et al*<sup>[8]</sup> had an angle of 15 degrees to the long axis of teeth, namely it simulated the situation for root fracture under lateral pressure load, while the

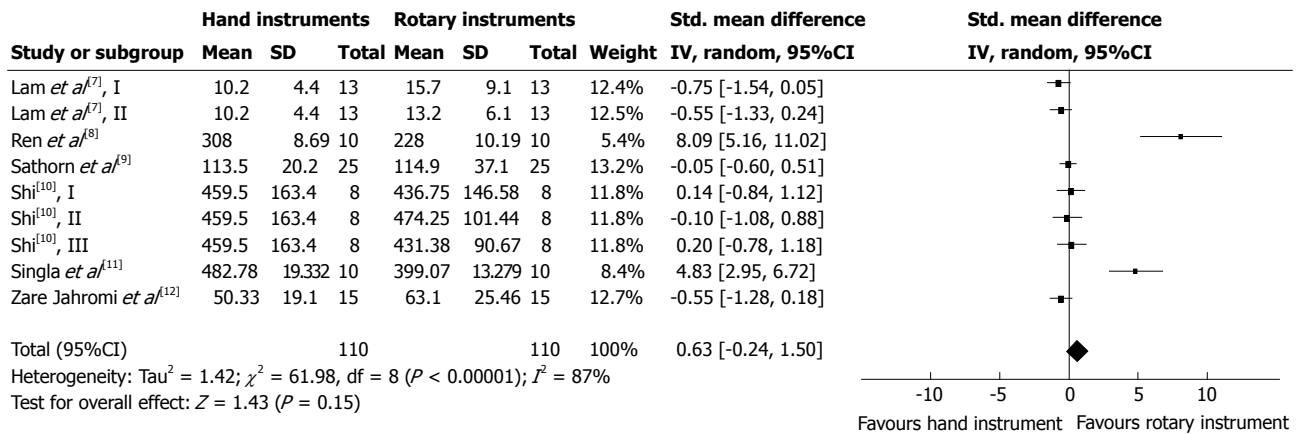


Figure 1 Forest plot of comparison of effects of root fracture resistance.

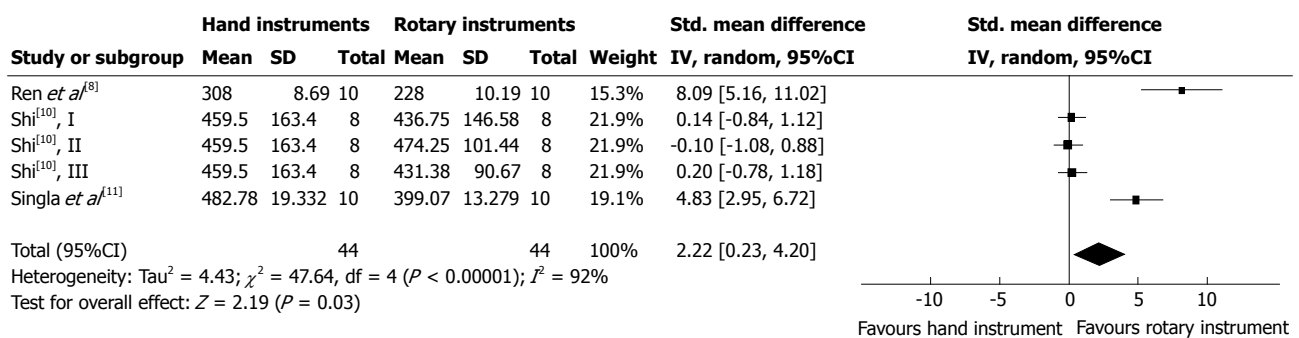


Figure 2 Forest plot of subgroup (premolar).

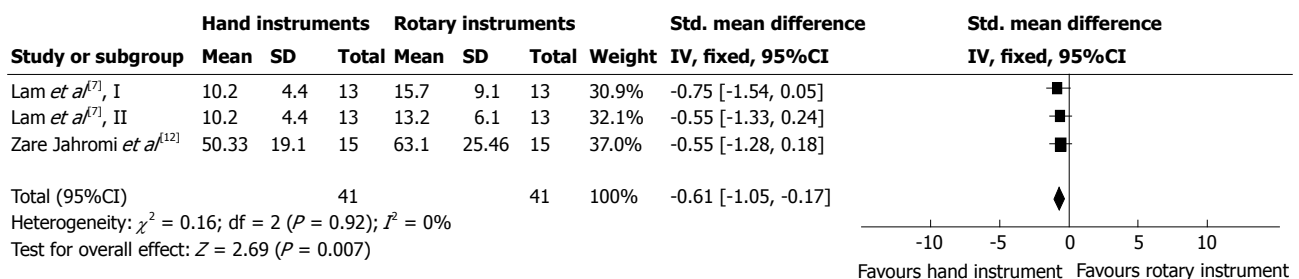


Figure 3 Forest plot of subgroup (molar).

pressure loading directions utilized in other references were paralleled to the long axis of teeth, namely they simulated the situation for root fracture under vertical pressure load. The research showed that the maximal VON MISES stress, the maximal tensile stress and the maximal compressive stress of tooth at lateral loading should be significantly higher than those at vertical loading under the same loading conditions, and they should be located at the middle parts of roots<sup>[13]</sup>. The studies also confirmed that the diameter of the middle part in the root canal after preparation with Ni-Ti rotary instruments was significantly bigger than that in the root canal after preparation with manual stainless steel instruments<sup>[14,15]</sup>. And the strength of root canals was closely related to the thickness of root canals, so the above factors may contribute to the heterogeneity.

The teeth roots were used in the loading tests after preparation but not filling up in the reference of Singla<sup>[11]</sup>. Studies have shown that the fracture resistance of root canal only after preparation was significantly lower than that after perfect root canal treatment<sup>[16,17]</sup>. Some scholars also found that filling sealer could significantly enhance the strength of the prepared root canal<sup>[18,19]</sup>. So the literature had large heterogeneity.

## DISCUSSION

Root canal preparation is an important procedure for root canal therapy, and excellent root canal preparation is the prerequisite for successful root canal therapy. With the development of dentistry, various kinds of Ni-Ti



rotary instruments appear, which have good flexibilities and toughnesses. Using them can decrease root canal perforation and displacement apparently and shorten handling time. Increase in the taper of the instruments can effectively clean and prepare root canals, but it may damage more dentin and thus decrease the strength of tooth root. Many studies demonstrated that there was a positive relationship between the quantity of dentin and intensity of tooth root. There was a lower resistance in teeth after root canal preparation than in teeth without root canal preparation according to all inclusive literature. The statistic difference was significant ( $P < 0.05$ ), which confirmed that root canal preparation decreases intensity of tooth root as well.

Dentin cutting was required for root canal preparation, while the remaining dentin thickness was the most important factor influencing the strength of teeth roots<sup>[20]</sup>. At 0.5 mm away from apical stop, same amount of dentin was cut by using manual stainless steel instruments and Greater Taper (GT) rotary instruments, while only 0.25 mm more dentin was cut by using Lightspeed (LS) rotary instruments. But at 4.5 mm away from apical stop, a little more dentin was cut by using GT rotary instruments than using other two kinds of instruments<sup>[7]</sup>. Certainly, more dentin is cut by using Ni-Ti rotary instruments than by using manual instruments, but the cross sections are arc-shaped triangles, which decreases the contacting area between rotary instruments and dentin in root canal walls. In addition, since the root canal compactibility was satisfactory, so the root canal taper after preparation was continuous and uniform and the stress could be effectively scattered, which could not only improve the cutting efficiency, but also decrease the stress on root surface during root canal preparation<sup>[21]</sup>. So this method can offset the deficiency that cuts more dentin in a certain degree. At the same time, the experiment *in vitro* have established that masticatory force could disperse quickly along the long axis of teeth *via* dental crown under vertical pressure load. Even root canal preparation and filling in large taper were also relatively safe<sup>[22]</sup>.

The clinical trials confirmed that the stress concentration area in the tooth root was almost consistent with the direction of root fracture. And the stress concentration was closely related to root fracture<sup>[23]</sup>. Manual stainless steel instruments cut less dentine, but repeated lifting and dragging was required for preparing ideal root canal morphology, which lead to over-straightening of root canal. The weak parts were liable to fracture because of uneven forces on different parts of root canal wall. Moreover, relatively big stress would be produced on root canal wall and decreased the strength of tooth root during repeated lifting, dragging, enlarging and scraping<sup>[24]</sup>. From the point of view of mechanics, structure defects, crack or improper root canal preparation, which would produce multiplied stress, were likely to be the key factors influencing the root canal strength<sup>[25]</sup>. Other studies considered

that the rigider root canal file caused stronger stress concentration, which increased the risk of dentin defect and lead to root fracture<sup>[26]</sup>.

Meanwhile, with the development of digital modeling technique, some scholars analysed the stress of root canal preparation by tooth three-dimension finite element model. The studies showed that the tendency of whole stress distribution on prepared teeth was similar, and the stress at the root canal orifice in the stainless steel instrument group was the highest, but the differences in the stress on root canal wall between root tips and middle parts of root canals were not statistically significant<sup>[27]</sup>. Furthermore, the ultimate compressive strength of dentine is 232-305 MPa and the tensile strength is 48-105.5 MPa. Therefore, different root canal preparation methods are safe and reliable without other effective factor. In general, the preparation methods by using Ni-Ti instruments and manual stainless steel instruments may decrease the strength of tooth roots, but the mechanisms are different and the effects on root fracture resistance have not been well defined.

Previous studies have shown that premolar and mesiodistal root canals of mandibular first molar after preparation were liable to fracture, thus most of the researches utilized them as the teeth for tests<sup>[28]</sup>. However, premolar and the root of mandibular first molar are different in their morphology, and subgroups (1) and (2) indicated that the test results were slightly different. The root of premolar is straighter and thicker than the first molar. The two kinds of preparation methods can easily produce smooth and continuous cone-shaped root canals, and stress concentration is not easily produced. Therefore, the amount of dentin cutting becomes a major factor affecting root fracture resistance, so manual stainless steel instruments are more advantageous. In contrast, mesiodistal root canals of molars are relatively thin and curved in root tips, and the flexibility of manual stainless steel instruments is relatively poor, so weak parts and stress concentration areas are liable to be produced during root canal preparation. Manual stainless steel instruments may be liable for root fracture in comparison to Ni-Ti rotary instruments.

All references included in the present study utilized *in vitro* loading tests. The methods were simple, and the experiments can be easily repeated, thus they have become the main method for investigating the effects on the root strength of preparation by using different root canal preparation instruments. However, *in vitro* loading tests also have their limitations: the direction of forces in loading tests is single, the maximal load exceeds the physiological chewing force and it could not mimic the physiological force loading of teeth in oral cavity. However, the direction of forces on teeth is one of the important influencing factors for root fracture resistance and changes in loading direction may change the research results. Among all of the references included in the present study, the maximal loads of tooth roots

all exceeded the physiological chewing force in oral cavity. Direction<sup>[29]</sup> and positions<sup>[30]</sup> of forces may lead to significant effects on the test results. Lateral forces may be liable to cause stress concentration in teeth roots in comparison to vertical forces under the same loading conditions. Therefore, the seen root fracture in clinical practices is always induced by lateral stress. Meanwhile, high frequency of load may be produced when teeth play the role in chewing under physiological conditions, so the fatigue resistance of tooth also affect fracture resistance. The effects of different root canal preparation methods on root fracture resistance require more tests on lateral forces and fatigue tests.

The present study confirms that the effects of root canal preparation by Ni-Ti rotary instruments or manual stainless steel instruments on root fracture resistance are not statistically significant. These two preparation methods are both safe and effective if dentine is not excessively cut under normal chewing conditions.

## COMMENTS

### Background

Root canal therapy is a perfect treatment method for pulpitis and periapical disease. And root canal preparation is one of the key procedures for root canal therapy, which includes traditional hand stainless steel instruments preparation method and rotary nickel-titanium instruments preparation method. Rotary nickel-titanium instruments, which have excellent root shaping ability, ideal remotion ability and flexibility and high preparation efficiency are research hotspots. But many studies have shown that the teeth prepared by rotary nickel-titanium instruments may show an inclination towards longitudinal fissure, because more dentin is cut off.

### Research frontiers

Many researches have carried out to study the different effects of two root canal preparation methods on root fracture resistance, but different results were obtained, which have led to puzzles in clinical operations for dentists.

### Innovations and breakthroughs

Meta-analysis was done for the effect of root fracture of Ni-Ti rotary instruments and stainless steel hand instruments preparation methods. Meta-analysis provides a high quality system review.

### Applications

The result can provide evidence for clinical therapy. Dentists can choose different root canal preparation methods according to the tooth type or tooth position and root curvatu.

### Terminology

Meta-analysis is a quantitative statistical analysis of several separate but similar experiments or studies in order to test the pooled data for statistical significance.

### Peer-review

This paper is potentially valuable.

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**EDITORIAL**

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*Sharma G*

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*WJS* covers topics concerning oral and craniofacial sciences, oral and craniofacial development/growth, dental tissue regeneration, craniofacial bone and cartilage research, oral and maxillofacial genetic diseases, developmental abnormalities and soft tissue defects, pulpal and periapical diseases, periodontal diseases and oral mucosal diseases, salivary gland diseases, oral and maxillofacial vascular/nervous diseases, jaw bone diseases, taste abnormalities, oral and maxillofacial pain, occlusion and temporomandibular diseases, repair and treatment of tooth defects, loss and dento-maxillofacial deformities, oral and maxillofacial biomechanics and biomaterials, new techniques for diagnosis/treatment of oral and maxillofacial diseases; and stomatology-related evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of stomatologic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## Diagnostic aids in detection of oral cancer: An update

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### Abstract

Oral cancer is the sixth most common malignancy with almost 500000 new cases reported worldwide annually. The diagnosis of oral cancer at an early stage has a good prognosis as the survival rate is high (around 80%). However, the majority of oral cancer cases are diagnosed at a later stage with a considerably

poor 5-year survival rate of 50% according to World Health Organization statistics. Thus, an effective management strategy for oral cancer will depend on its early identification and intervention which would pave the way for superior prognosis. Despite the obvious advantage of earlier diagnosis of oral cancer, no approach has yet proven to be a reliably successful in diagnosis of oral cancer at an early stage. Currently, the primary line of screening of oral cancer is performed by visual inspection, which is a subjective examination. Among the screening tests or diagnostic aids now available for oral cancer, few (toluidine blue, brush biopsy, salivary and serum bio-markers) have been utilised and studied for many years while others have recently become commercially available. The authors in the present article review all the modalities of screening aids used in oral cancer detection and provide an update on the latest screening tools used in oral cancer detection.

**Key words:** Oral cancer; Diagnostic aids; Brush biopsy; Tissue fluorescence

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**Core tip:** The overall 5-year survival rates for oral cancer have remained low (50%) for the past decades and are considered among the worst of all cancer death rates. Despite the obvious advantage of earlier diagnosis of oral cancer, no approach has yet proven to be a reliably successful in diagnosis of oral cancer at an early stage. Currently, the primary line of screening of oral cancer is performed by subjective visual inspection. Recent advancements in oral cancer research have led to the development of potentially useful diagnostic tools at the clinical and molecular level for early detection of oral cancer.

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## INTRODUCTION

Oropharyngeal malignancies are the 6<sup>th</sup> most frequent category in the world. Squamous cell carcinoma of the oropharynx area and lip is typically delineated as Oral cancer. The survival rates (five-year) for oral malignancies have continued to remain poor (about 50%) for the previous few years and are contemplated amongst the poorest of all malignancy death rates including colorectal cancer, cervical cancer and breast cancer<sup>[1]</sup>. It is also correlated with excessive frequencies of second oral cancers, with nearly one-third of cases experiencing a reappearance of the occurrence of a second primary carcinoma in spite of a rigorous follow-up. Though substantial advances in management of oral cancer have occurred, the timely recognition of oral cancer and its various predecessors continues to be the most excellent strategy to safeguard survival rates of patient and better life quality of patients<sup>[1]</sup>.

The key risk reasons of oral malignancies are tobacco (both smoking and smokeless tobacco) and alcohol abuse<sup>[2]</sup>. Absence of knowledge of the various indications, clinical presentation and predisposing reasons for cancers of the oral cavity are considered to be responsible for the diagnostic delay. Lately, World Health Organization (WHO) highlighted the importance of health care professionals in reducing around 30% of a projected 15 million malignancies and moreover, successfully management of one-third by effectively organizing oral carcinoma examination and diagnostic stratagems<sup>[2]</sup>.

Currently, the primary line for cancer screening is achieved through a subjective visual examination. An improvement in the proficiency of health care workers to identify premalignant conditions and lesions at an initial stage is required to help in early detection<sup>[3]</sup>. This can be accomplished by intensifying public attentiveness concerning the relevance of routine intra-oral examination and the development of diagnostic aids that can be used by the oral health care professionals to swiftly identify oral premalignant lesions<sup>[3]</sup>. Various adjunctive screening techniques have been established to enhance the recognition and dissimilarity between an innocuous lesion and oral premalignant and malignant lesion<sup>[3]</sup>. The progress of diagnostic tools at the genetic level in the prompt and timely diagnosis of oral cancer has further provided another depth to oral cancer research<sup>[1]</sup>.

## CONVENTIONAL ORAL EXAMINATION

Conventional oral examination has various disadvantages like false positive findings, including psychological trauma, over-diagnosis, increased human and financial resources, recognition of varied clinical presentations

of premalignant lesion<sup>[4]</sup>. Only a minor fraction of leukoplakias become cancerous and there is impossibility of distinction amongst cancerous lesions and their equivalents that do not convert into malignancy<sup>[4,5]</sup>.

## BRUSH BIOPSY

In 1999, the OralCDx Brush Test System (Brush Biopsy) was presented as a probable oral malignancy detection method. The examination of clinical lesions that would typically not be subjected to biopsy because the index of suspicion for malignancy was low established upon clinical features were the primary target areas for brush biopsy. There is typically collection of an epithelial sample (including the superficial, intermediate and parabasal/basal layers) of cells from a mucosal lesion. When an atypical or positive outcome is conveyed, the practitioner should supplement with a biopsy (scalpel) of the suspicious condition, since the usage of oral CDx (brush biopsy) does not specifies conclusive finding<sup>[2,4]</sup>.

In a patient with multiple suspicious malignant areas brush biopsy would be valuable, as it is implausible that patient would swiftly comply with numerous scalpel biopsies<sup>[4]</sup>. Brush biopsy would be advantageous in a clinical scenario where patient is improbable to revisit for a continuation intra-oral examination or consents to an instantaneous recommendation to a maxillofacial surgeon<sup>[4]</sup>. Though there is uncertainty of brush biopsy as a diagnostic support in oral malignancies, the thoughtful usage of this technology may be clinically beneficial<sup>[4]</sup>.

## VITAL TISSUE STAINING

Toluidine blue (tolonium chloride) stains mitochondrial DNA, dysplastic cells which have increased DNA content or modified DNA in cancerous cells<sup>[5]</sup>. The local application of toluidine blue (a metachromatic dye) facilitates in recognizing malignant alterations and potential areas of high-grade dysplasia. Lugol's solution is used for delimitation of the cancerous alteration that generates a brownish black stain when glycogen reacts with iodine. The usage of combination of Lugol's iodine and toluidine blue provides a valuable addition for diagnosis of patients who are at an increased risk and for selecting the site for biopsy with wide field cancers prior to management<sup>[6]</sup>.

The overall sensitivity of vital tissue staining for the recognition of malignancies in oral cavity has varied (0.78-1.00) and the specificity has also ranged from 0.31 to 1.00<sup>[4]</sup>. Various disadvantages of toluidine blue staining are no randomized controlled trials, dearth of research studies organized in a primary care setting, lack of usage of gold standard (histopathological diagnosis), dissimilarity in approaches ranging from one time rinse, double time rinse, oral mucosal "painting" and uncertainty of using or defining pale staining which is subjective<sup>[4]</sup>. There is necessity to assess toluidine blue staining with histopathology, genetic and molecular



risk prognosticators and with conclusion (*i.e.*, malignant transformation)<sup>[7]</sup>.

## CHEMILUMINESCENCE

Chemiluminescence [commercially available as ViziLite (Zila, Batesville, AR, United States)] is an intraoral examination diagnostic tool to increase recognition, assessment and scrutinizing of oral mucosal aberrations in patients with increased possibility of malignant transformation<sup>[3]</sup>. Disposable chemiluminescent light packet is used in ViziLite plus whereas the MicroLux unit utilizes a light source which is battery-powered and reusable. The usage of acetic acid (1%) wash is done to eliminate superficial residues and to improve the conspicuousness of nuclei of the epithelial cells, perhaps as an outcome of slight dehydration of the cells. Normal epithelium appears lightly bluish under blue-white illumination whereas aberrant epithelium looks noticeably white in appearance (acetowhite)<sup>[4]</sup>.

The usage of a disposable chemiluminescent light stick which is conveniently hand-held for single time is done that emanates varied light at wavelengths of 430, 540 and 580 nm<sup>[8]</sup>. Light is absorbed by usual epithelium that appears dark while precancerous conditions and lesions emerge whitish. The alteration in colour is correlated to distorted thickness of epithelium and the greater nuclear substance and matrix of mitochondria that specially reflects light in the precancerous lesions and conditions<sup>[8,9]</sup>.

The distinction between cancerous, benign and inflammatory oral lesions cannot be done. Another disadvantage is its increased cost, reduced specificity, increased frequency of false positives, leading to unwarranted biopsies<sup>[10]</sup>. Vizilite has been found to be more accurate in detecting leukoplakias than erythroplakias and red lesions<sup>[11]</sup>. Future research is essential to evaluate the sensitivity and specificity of vital tissue staining with respect to histopathological and clinical attributes and to establish its accurate practicality for standard intra-oral examinations of the oral cavity<sup>[12]</sup>.

## NARROW-EMISSION TISSUE FLUORESCENCE

The usage of tissue auto fluorescence in the examination and identification of premalignant conditions in the cervix, skin and lung has been suitably verified<sup>[8]</sup>. When tissues are exposed to a light of particular wavelength, there is auto fluorescence of cellular fluorophores after excitation (Fluorescence imaging). A visual examination of variation in colours is observed due to cellular changes that modulate fluorophores' concentrations affecting the absorption of light in the cells<sup>[4]</sup>.

Visually Enhanced Lesion Scope (VELscope system; LED Dental Inc., White Rock, B.C.) comprises of light-source (wave length: 400-460 nm) and a component

(manual) to assist in detailed examination or inspection<sup>[12]</sup>. Typically oral mucosal tissues emanate a auto-fluorescence light of green colour but anomalous oral mucosal lesions absorbs the auto-fluorescent light and emerge as darker areas<sup>[12]</sup>. However its routine usage is not corroborated since there is an increased specificity, expense and the absence of scientific verification<sup>[12]</sup>. A recent research revealed that the VELscope was beneficial in substantiating oral premalignant lesions like leukoplakia and erythroplakia. However the difference between greater-risk and lower-risk lesions could not be done<sup>[13]</sup>. However, VELscope system is displaying promise due to its efficiency in identifying mucosal lesions and their borders that are covert to intra oral clinical inspection under white light<sup>[2,14]</sup>.

## CONFOCAL *IN-VIVO* MICROSCOPY

Confocal reflectance microscopy is an optical technology that delivers comprehensive descriptions of tissue structure and morphological characteristics of cell trans-epithelium in real time<sup>[15]</sup>. Confocal *in vivo* microscopy assists the compilation of pathological level high resolution imaging from the tissue for disease recognition in cell biology with an advantage of optical sectioning<sup>[16]</sup>. *In vivo* confocal images from the oral cavity show the distinctive characteristics like variability in nucleus findings that can recognize malignancy from normal oral mucosa<sup>[6,16]</sup>.

## TISSUE FLUORESCENCE SPECTROSCOPY

The illumination of oral cavity tissue with UV-Visible light region results in the absorption of photons by fluorophores. It results in the excitation of fluorophores that causes emission of lower energy photons which are perceived as fluorescence from the mucosal surface<sup>[17]</sup>. The auto fluorescence spectroscopy system contains an optical fibre which is small and similarly generates wavelengths of variable excitations and consists of a spectrograph that collects the continuums of reflected fluorescence from the cellular structures and analyses the received information on a computer<sup>[2,14]</sup>. A study revealed that 405 nm wavelength excitation best differentiates normal oral mucosa with oral premalignant lesions<sup>[18]</sup>. However, a disadvantage is the reduced specificity in recognition of potentially malignant conditions. Auto fluorescence is typically caused by protoporphyrin and the variable concentration of blood components that vacillates proportionately during cancerous progression and retrogression<sup>[19]</sup>. The addition of fluorescence-reflectance or dual digital systems, backscattered light analysis and ultraviolet spectra can overwhelm the disadvantages of auto fluorescence<sup>[17]</sup>.

## COLPOSCOPY

Colposcopy (direct microscopy) is a recognized medical

diagnostic technique used to inspect the tissues of the vagina, vulva, and cervix, carried out under illuminated light with a magnified view of the area of interest<sup>[20]</sup>. Colposcopy provides three-dimensional images of the tissue surfaces examined with portable video cameras attached and viewed on a television monitor screen. The colposcope is mounted with a green/blue filter to enable the inspection of alterations in vascularity and color quality as unfiltered white or yellow light diminishes the dissimilarity concerning the adjoining tissue and the arterioles. An optimum working distance of 200 mm for the focal length of the microscope is required. The accurateness of colposcopy was 70%-98% for the recognition of oral mucosal alterations with a study showing that colposcopy of oral premalignant lesions had benefits in choosing a representative area of biopsy<sup>[20,21]</sup>.

## SALIVARY BIOMARKERS

Greater than a hundred probable oral cancer biomarkers in saliva have been described in the English literature, established primarily on comparing the quantities obtained in oral cancer patients to the quantities acquired in persons who act as controls<sup>[22]</sup>. Various salivary proteins like  $\alpha$ -amylase, interleukin 8, tumor necrosis factor- $\alpha$ , Statherin, CA 125, Endothelin-1, CD44, Catalase, Cyclin D1, CEA, Maspin, Lactate dehydrogenase and Transthyretin have been evaluated<sup>[22]</sup>. Salivary biomarkers are a promising non-invasive approach but there are still some challenges. Absence of calibration for the method of salivary sample collection, variability in processing and storing; extensive capriciousness concentrations of probable oral cancer biomarkers in saliva of both the non-malignant individuals and oral cancer cases and a requirement for additional validation are the few challenges in usage of salivary biomarkers<sup>[22]</sup>.

## CELL AND TISSUE MARKERS

There are numerous categories of cell and tissue markers that could offer supplementary knowledge in addition to intra-oral clinical assessment and pathological analysis<sup>[23]</sup>. Tumour growth markers like epithelial growth factor (EGF), Cyclins, AgNOR, bcl2 and telomerase have been used<sup>[23]</sup>. Three angiogenic biomarkers CD105 and Eph receptor tyrosine kinases (Ephs), vascular EGF and four hypoxia biomarkers (GLUT-1, carbonic anhydrase IX, hypoxia inducible factor 1a, and erythropoietin receptor) were identified as biomarkers<sup>[24]</sup>.

Retinoblastoma protein, p53 and Cyclin-dependent kinase inhibitors are the examples of tumour suppression markers and anti-tumor response<sup>[23]</sup>. The matrix metallo proteins are proteases typically expressed by invasive cancers and the contiguous stroma and their expression has often been reviewed in various studies<sup>[25]</sup>. Cathepsins, Integrins and desmoplakin have also been found as markers of tumor invasion<sup>[23]</sup>. Cytokeratins,

filaggrins, involucrin and glutathione S-transferase have all been investigated<sup>[23]</sup>.

## ELASTOGRAPHY

Lymph node hardness (elasticity) is a major criterion to differentiate between an inflammatory enlargement and a malignant enlargement. Elastography assesses the behaviours of compliance of cellular structure. The compression to tissues generates displacement or strain in the tissue structure and hence by measuring tissue strain, hardness of the tissue can be estimated. The images obtained by elastography are evaluated before and after compression of cervical lymph nodes<sup>[26]</sup>.

## SURFACE ENHANCED RAMAN SPECTROSCOPY

Raman spectroscopy delivers a factual, great - exactitude and sensitive procurement of the molecular tissue structure due to the particular interaction of cellular molecules with photons<sup>[27]</sup>. The spectral characters of lipids, nucleic acids and proteins functions as precise Raman biomarkers to differentiate between malignant and normal oral mucosal area<sup>[27]</sup>. Raman spectroscopy brings knowledge which is corresponding or even advanced to recognized procedures in oral carcinogenesis. The disadvantages are that it is random and nonimaging, requires expensive equipment, extensive process, lack of spatial information and multifaceted algorithms to discern various categories of tissues<sup>[17]</sup>. These concerns impart trials for their forthcoming usage in the clinical setting. Recently, a multispectral optical imaging device for diagnosis of premalignant lesions was done<sup>[28]</sup>.

## OPTICAL COHERENCE TOMOGRAPHY

The recording of subsurface images to develop an overall cross-sectional tissue structural representation is optical coherence tomography. The multimodal distribution of polyethylene glycol linked gold nanoparticles that are antibody-conjugated augments the distinction in *in-vivo* images of cancerous lesions in oral cavity in a hamster model<sup>[29]</sup>. The practicality of managing optical coherence tomography to detect structural modifications in cancerous molecules was observed in a recent pilot research in 27 cancerous patients<sup>[30]</sup>.

## POSITRON EMISSION TOMOGRAPHY

Fluorodeoxyglucose-positron emission tomography (FDG-PET) examination shows proficient precision and prognostic significance in defining lymphatic condition and thus helping in assessment and timely diagnosis of oral malignancy in affected patients<sup>[6,31]</sup>. PET/computed tomography (CT) can identify and distinguish surgical

and radiation-induced variations from residual or recurrent neoplasias because cancerous cells uphold greater FDG for lengthier intervals of time as compared to infectious and inflammatory structures<sup>[32]</sup>. Recent research have revealed that PET/CT had a high (> 90%) accuracy for locating the recurrent tumour<sup>[32]</sup>.

## ROSE BENGAL STAINING

Rose Bengal stain (RB), the 4, 5, 6, 7-tetrachloro-2', 4', 5', 7'-tetraiododerivative of fluorescein, can be utilized as a screening tool to detect oral precancerous lesions<sup>[33]</sup>. Du *et al*<sup>[34]</sup> concluded in a study that RB staining may be better than toluidine blue staining. Future research can ascertain the RB stain as an effective diagnostic tool in the recognition of oral precancerous lesions.

## BIO-NANOCHIP

Recently, a novel bio-nanochip (BNC) sensor which is a fast oral-cytology test that amalgamates the power of cytological morphometric examination with quantification of neoplastic biomarkers was documented<sup>[35]</sup>. Generally, microfluidics technology (lab-on-a-chip) is the adjustment, miniaturization, amalgamation, and automation of analytical laboratory procedures into a solitary chip<sup>[29]</sup>. The conducted study on quantitative BNC method to oral cytology effectively revealed cancerous and pre-cancerous conditions in a short time duration (< 45 min)<sup>[35]</sup>. The recognition of cancerous cells in the BNC sensor utilized membrane-related cell proteins that are especially present on the cellular membrane structure of neoplastic cells<sup>[36]</sup>.

## DNA PLOIDY ANALYSIS

Recent research has described the probable use of DNA ploidy analysis to predict the character of premalignant lesions in oral cavity. Aneuploidy (chromosomal imbalance) in dysplastic cells seen in premalignant lesions, as found by high resolution flow cytometry is suggestive of high possibility of oral malignancy transformation<sup>[37]</sup>. DNA ploidy analysis helps in compensating for intra- and inter-observer irregularity in the grading of dysplasia observed in premalignant lesions and might potentially aid in directing the management of the lesion, and probably suggest more aggressive treatment<sup>[38]</sup>.

## CONCLUSION

The WHO has noticeably recognized prevention and early recognition as the chief objectives in the crusade to limit the cancerous conditions internationally<sup>[2]</sup>. Various diagnostic tests shown promising findings, but lack of their definite substantiation is the major hurdle. Limitations include low sample volumes, absence of systematically comprehensive clinical studies, deficient usage of histopathological and cellular plotting of optically modified mucosa, necessity of more com-

prehensive investigation of reasons and absolute evaluation with other recognition techniques<sup>[2]</sup>. There has been a dramatic escalation in the growth of many probable pre-cancerous investigation techniques and still superior diagnostic aids are required to combat this deadly disease. More exploration is necessitated to confirm the effectiveness of these diagnostic aids and they need to be validated and financially viable to be relevant in the developing nations.

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## When will RNA-based tests similar to Oncotype DX be used for oral cancer?

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### Abstract

Methods for detection, diagnosis and predicting treatment outcomes for oral squamous cell carcinoma (OSCC) have not changed in decades. Information from studies about molecular changes that occur with these tumors are not useful in the clinic. This is in contrast to breast cancer where global gene expression analysis in the form of the Oncotype DX and Mammprint tests are used routinely to determine ideal treatment for a large subset of breast tumors. While the first large scale studies of gene expression in both cancer types were done over a dozen years ago, research on OSCC has not led to gene expression profiles that are useful in the clinic. Global gene expression data for well over a thousand breast tumors linked to clinical outcomes has been available online for nearly ten years. This accelerated the development and validation of multiple RNA classifiers used to predict breast cancer treatment outcomes. Molecular characterization of oral and head and neck cancer research has been handicapped primarily due to low sample numbers. The recent release from The Cancer Genome Atlas of global gene expression analyses of over 500 head and neck tumors, including 308 oral tumor samples, obtained by standardized methods, along with linked clinical outcome data, should change this. It makes the vision of including gene expression analysis in OSCC treatment planning an obvious and attainable goal that could occur in the next five years.

**Key words:** Treatment outcome; Oral squamous cell carcinoma; Gene expression classifier

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**Core tip:** Methods for characterizing oral squamous



cell carcinoma have not changed in decades. This is in contrast to breast cancer where global gene expression analysis is often used to determine ideal treatment. Studies focusing on molecular changes in oral cancer have suffered from lack of uniformity and small size. The recent release from The Cancer Genome Atlas of global gene expression analyses of over 500 head and neck tumors, including 308 oral tumors, should bring to the clinic in the next few years gene and gene expression analysis, and improved outcomes.

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## INTRODUCTION

Detection and diagnosis of oral cancer is done today largely the same way it was done 30 years ago. White light is used to visually scan the oral cavity for unexplained lesions, followed by cervical lymph node visual examination and palpation. Suspicious oral lesions are then surgically biopsied and, after sectioning and staining, the pathologist provides a diagnosis based on tumor cell nuclear size and stain intensity, cell morphology and an examination of the mucosal architecture. While vital stains such as Toluidene blue can be used to stain the oral cavity, making lesions more easily detectable, and brush cytology is available to noninvasively assay cell and nuclear size and shape, these adjunct methods themselves are decades old and have not gained widespread usage<sup>[1]</sup>. Unlike detection, diagnosis, and even treatment planning with other cancers, measurement of molecular changes are seldom done with oral cancer.

In 2002, just two years after the original global gene expression analysis of breast tumors was published<sup>[2,3]</sup>, one of the first relatively large scale studies of global gene expression in 26 head and neck tumors was revealed<sup>[4]</sup> (Table 1). At that time there was great optimism that those types of studies would provide gene expression signatures that could be used to diagnose and type oral tumors. However, there were problems early on including the usage of non-ideal statistical methods for studies with low sample numbers that often resulted in over-fitted data. The inclusion of multiple tumor subtypes compounded the problem of insufficient sample numbers and also made interpretation complex<sup>[5]</sup>. Finally, comparisons were often done between RNA from tumor and healthy mucosa; and not tumor vs benign lesions that can be mistaken for oral squamous cell carcinoma (OSCC)<sup>[6]</sup>. One way to rectify these problems is to study a subgroup of tumors in a single high risk group, such as tobacco or betel nut users, and to compare these

tumors to benign pathology<sup>[5]</sup>. Until these factors are considered, improved detection of head and neck cancer using gene expression based methods will not move to the clinic and even then there is unlikely to be a single genetic classifier for all OSCCs.

Another potential role for gene expression analysis of OSCC is in the prediction of treatment outcomes. Currently OSCC staging is based on the universally used TNM system of the Union International Contre le cancer and the American committee on cancer. TNM staging is based on anatomic extent of the tumor only. Specifically T stands for tumor size, N indicates nodal involvement and M indicates presence or not of distant metastasis. The shortcomings of the currently used TNM staging system for head and neck and OSCC are elegantly discussed by Takes *et al.*<sup>[7]</sup>. It is unfortunate that despite these limitations OSCC staging plays a key role in treatment decisions that ultimately impact survival. Studies have indicated that tumor specific histopathologic characteristics impact on outcomes and survival, such as depth of invasion, tumor volume and thickness, presence of extracapsular extension, perineural invasion, pattern of invasion, lymphovascular invasion, but these research findings are not routinely included in staging or treatment decision-making for multiple reasons<sup>[8-14]</sup>. Typically, early stage tumor patients are treated with single modality therapy, surgery alone or, rarely, radiotherapy alone, while more advanced stage tumors receive multimodality treatment with surgery and adjuvant therapy such as radiation with or without chemotherapy. The rationale is that stage I or II tumors, which are by definition without lymph node involvement, can be reasonably controlled with surgery or localized irradiation. Systemic genotoxic treatment provides no advantage and has potentially more toxic side effects. While this approach has spared patients unnecessary adjunctive treatment, it would be better to know which tumors have a propensity to progress and need multimodality treatment. Much effort has been made to develop a gene expression-based classifier for OSCC that does not just stage the tumor but also predicts aggressiveness. For example, this was attempted by recording changes in gene expression pattern in tumor tissue that correlate with lymph node invasion and/or tumor recurrence<sup>[15-19]</sup>. A problem in these studies may have been insufficient sample numbers. A second lesser problem was the seeming paradox that there was very little overlap between marker RNAs identified by one group and that of another, the latter creating a level of doubt about the methodology (needs a period).

## ORAL CANCERS LIKE BREAST CANCERS ARE NOT ALL ALIKE

The state of the gene expression-based staging of breast cancer offers a contrast in clinical value<sup>[20,21]</sup>. The Oncotype DX treatment response predictor has been used over one-half million times for breast cancer

**Table 1 Major events in global gene expression analysis of breast and head and neck cancer**

Breast cancer	Events	HNSCC
2000 (Perou <i>et al</i> <sup>[23]</sup> )	First large scale global gene expression analysis	2002 (Méndez <i>et al</i> <sup>[43]</sup> )
2001 (Sorlie <i>et al</i> <sup>[33]</sup> )	First identification of tumor subtypes based on global gene expression analysis	2004 (Chung <i>et al</i> <sup>[22]</sup> )
2002 (van de Vijver <i>et al</i> <sup>[35]</sup> )	First published classifier to advise treatment based on global gene expression analysis	2005 (Roepman <i>et al</i> <sup>[18]</sup> )
2003 (Sorlie <i>et al</i> <sup>[34]</sup> )	First confirmation of tumor subtypes based on global gene expression analysis	2013 (Walter <i>et al</i> <sup>[23]</sup> )
2006 (Paik <i>et al</i> <sup>[28]</sup> )	First validated classifier to advise treatment based on global gene expression analysis	Still waiting
2006 (1200 samples)	More than 1000 samples global gene expression analysis data available	2013 (1200 samples)

HNSCC: Head and neck squamous cell carcinoma.

staging. This gene expression-based test fills a void left by the uncertainty over which stage I and II breast cancers require chemotherapy after surgery. It was known early on that a subset of early-stage estrogen receptor positive breast tumors tended to progress if chemotherapy was withheld<sup>[20,21]</sup>. In 2000 and 2001, it was first noted that breast cancer could be divided into more than 4 subtypes based on gene expression analysis<sup>[2,3]</sup>. These groups roughly coincided with the older histological classifications. The realization that breast tumors were a heterogeneous group made it clear in the beginning that studies of gene expression in breast tumors would require large numbers of samples or a focus on one subtype, or both, to produce meaningful results. An effort was made to maximize the number of cases in studies and to make data available to multiple groups *via* the web. By contrast, in 2004 Chung *et al*<sup>[22]</sup> made the observation that head and neck tumors fell into 4 groups, but there was no clear association with etiology or histology. Attempts to link gene expression with targeted treatment were unsuccessful<sup>[23]</sup>. And the only accepted subgroup of head and neck cancers, oral pharyngeal cancers with transforming human papillomavirus (HPV) was not linked to a specific gene expression subtype till years later<sup>[23-25]</sup>. In short, it was difficult to discern how real the subgroups were and what the gene expression similarities meant until two gene expression studies done about a decade later on 138 and 279 head and neck tumors respectively showed the same head and neck squamous cell carcinoma (HNSCC) subtypes based on gene expression and/or DNA alterations<sup>[23,24]</sup>. A meta-analysis published in 2015 after 9 years and over 20 studies totaled 1300 samples and revealed a further subdivision of two of the subtypes<sup>[26]</sup>. This evidence shows that HPV-negative HNSCC and OSCC are not homogenous cancers but fall into separate subtypes.

Starting in the early 2000s, several groups sought to design a gene expression-based classifier that could aid in diagnosis and treatment decisions for breast cancer (Table 1). The group that ended up producing the Oncotype DX gene expression-based classifier made several decisions that probably facilitated their dominance in the United States market for breast cancer analysis<sup>[27]</sup>. First, they largely focused on genes already shown to be important for cancer, thus reducing the number of samples required for a statistically valid analysis. Next, they optimized analysis of RNA from fixed tumor tissue in paraffin blocks, already the standard method for storage of biopsy material. Finally, they used large numbers of samples and focused on one subset of breast tumor patients, those with estrogen receptor enriched but lymph node negative breast cancer. Finally, their test answered an important clinical question: Which patients with node negative tumors that were estrogen receptor positive would best be helped by being treated with genotoxic chemotherapy after surgery<sup>[28]</sup>? Research on head and neck and oral cancer did none of these things. Typically, frozen tissue was required and low numbers of samples were used so while classifiers for head and neck and oral cancer were produced they were not validated for clinical usage. For example, early work suggested a role for the epidermal growth factor receptor in the oral cancer process and treatments that target this protein have been tested but there has been little success<sup>[29]</sup>. The lack of targeted therapies for oral cancer is likely due to the lack of sufficient numbers of molecularly well characterized oral cancer tumor samples.

## WHAT NEED DO THE ONCOTYPE DX, MAMMAPRINT AND OTHER SIMILAR GENE EXPRESSION-BASED TESTS FILL?

Breast cancer diagnosis routinely entails histology, histochemistry to measure estrogen, progesterone and estrogen receptors, and finally the FISH assay to directly measure *HER2* gene amplification. In addition, immunohistochemistry measures the Ki-67 level, which is proportional to tumor proliferation and correlates with responsiveness to genotoxic chemotherapy<sup>[20,21]</sup>. By contrast, tumors that show low proliferation rates seldom recur and do not respond to genotoxic chemotherapy. This makes measuring cell proliferation rates in tumors crucial, but Ki-67 immunohistochemistry is prone to variation depending on tissue preparation, antibody staining, and pathologist quantification. As a result, Ki-67 protein is a poor marker. Tumor grade, which is a measure of how differentiated the tumor cells appear and correlates with Ki-67 levels and is also a predictor of recurrence, is also difficult to quantify accurately and consistently between laboratories. As is now well understood, Oncotype DX and the 16 cancer genes it measures<sup>[27]</sup>, Mammprint with the 70 genes it measures<sup>[30]</sup>, and the Genomic Grade Index

that originally measured 96 genes<sup>[31]</sup>, include a large percentage of genes that vary with cell proliferation rates. Because so many genes change in expression levels with changes in proliferation rates, it is possible to have 3 different working gene expression tests-Oncotype DX, Mammaprint, and the Genomic Grade Index - for prediction of treatment response of node negative estrogen receptor positive tumors, with little overlap in the markers that are measured. Remarkably, the markers for the different tests were selected based on different criteria such as their ability to predict survival or differentiate early vs late stage tumors among different subsets of breast cancer groups, yet they all contain a large percentage of markers for cell proliferation<sup>[27,30,31]</sup>. While they also can predict estrogen receptor status, it is now recognized that their ability to more accurately and reproducibly quantify tumor cell proliferation than Ki-67 immunohistochemistry and tissue grade is what makes them valuable in the clinic.

## CONCLUSION

The Oncotype DX and other tests all address an important and frequent question about treatment in a common cancer: When to use conventional chemotherapy in early breast cancer? While there are newer gene expression-based tests that better address questions of optimal treatment for longer survival (10 years vs 5 years) and that may help more patients, the current tests now help many patients and that is why they exist<sup>[20,21]</sup>. There is a similar clinical question for OSCC patients, in that clinicians have to make decisions about which patients will get adjuvant therapy with radiotherapy or chemoradiotherapy after surgery. Recent work by The Cancer Genome Atlas (TCGA) will help to address this. TCGA has characterized over 500 head and neck tumors in regard to genomic changes, miRNA and mRNA expression changes, along with large amounts of clinical information including treatment follow up and cancer recurrence<sup>[32]</sup>. Genetic studies from TCGA allow the identification of pathways that are altered with OSCC<sup>[24]</sup>. For example there is a subgroup of tumors that lack HPV but have an intact *p53* gene and have long recurrence-free survival times. TCGA work also confirms the 4 gene expression based subgroups of head and neck cancer and for oral cancer. This will make easier the identification of targeted and conventional genotoxic-based chemotherapies that will show efficacy with individual subgroups of tumors but not all OSCCs. It is not hard to believe that a validated classifier for OSCCs that respond best to treatment will be in the clinic before long, simply because the numbers to begin these studies in earnest are beginning to be available to researchers<sup>[26,33]</sup>. While the heterogeneity of OSCC makes the development of a single classifier for OSCC difficult, it makes the vision of including gene expression analysis in OSCC treatment planning an obvious and attainable goal that could occur in the next five years if enough tumor samples are characterized using

standardized methods.

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## About gravity and occlusal forces in the jaws: Review

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### Abstract

Mechanical forces resulting from gravitation seem to be essential for structural adaptation and remodeling of skeletal bones. These forces have the capability of delivering powerfully distorting stimuli to skeletal bones

in a very short time, several times a day, in a uniform direction. Facial and jaw bones are not subjected to gravity impact forces. These bones need a mechanism of "compensation" for this deficiency. The goal is achieved by a unique mechanism that substitutes for gravity impact forces - the mechanism of occlusal load transmission to the bone *via* the periodontal apparatus space. In cases of early loss of teeth and loss of periodontal ligament this mechanism will be missing resulting in premature bone aging.

**Key words:** Gravity; Occlusal; Forces; Bone; Implant; Periodontal ligament

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**Core tip:** The anatomy and physiology of the periodontal ligament is structured to oppose occlusal forces that impact facial bone in multidirectional vectors. This mechanism is different from the long bones that oppose only vertical forces. Dental implants planning and placement should be compatible with these principles.

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### INTRODUCTION

The masticatory system is challenged on a daily bases by a variety of high magnitude mechanical forces resulting from occlusal contacts. Occlusal loads are transmitted to jaw and facial bone by a special organ: The periodontal attachment apparatus; root cementum, periodontal fibers, alveolar bone, and gingivae.

In the recent years implantology has revolutionized dentistry and has significantly improving the quality of life of many dental patients. However, in spite of the

Direction of forces applied on skeletal bones

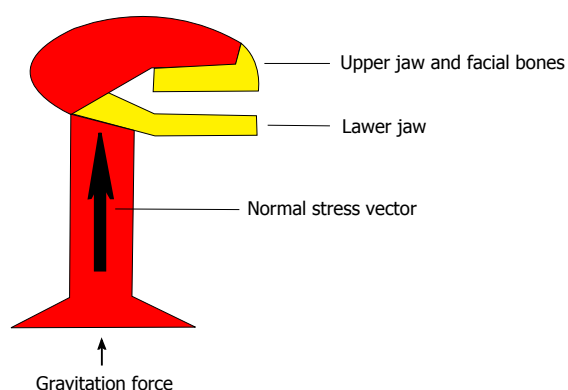


Figure 1 Vertical forces applied to the long bone are negated by the strength of bone trabecula rearranged along the long bone axis.

great successes in patient's oral rehabilitation, some implant procedures are failing mainly because the basic principles of oral occlusion are not adhered to. The magnitude the occlusal force in the jaws is enormous and their direction and counter balancing are significantly different from the forces applied on the skeletal bones.

The purpose of the present manuscript is to review the literature that is pertinent to the basic principles of occlusal forces in the facial bone compared to the skeletal bone. In a consecutive manuscript (part II) we plan to describe an implant based on these principles and describe cases associated with this technique.

## LITERATURE REVIEW AND DISCUSSION

We have used the PubMed website to search for publications with the following key words: Occlusal, forces, balanced, periodontal ligament, jaws skeletal. The search was limited to the English literature and the time frame used was 1900 to present. We have also cited classic text books that are considered to pioneer the field.

The gravity force that affects our skeleton is the result of acceleration of our body against the ground. The outcome of this force over the small area of the feet reveals an intensified stress that is applied to the skeleton. The result is a prominent stress vector (Figure 1) with uniform direction that repeats itself several times a day for short period intervals. The importance of this vector is in the fact that it is turned into a principle stress vector<sup>[1]</sup>. To negate this force of the bone, trabeculae rearrange along the axis of this vector and build the long bones. The new architecture enables the bone not only to resist compressive stress but also to minimize shear stress according to Mohr's circle<sup>[2]</sup>. Compressive stress is a most effective stress for bone remodeling. While this kind of stress activates bone remodeling, it needs a relatively high threshold to become a destructive stress<sup>[1]</sup>. The more intense the stress, the thicker and closer the trabeculae will become. The most hazardous stress for the bone is shear stress that stimulate bone

Direction of masticatory forces applied on jaw bones

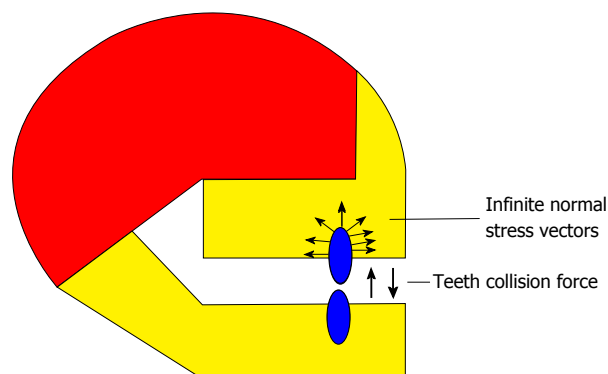


Figure 2 Occlusal loads in the jaw are converted into compressing vectors around the root surface of the tooth.

degradation (law threshold is needed for destruction). Obviously, shear stress demands increased density to protect the bone. Torsion and bending, which comprise shear stresses, cause the bone to protect itself by intensifying bone mineralization density (BMD) and thickening compact bone<sup>[1,3]</sup>. The greater these stresses, the thicker the compact bone. The impact gravity activities are shown to increase cortical thickness in long bones of athletes<sup>[4]</sup>. This is done in addition to increasing BMD. Non-impact horizontal activities (like swimming) do not cause thickening of the bone's cortex and cause a lesser degree of BMD. Most of the actions like walking result in reduction of the risk of hip fractures<sup>[5,6]</sup>. When these activities are intensified, the risk for hip fractures decreases even more. Non-gravitational activities like swimming do not reduce the chances of hip fractures<sup>[5,6]</sup>.

Facial and jaw bones are in an exceptional geographic position, as they are not on the principle stress axis (Figure 1). This group of bones is not prone to gravity collisions and need a substitute to compensate for this deficiency. According to analysis done for occlusal loads, it has been shown that transmission to the alveolar bone occurs *via* the periodontal ligament space<sup>[7]</sup>: Occlusal loads are converted into normal compressing vectors all around the root surface of the tooth. These vectors are perpendicular to the root surface (Figure 2) and are equal in their magnitude. Bone distortion is accepted as a result of a spherical stress tensor that compresses the bone all around the root surface. Arrangement of trabeculae during remodeling is done along the principal vectors which in this case are an eigenvector<sup>[1]</sup>. The result is that the trabeculae are radiating from the root. This arrangement helps in limiting shear stress and turns the alveolar bone into a cushion hammock that absorbs occlusal loads on one side and transmits them in a radiating direction to distal bony structures on the other side. Macro structure of facial bones is constructed in a way that enables maximal strength with minimal mass<sup>[3]</sup>. According to this principle, facial and jaw bones have air spaces and get their strength from the bone that border them. Impact loads that hit the maxillary tooth will cause deformation not only in the

alveolar bone nearby the root, but also in other supra alveolar structures like the orbits, nasal meatuses and the paranasal sinuses, and the partitions in-between them. As maxillary occlusal impact loads may regulate upper jaw facial and forehead bone adaptation, it is done in a dual action; mechanical compression that aims at trabecular bone remodeling and bending or torsion stress that is responsible for remodeling and maintenance of the cortical surfaces<sup>[1]</sup>.

Mandibular bone, unlike the upper face bones, is a modification of long bone and is more prone to bending and torsions distortion. Therefore, the mandible will express a thicker compact bone. The fact that edentulous mandibles were shown to have thinner cortical bone in contrast to dentulous mandibles support this thesis<sup>[8]</sup>. In skulls affected by early loss of teeth, facial bones express early aging appearance<sup>[9]</sup>. According to this theory, the stress tensor that acts directly on the alveolar bone influences also distant bony structures. Early loss of teeth may explain premature aging and deformation of the face because of loss of bone mass. Installation of dental implants is aimed to partially delay facial aging. Dental implants were an obvious outcome of harnessing of orthopedic screws in an attempt to reconstruct artificial dental roots. While orthopedic screws are meant for fixation of bone fractures for at least the period of bone repair, dental implants are intended to permanently replace natural dental roots. Contemporary implants are aimed mainly for retention and stabilization of the bone, and osseous integration is used to substitute for attachment by periodontal ligament (PDL).

Dental implants transmit stress to bone by a stress tensor that includes compressive but also shear stress vectors. Obviously the suggested mechanism of the PDL apparatus does not exist and implants are prone to shear stress and bone degradation. This is supported by clinical observations and retrospective studies that demonstrate bone loss along dental implants during the years<sup>[10-12]</sup>. Bone degeneration and periimplantitis around dental implants is reported to be up to 28% of the cases. Furthermore, the older the implant, the greater the rate of bone absorption.

Nevertheless, dental implants have a high rate of survival and are usually the better solution for reconstruction of missing teeth. It is suggested that in cases of plastic facial rejuvenation, attention would be directed to occlusion rehabilitation before any procedure is done in an attempt to achieve more efficient and long lasting results.

## CONCLUSION

Impact forces are essential for mechanical bone adaptation and for achieving bone strength. The impact gravity loads serve the goal of strengthening skeleton bones. Impact occlusal loads are suggested to serve the same aim for facial and jaw bones. The impact of occlusal forces depends on their magnitude, frequency, and direction.

The result is a clear strain vector signal that leads to forming bone cells. Dental implants lack the ability to compress purely nearby bone; they serve merely to preserve reservation facial bone.

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## Laser assisted periodontics: A review of the literature

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### Abstract

Over the years, the use of the laser within health field and more particularly dentistry has been increasing and improving. The application of laser in the periodontal treatment takes part of a non-surgical and surgical approaches, is used for the decontamination of perio-

dontal pockets due to its bactericidal effect, and the removal of granulation tissues, inflamed and diseased epithelium lining, bacterial deposits and subgingival calculus. However in spite of all the marketing surrounding, the use of laser highlighting its beneficial effect, the capacity of laser to replace the conventional treatment for chronic periodontitis is still debatable. In fact there is no evidence that any laser system adds substantial clinical value above conventional treatments of chronic periodontitis. Some studies showed a significant positive effect on clinical attachment level gain and probing depth reduction. In the other hand, several articles demonstrated no evidence of the superior effectiveness of laser therapy compared to root planing and scaling. Our aims is to review the literature on the capacity of erbium:Yttrium-aluminum-garnet and neodymium:Yttrium-aluminum-garnet laser to either replace or complete conventional mechanical/surgical periodontal treatments.

**Key words:** Laser; Review; Scaling and root planning; Erbium:Yttrium-aluminum-garnet; Neodymium:Yttrium-aluminum-garnet; Periodontitis

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**Core tip:** Faced with the increased use of lasers in dentistry, we tried to demystify, in this review, the real benefits and disadvantages of the use of the neodymium:Yttrium-aluminum-garnet and erbium:Yttrium-aluminum-garnet lasers in periodontics. Many trials showed that the use of lasers is an effective and safe method of root planing in periodontal non-surgical treatment of chronic periodontitis. However, due its possible side effects and less effective results when used alone, lead some authors to state that the use of lasers as a replacement of the conventional mechanical treatment is still doubtful.

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## INTRODUCTION

Chronic periodontitis is defined as inflammation of the gingiva extending into the adjacent attachment apparatus. The disease is characterized by loss of clinical attachment due to destruction of the periodontal ligament and loss of the adjacent supporting bone<sup>[1]</sup>. Clinical findings include attachment loss, gingival recession, alveolar bone loss and pocket formation. Although chronic periodontitis is the most common form of destructive periodontal disease in adults, it can occur over a wide range of ages. It usually has slow to moderate rates of progression, but may have periods of rapid progression. Clinical features may include combinations of the following signs and symptoms: Edema, erythema, gingival bleeding upon probing, and/or suppuration<sup>[1]</sup>. The development of periodontitis appears to be associated with a shift from a predominantly Gram-positive flora to a predominance of anaerobic Gram-negative rods<sup>[2]</sup>.

Several characteristics can be observed in contaminated periodontal pockets. Usually, biofilm deposits, calculus and bacterial endotoxins infiltration into the cementum of root surfaces are reported. Mechanical scaling and root planning with manual and/or ultrasonic instruments represents the initial phase of periodontal non-surgical therapy. However, this therapy is not always effective for complete removal of bacterial and their endotoxins deposits. In fact, complex root anatomy makes access to areas such grooves and furcations difficult<sup>[3]</sup>. Although systemic and local administration of antibiotics into periodontal pockets is occasionally effective for disinfection, but risk of producing resistant microorganisms limits this approach.

Furthermore, conventional mechanical therapy is often uncomfortable for both patients and operators. Indeed, this time - consuming technique depends on the operator's dexterity. The power and the curette's angulation vary from one operator to another and can give totally different results. In addition, noises and vibrations of ultrasonic instruments are often source of stress and fear in some patients. All these constraints led searchers to explore other therapeutic approach to replace or complete the conventional periodontal mechanical therapy, such as lasers. Recently, the application of laser - assisted treatments for removal of granulation tissues, inflamed and diseased epithelium lining, bacterial deposits and calculus has been proposed as alternative or as adjunctive treatment to the more conventional periodontal mechanical therapy<sup>[4]</sup>.

The word Laser is the acronym for light amplification by stimulated emission of radiation. Lasers can be distinguished from other light sources by their coherence, allowing lasers to be focused to a tight spot<sup>[5]</sup>. Since Albert Einstein's theory of stimulated emission of electromag-

netic radiation and Maiman's first functioning laser using a synthetic ruby crystal in 1960<sup>[5]</sup>, laser research has produced a variety of improved and specialized laser types, optimized for different application such as dentistry. In fact dental lasers are recognized today for their ability to ablate hard and soft tissues, to reduce bacteria counts and even to provide hemostasis of soft tissues during their use with minimal anesthesia<sup>[6]</sup>. Lasers used in dentistry emit wavelengths between 377 nm and 10.6  $\mu\text{m}$ . The most common types are CO<sub>2</sub>, diode, erbium:Yttrium-aluminium-garnet (Er:YAG) and neodymium:Yttrium-aluminium-garnet (Nd:YAG) lasers.

The use of lasers in periodontal therapy has evolved since a laser for periodontal applications was first introduced in 1985<sup>[7,8]</sup>. Initially, most articles that advocated the use of lasers for soft tissue surgery were anecdotal. Nowadays, it appears that research in soft tissue applications is increasing exponentially, and the claims of decreased bleeding, swelling, pain, and bacterial populations are being referenced in several publications<sup>[6]</sup>.

Four types of interactions may occur when biological tissue is irradiated with laser light: Reflection, scattering, absorption, or transmission. Basically, the reflection, scattering and transmission decrease, as the absorption increases. The type of interaction that takes place depends on the wavelength of the laser. For most biological tissues, higher absorption occurs in wavelengths with greater absorbance in water. The lasers with greater absorbance in water are the Er:YAG lasers. Erbium radiation is readily absorbed by most tissues, and this translates into less penetration and a shallower layer of laser-affected tissue<sup>[9]</sup>.

Laser irradiation exhibits strong ablation, hemostasis, detoxification and bactericidal effects on the human body. These effects can be useful during periodontal treatment, especially for handling of the soft tissue as well as for the debridement of diseased tissues. Thus laser treatment may serve as an alternative or adjunctive therapy to mechanical approaches, in periodontal therapy. However, the high cost of laser equipment and the lack of reliable clinical research are a significant barrier for the laser utilization by the dentist. Also, each laser has different characteristics because of their different wavelengths. Thus the operator must be aware of the possible risks involved in clinical applications, and precaution must be exercised to minimize these risks when performing laser therapy. The most important precaution in laser surgery is the use of glasses to protect the eyes of the patient, the operator and the assistants. Protection of the tissues surrounding the target is also recommended. Second, thermogenesis during the interaction of the laser with the tissues must be addressed and well controlled<sup>[9]</sup>.

In lasers that exhibit deep-tissue penetration, such as the Nd:YAG, the thermal injury to the pulp tissue and underlying bone tissue can be a concern during treatment. Also, a root surface that has received major thermal damage could render the tissue incompatible for cell attachment and healing. During treatment of

hard tissue, the use of water spray can minimize heat generation by cooling the irradiated area and absorbing excessive laser energy. Therefore, thermal injury must be prevented by using irradiation conditions and techniques that are appropriate for the lasers used. In addition, in periodontal applications, there exists the risk of excessive tissue destruction as a result of direct ablation and the possibility of thermal side effects in periodontal tissues during irradiation of periodontal pockets. Improper use of lasers could cause further destruction of the intact attachment apparatus at the bottom of the pocket wall as well as excessive ablation of root surfaces and the lining of the gingival crevice<sup>[4]</sup>.

Damage of the tooth surface should also be avoided during irradiation with Er:YAG lasers, as the enamel and dentin easily undergo melting, carbonization or ablation by these types of lasers. Thus, in order to use lasers safely in clinical practice, the practitioner should have precise knowledge of the characteristics and effects of each laser system and their performance during application, and should exercise appropriate caution during their use<sup>[4]</sup>.

The aim of this study is to review the literature on the effectiveness of Er:YAG and Nd:YAG lasers in periodontics, as either a complete treatment or as an adjunctive treatment. We performed a review of the recent literature in Pubmed and Mesh databases.

## POSITIVE EFFECT

The erbium family of dental lasers consists of two wavelengths with similar but not identical properties. The Er:YAG laser produces a wavelength of 2940 nm and the erbium, chromium: Yttrium-scandium-gallium-garnet laser produces a wavelength of 2780 nm. The erbium family of lasers has been used for cavity preparation and caries removal and has shown promise as a laser system for periodontal treatment approaches on hard tissues. The Er:YAG laser has the most shallow penetration into soft tissue of any dental wavelength and can ablate both soft and hard tissues safely with water irrigation and are applicable to periodontal treatments such as scaling, debridement and bone surgery, and have minimal thermal effect<sup>[4]</sup>.

Er:YAG laser seems to be the only laser, used today in dentistry, able to remove calculus and lipopolysaccharides from root surfaces<sup>[10]</sup>. In fact its wavelengths have the highest absorption in water and hydroxyapatite compared with the diode and Nd:YAG lasers (respectively 10 times and 20000 times greater)<sup>[11]</sup>. When using the Er:YAG laser, the energy is highly absorbed in water which is then vaporized by thermal effect leading to micro explosions rather than heating the surrounding tissue (resulting in minimal thermal side effects). These beneficial properties of the Er:YAG laser and its capacity to ablate both soft and hard tissue led to its approval in 1997 by the Food and Drug Administration in the United States for preparation of dental cavities, for incisions, excisions, vaporization,

ablation and hemostasis of soft and hard tissues in the oral cavity<sup>[9]</sup>. A special optical fiber or a hollow waveguide permit the use of this laser in periodontal pockets.

The Er:YAG can not only be used to remove calculus from root surfaces but also to significantly reduce bacteria load in diseased tissues from root furcations or intrabony pockets. As with other soft tissues lasers, there is a proven bactericidal effect. It can also be used on contact mode to cut or ablate soft tissues with precision with a good hemostasis and almost no need of anesthesia. Because of the potential for possible soft and hard tissue applications, use of this laser has been investigated in periodontal therapy for scaling, root debridement and periodontal and peri-implant surgeries<sup>[12]</sup>.

The Er:YAG laser is capable of easily removing subgingival calculus and root smoothing without a major thermal change of the root surface. The level of calculus removal by this laser seems similar to that of ultrasonic scaling<sup>[4]</sup>. In fact, in 1994, Aoki *et al.*<sup>[13]</sup> were the first to suggest the use of Er:YAG as an alternative to remove subgingival calculus. The capacity of Er:YAG laser to remove calculus was then examined on human extracted teeth with subgingival calculus. They concluded that the pulsed Er:YAG laser used with irrigation was capable of subgingival calculus removal without damaging the surrounding tissue with a slight increase in temperature during the laser application. Watanabe *et al.*<sup>[14]</sup> showed the safety and usefulness of Er:YAG laser therapy for subgingival calculus removal in nonsurgical pocket therapy. Although some randomized, controlled clinical studies showed improved clinical results following Er:YAG laser irradiation, most failed to show consistently superior and/or additional benefits of the laser therapy. Similar or sometimes better results were obtained with Er:YAG laser therapy than conventional scaling and root planing therapy in terms of reduction of bleeding on probing, pocket depth and improvement of clinical attachment level<sup>[15]</sup>. In addition, these clinical improvements could be maintained over a 2-year period<sup>[16]</sup>. Significant clinical improvements were exhibited 6 mo following Er:YAG laser therapy, but they were similar to those obtained using the ultrasonic scaler alone<sup>[17]</sup>. However, the treatment with the Er:YAG laser resulted in significantly higher pocket depth reduction and clinical attachment level gain at 2 years post-therapy in comparison to treatment with an ultrasonic scaler<sup>[18]</sup>. One important finding of this study was that at 1 year post-treatment, there was increase of pocket depth and attachment loss in the ultrasonic group, whereas stability of Er:YAG laser-treated pockets was noted until 2 years following treatment<sup>[18]</sup>.

Regarding bacterial reduction no superior reduction in bacterial number was observed following treatment with the Er:YAG laser in comparison to ultrasonic scaling<sup>[19]</sup>. However, in the same study<sup>[19]</sup>, when the patients' perceptions were investigated, ultrasonic scaling was more pleasant than therapy with an Er:YAG laser or hand curet instrument. Furthermore, in a study evaluating treatment of periodontal pockets using an Er:YAG laser, in

a periodontal maintenance program, no differences were reported in the microbial profiles between treatment with the Er:YAG laser and ultrasonic scaling, although faster healing (pocket depth reduction and clinical attachment level gain) and less discomfort during treatment were observed in the group treated with the Er:YAG laser<sup>[20]</sup>.

In 2012, a systematic review and a meta analysis, made by Sgolastra *et al*<sup>[21]</sup>, tried to determine the efficacy of Er:YAG, when used as alternative treatment to scaling root planing (SRP) in the treatment of patients with chronic periodontitis. Five random controlled trials, with a total of 85 patients and 3564 sites, were entered in the meta-analysis to investigate clinical attachment level gain, probing depth reduction, and gingival recessions changes in the Er:YAG laser and SRP groups. The meta-analysis revealed no significant differences for any investigated parameter at 6 and 12 mo and concluded that there was no evidence of the superior effectiveness of the Er:YAG laser compared to conventional SRP.

Lopes *et al*<sup>[22]</sup> in 2008, in a controlled clinical study with twenty-one subjects evaluated clinical and immunological effect on root surfaces irradiated with an Er:YAG laser with or without conventional SRP. The results pointed out that after thirty days both treatments demonstrated significant reductions in gingival indices and probing depth. An increase of the gingival recession was observed in the both groups. No difference in the interleukin IL-1 $\beta$ , was detected among groups and periods.

In spite of the lack of well-controlled clinical trial with high level of evidence, and all the contradictory results in the literature, the American Academy of Periodontology state in 2011 that: "Erbium lasers show the greatest potential for effective root debridement (SRP)"<sup>[23]</sup>. At a low energy level, the Er:YAG laser had shown a bactericidal effect against periodontopathic bacteria in addition to its capacity to remove toxins present in the root cementum such as lipopolysaccharides<sup>[24-26]</sup>.

For optimal tissue regeneration and successful surgical procedure, the root surface and the bone defect should be debrided and decontaminated. Lasers in periodontics had shown effective results in debriding intrabony defect and furcation areas where mechanical conventional instruments are less effective. In addition, many studies showed that Er:YAG laser application is effective and easy to use in root surface debridement and granulation tissue removal during surgical procedures<sup>[4,9]</sup>.

Sculean *et al*<sup>[27]</sup> reported that the Er:YAG laser is an effective and safe method with significant clinical improvement six months after a treatment of periodontal intrabony defect with access flap surgery. Gaspiric and Skaleric<sup>[28]</sup> compared, in a long term clinical outcome, the conventional method using the modified widman flap to Er:YAG laser assisted flap surgery. Significant reduction of pocket depth and a gain of clinical attachment level were found in the laser group at 6-36 mo after surgery. Therefore, application of the Er:YAG laser for surgical degranulation is a promising approach, and its effectiveness and safety have been demonstrated

clinically<sup>[4,9]</sup>.

Furthermore, Schwarz *et al*<sup>[29]</sup> demonstrated in an animal study that Er:YAG lasers also seems to induce new cementum formation. Thus, laser treatment in periodontal pockets may promote more periodontal tissue regeneration than conventional mechanical treatment.

On other hand, the Nd:YAG laser typically emit light with a wavelength of 1064 nm, in the infrared light and is theoretically not absorbed by hard tissues such as cement and dentin. It affects merely soft tissues like gingiva and pocket epithelial lining. Nd:YAG lasers operate in both pulsed and continuous mode and is delivered through a fiber optic tip. The Nd:YAG is commonly used in gingivectomy, gingivoplasty, frenectomies, operculum removal and biopsies procedures<sup>[5]</sup>. It can be used in a contact or a noncontact mode and is useful for soft tissue surgery. Due to the characteristics of penetration and thermogenesis, the Nd:YAG laser produces a relatively thick coagulation layer on the lased soft tissue surface, and thereby shows strong hemostasis<sup>[6]</sup>. The Nd:YAG laser is very effective for ablation of potentially hemorrhagic soft tissue. Some studies had shown also a reduction in postoperative pain because of its minimal deep thermal damage<sup>[4]</sup>. The strong affinity for chromophores in pigmented tissues theoretically makes the Nd:YAG useful in eliminating pigmented bacteria found in periodontal diseases<sup>[6]</sup>, however still no clear in the literature if black pigmented bacteria's as *porphyromonas gingivalis* actually express a pigmented phenotype when colonizing the periodontal pocket or the gingival tissues. Several studies demonstrated the decontamination effect and the inactivation of the endotoxins in the contaminated root surface treated by Nd:YAG lasers<sup>[4,9]</sup>. However, this laser capacity to replace conventional SRP treatment for chronic periodontitis is still debatable, also the Nd:YAG laser seems to be ineffective for calculus removal when a clinically suitable energy is used<sup>[30]</sup>.

Moreover, in comparison to conventional mechanical instruments, lasers seem to be more effective for complete curettage of soft tissue. In fact, Gold and Vilardi<sup>[31]</sup> demonstrated the safe application of the Nd:YAG laser for removal of the pocket-lining epithelium in periodontal pockets with no negative effects as necrosis or carbonization of the underlying connective tissue *in vivo*<sup>[31]</sup>. Yukna *et al*<sup>[32]</sup> advocated the use of Nd:YAG laser in a laser-assisted new attachment procedure (LANAP) to remove the diseased soft tissue on the inner gingival surface of periodontal pockets. The authors reported that this procedure is associated with cementum-mediated new connective tissue attachment and apparent periodontal regeneration on previously diseased root surfaces in humans. The utilization of this protocol among the dental community seems to be increasing, with several case reports studies clear showing the potential of the technique, however more well controlled and independent studies are need to validate those claims.

The earliest clinical studies regarding the application

of lasers in the nonsurgical pocket treatment of periodontitis began in the early 1990s using an Nd:YAG laser. However, clinical applications of lasers in periodontal pockets began with the development of flexible optical fiber. Many clinical studies reported a strong bactericidal effect of Nd:YAG lasers in periodontal pocket. But the superiority of lasers in root planing compared to conventional therapy is still hard to prove<sup>[33]</sup>. Neill and Mellonig<sup>[34]</sup> demonstrated, in their double blinded randomized clinical study, that the use of Nd:YAG as an adjunctive treatment to conventional scaling and root planing led to a significant improvement in gingival index and bleeding on probing. But no differences in attachment level were found. In addition, greater results were found when Nd:YAG laser treatments were followed by mechanical treatments six weeks later compared to the reverse. Moreover, adding local Minocycline to Nd:YAG laser irradiation showed good improvement in pocket depth reduction, attachment gain and reduction of periodontopathic bacteria in comparison with laser treatment alone<sup>[35]</sup>.

In 2013, Qadri *et al.*<sup>[30]</sup>, tried to assess through a short term prospective study the effect of water-cooled pulsed Nd:YAG laser used as an adjunct to SRP compared to treatment with the laser alone. Thirty-nine patients were then equally divided into three groups. The first group received Nd:YAG laser treatments. The second group was treated with SRP alone and the third group Nd:YAG laser application immediately after SRP. Results showed a significant decrease of the probing pocket depth, gingival index and gingival crevicular fluid in group 3 compared to groups 1 and 2, in the one-week and three-month follow up. SRP treatment combined to a single application of water-cooled Nd:YAG seems to be more effective in treating periodontal inflammatory conditions. In fact, SRP mechanically disrupts the subgingival biofilm and removes calculus, whereas Nd:YAG laser therapy significantly reduces periodontopathogenic bacteria. Furthermore, Tseng and Liew<sup>[36]</sup> suggested that the use of SRP after Nd:YAG laser treatment may be more efficient in removing root deposition.

Traumas from laser treatment are not well documented in the literature unlike ultrasonic and manual instrumentations. For this reason, Dilsiz and Sevinc<sup>[37]</sup> evaluated and compared the immediate effect of trauma after non-surgical periodontal treatment with ultrasonic and Nd:YAG laser. The study included 144 sites selected from 24 chronic periodontitis patients. Plaque index, probing depth and probing attachment level (PAL) were assessed before and 7 d after treatments. The results showed an immediate PAL loss of 0.68 mm after periodontal treatment with ultrasonic treatment, whereas, the Nd:YAG laser treatment caused no PAL loss and seems to reduce significantly the trauma from instrumentation. However, some studies report that the use of dry laser irradiation leads to a significant increase in thermal energy delivered, and can cause tissue damage<sup>[38]</sup>. Water coolant associated to laser seems to

reduce these negative thermal effects<sup>[39]</sup>.

Recently data from a multi-center, prospective, longitudinal, clinical trial comparing four different treatments for periodontitis, the LANAP protocol utilizing pulsed-Nd:YAG laser; flap surgery using the Modified Widman technique (MWF); SRP; and coronal debridement. The authors found no statistical treatment differences between SRP, MWF, and LANAP with the exception of less post-treatment patient discomfort with LANAP compared to MWF. In addition there was greater reduction in bleeding in the LANAP<sup>TM</sup> quadrant than in the other three at both 6 and 12 mo<sup>[40]</sup>.

Finally, Sjöström and Friskopp<sup>[41]</sup> observed, in their split-mouth study, an increase of 15% in the debridement time needed. The authors claim also a significant decrease in local anesthesia needed, a haemostatic effect, and less postoperative pain and swelling reported by patients.

## NEGATIVE EFFECT

Variation in experimental design, in laser parameters and a lack of proper controls make studies difficult to compare. In consequence, some authors suggest the use of lasers as a replacement of the conventional mechanical treatments whereas others are much more skeptical. Another problem that arises from this lack of standardized protocols is the possibility of potential negative and yet unknown effects caused by the incorrect use of the laser.

Because of its ablative capacity on mineralized tissues, some *in vitro* studies showed residual rough root surfaces after treatment with the possibility of heat cracking and cratering. Moghare Abed *et al.*<sup>[42]</sup> in 2007, compared the effectiveness of subgingival scaling and root planing with Er:YAG laser and hand instrumentation *in vitro*. Their results indicated a degree of roughness in all of the laser group samples. However, very long pulses (750-1000 µs) of the Er:YAG laser left a smoother surface, in addition to its greater capacity to remove calculus. They then proposed to decrease the energy to less than 22.6 mJ at the finishing stage to obtain a complete smooth surface. The use of water coolant with laser irradiation prevents thermal side effects without compromising its efficiency. Root surfaces irradiated by Er:YAG laser combined with water coolant presented minimal affected layer with no cracks or major changes in root cementum and dentin structure which can be observed after Nd:YAG irradiation<sup>[43-45]</sup>. Indeed characteristic micro irregularities and structures<sup>[44]</sup> were reported on the root surface treated by Er:YAG laser. This micro structured surface appears to be incompatible with cell attachment<sup>[46]</sup>. In contrary, some *in vitro* studies reported that Er:YAG irradiation, at a proper energy level, seems to leave a favorable surface for fibroblast attachment compared to conventional mechanical scaling and root planing<sup>[47,48]</sup>.

In spite of the potential for root surface damage during the process of calculus removal since the Er:



YAG is a hard tissue laser and the operator would not be able to visualize what is being lased, clinical data on attachment level changes when compared to SRP alone are conflicting. Some studies show slight benefit while others find no benefit. Further study is needed to determine if Er:YAG laser-assisted SRP has a real beneficial effect.

As for the Er:YAG, side negative effects as surface pitting, cracks, carbonization and melting were reported even when the Nd:YAG irradiation was parallel to the root surface<sup>[49]</sup>. Nevertheless, these alterations seem to be reversible. In fact additional root treatment such as polishing and root planing can restore root surface biocompatibility, essential for fibroblast attachment<sup>[50,51]</sup>. In addition, because of its capacity to penetrate deeply tissues, the Nd:YAG lasers can induce irreversible intrapulpal thermal damages. However the application of proper protocols seems compensate the potential harmful potential of those lasers and new researches testing different protocols are need to validate the safety and effectiveness of the utilization of Nd:YAG in periodontal treatment.

Thus, many studies tried to determine the Nd:YAG laser place in all therapeutic options in periodontics. When used alone in the nonsurgical treatment of periodontal pockets, the Nd:YAG laser showed less effectiveness for root debridement compared to conventional root planing and scaling. The use of Nd:YAG laser was then suggested as an adjunctive therapy following conventional mechanical therapy in the non surgical treatment of periodontitis.

## CLINICAL RECOMMENDATION

While many trials demonstrated that the use of the laser is an effective and safe method of root planing in periodontal non-surgical treatment of chronic periodontitis. It is important to determine the place of lasers in all our treatment options.

It is clear that the use of lasers in periodontics appears to significantly reduce the intensity of pain experienced by the patient during treatment compared to conventional treatment<sup>[40,52]</sup>. The laser allows the use of less local anesthesia and a better collaboration by the patient<sup>[53]</sup>, thereby facilitating the achievement of the therapeutic goals.

However in view of the results obtained in different clinical and *in vitro* studies found in the literature, it is difficult to conclude of the effectiveness or the superiority of lasers in root planing compared to conventional therapy. Indeed, some authors showed better clinical results when using laser alone<sup>[13]</sup> while others report no real benefit<sup>[21]</sup>. Clinical trial with high level of evidence is still needed to determine if the use of laser in the periodontal treatment may one day replace conventional surfacing and root planing.

Furthermore some authors claim the safe handling of this tool, always well tolerated and without damage to the surrounding tissue<sup>[39,54]</sup>. The use of lasers leaves also

a slightly porous surface in favor of fibrin attachment, thus improving the fixation of the blood clot<sup>[41]</sup>. Other *in vitro* studies, however, mention the presence of a thermal effect on the surrounding tissue in addition to cracks on root surfaces, observed microscopically, weakening then the surrounding tissue<sup>[11,52,53]</sup>.

In addition, some studies were focused on the use of laser as adjuvant to conventional treatment of chronic periodontitis. The clinical trial of Qadri *et al.*<sup>[39]</sup> in 2010 has shown in short and long term, a significant positive effect of lasers coupled to manual and ultrasonic instruments. While other authors, such as Slot *et al.*<sup>[5]</sup>, had found no improvement compared to conventional therapy. It is again difficult to demonstrate a real benefit to the use of the laser as an adjunct to manual instruments and ultrasonic.

Finally the use of laser is part of a non-surgical treatment of periodontal disease process, that must respect very specific steps, including the assessment of the patient's medical status, periodontal diagnosis and the development of a treatment plan, patient information and the collection of informed consent, application processing procedures such patient education (oral hygiene, fight against risk factors including tobacco and stress, taking additional charge of systemic diseases such as diabetes) and patient follow-up.

## CONCLUSION

Despite of all the potential beneficial effect of lasers in periodontics, the ability to replace or even add on to our conventional periodontal treatment is still doubtful. Further studies are needed to determine laser effectiveness for root scaling and planing, calculus removal, bacterial decontamination and specially, randomized clinical trials performed by independent researches are essential to demonstrated the real role that lasers can play in the management of ours periodontal patients.

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## Retrieving dental instruments through endoscopy: A literature review

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### Abstract

Clinical accidents involving dental instruments and materials inside the oral cavity are reported in the medical literature. Specifically, ingestion and aspiration of foreign bodies have greater prevalence in the routine of medicine and dentistry. Despite being less harmful than aspirations, the accidental ingestion of dental instruments does not always culminate in favorable prognoses. Mostly, complex conditions require medical intervention through endoscopy or surgical approaches. The present research aims to review the literature pointing out the specialties of dentistry most involved with accidental ingestion of dental instruments, highlighting the important role of endoscopy for accurately locating and retrieving foreign bodies. Prosthodontics, operative dentistry, orthodontics, and maxillofacial surgery arose as the specialties in which these accidents are more prevalent. Based on that, general dentists and specialists must be aware for the essential care to avoid such clinical accidents, as well as to know the available tools, such as endoscopy, to overcome these situations in the routine of dentistry.

**Key words:** Endoscopy; Accidents; Dental instruments; Foreign bodies

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**Core tip:** An effort should be made to avoid breaking dental instruments by preventing their over-use and over-stress. Rubber dams should always be used for hygiene control and to prevent patients from swallowing instruments. When the use of a rubber dam is not



possible, dental instruments should be secured with wires to help avoid and accomplish retrieval. All parts of broken instruments must be retrieved immediately following breakage. If ingested broken instrument parts cannot be retrieved, the patient should be referred for a medical opinion.

Silva RF, Franco A, Picoli FF, Mundim MBV, Rodrigues LG. Retrieving dental instruments through endoscopy: A literature review. *World J Stomatol* 2015; 4(4): 137-140 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v4/i4/137.htm> DOI: <http://dx.doi.org/10.5321/wjs.v4.i4.137>

## INTRODUCTION

The acute perfectionism of dentistry often makes it necessary to use small instruments for dental procedures that require precise intervention, such as crown preparation for fixed prosthodontics, root canal procedures, and the bonding of orthodontic brackets. Consequently, there is always a risk of an instrument accidentally breaking or falling into the throat of patients and becoming ingested as a foreign body<sup>[1]</sup>. Following an accidental ingestion, the prognoses strongly depend on the morphology and anatomic location of the foreign body<sup>[2]</sup>. Favorable prognoses mostly require clinical and radiographic follow up of the foreign body inside the digestive tract<sup>[2]</sup>. Whereas, unfavorable prognoses often involve more invasive approaches, such as endoscopy<sup>[3]</sup> and surgical retrieval<sup>[4]</sup>. After an accidental aspiration, the airways are often compromised resulting in unfavorable prognoses. In this context, medical interventions, such as bronchoscopy<sup>[5]</sup> and surgical access<sup>[6]</sup> can become necessary. Considering that some fields of dentistry are more susceptible to ingestion accidents, the present research aimed to review the current literature to identify the dental specialties most involved with such accidents, and highlighting the important role of endoscopy for accurately locating and retrieving foreign bodies from the digestive tract.

## EPIDEMIOLOGY

Hisanaga *et al.*<sup>[1]</sup>, 2014, retrospectively analyzed 40 cases of accidental ingestion and the aspiration of foreign bodies that occurred during dental treatment over 4 years in hospital dental clinics. The accidental ingestion occurred most frequently as part of prosthodontic and operative dental treatments (50%), followed by orthodontics (15%) and maxillofacial surgery (7.5%). Approximately 97% of these cases ( $n = 39$ ) involved the accidental ingestion of dental instruments, of which only one instrument required endoscopic retrieval. The remaining ingestion accidents did not require clinical intervention.

A retrospective investigation of ingestion accidents over 10 years within a dental school was also conducted

by Tiwana *et al.*<sup>[7]</sup>. Twenty-five cases, out of the twenty-six, involved accidental ingestion. None of the cases required endoscopic or surgical retrieval. Similar to the previous study, prosthodontics and operative dentistry were involved in 50% of the dental instrument ingestion cases. Maxillofacial surgery contributed 19.2% of the ingestion cases, and orthodontics contributed 11.5%, of the ingestion cases.

A study by Obinata *et al.*<sup>[8]</sup>, identified 23 accidents over 5 years where patients had ingested dental instruments. Fifty-two percent of the accidents ( $n = 12$ ) occurred during prosthodontic procedures, while 13% of the accidents occurred during maxillofacial surgery and 8.7% of the accidents occurred during orthodontics. Only, three cases required endoscopic retrieval of the foreign bodies.

A study by Susini *et al.*<sup>[9]</sup>, 2007, analyzed the cases of 464 patients who had accidentally ingested or aspirated dental instruments that were reported to insurance companies. The type and number of dental instruments reported within the study indicated that patients having Prosthodontic treatment were most likely to suffer an accidental ingestion, and accounted for 45% of all the cases. The other dental specialties: Operative dentistry (33.6%) and endodontics (18.1%) also had a high incidence of patients suffering an accidental ingestion of dental instruments.

## DENTAL INSTRUMENTS AND ENDOSCOPY

In the medical and dental literature, several studies have reported the accidental ingestion of dental instruments used in prosthodontics and operative dentistry, such as metallic cores<sup>[10]</sup>, prosthetic crowns, dental drills<sup>[11]</sup> and even removable prostheses. Despite being uncommon, the accidental ingestion of entire prostheses were reported during traffic accidents, meals<sup>[12]</sup> and sleep<sup>[13]</sup>. Both the ingestion in the daily routine and the ingestion during dental treatment culminate with similar prognosis, making potentially necessary endoscopic retrieval.

In oral implantology there are reports of small screws being ingested by patients<sup>[14]</sup>, while in endodontics files and clamps are the most ingested instruments by patients<sup>[15-20]</sup>. In orthodontics, there are cases where patients had ingested entire and fragmented removable appliances<sup>[21,22]</sup>, as well as activation keys<sup>[23,24]</sup>, orthodontic bands<sup>[25]</sup> and orthodontic wires<sup>[26]</sup>. Several other instruments, used in general practice, were also found to be accidentally ingested by patients receiving routine dental treatments. Specifically, these instruments were ingested: (1) due to patients' biting and swallowing reactions in response to a dental instrument, where the instrument ends up being dropped into their mouth or throat and swallowed before the dentist can retrieve it; or (2) due to a professional accident: Where the instrument broke and fell into the patients mouth or throat during clinical procedures. Oncel *et al.*<sup>[27]</sup>, 2012,

illustrates the first situation reporting a case of accidental ingestion of intraoral mirror that fractured after a patient suddenly clenched his teeth. The mirror was retrieved through endoscopy after reaching the esophagus. On the other hand, cases reporting the lack of instrumental inspection to ensure there are no broken pieces was investigated by Sankar<sup>[28]</sup> and by Tsitrou *et al.*<sup>[29]</sup>. Both authors reported cases of endoscopic retrieval of triple syringe tips, measuring 12 cm and 9 cm of length respectively, unscrewed during procedures for dental restoration.

## DISCUSSION

Dentists have a critical role in preventing the breakage of instruments by preventing their over-use and over-stress. Rubber dams should always be used for hygiene control and to prevent patients from swallowing instruments. When the use of a rubber dam is not possible, dental instruments should be secured with wires or floss to help avoid and accomplish retrieval<sup>[3]</sup>. By following these safety measures the ingestion of dental instruments by patients can be prevented. If the safety measures fail, all parts of broken instruments must be retrieved immediately by the dentist following breakage. If any ingested broken instrument parts cannot be retrieved, the patient should be referred for a medical opinion.

Immediately following the instrument ingestion by a patient, the first priority is to attempt to retrieve the instrument to prevent it from blocking the patient's airway. If the instrument cannot be retrieved, it is essential to halt dental treatment, remove rubber dams and devices from the mouth, and to monitor the patient's vital signs, followed by the observation of continuous coughing, voice alterations, discomfort, and other clinical signs and symptoms that may aid the differentiation between accidental ingestion and aspiration<sup>[2]</sup>. If a patient has trouble breathing or is losing consciousness, the emergency services must be called to attend to the life-threatening condition of the patient. If a patient's condition is not life-threatening they must be referred for a medical exam. If the instrument is not visible a radiographic inspection of thorax and abdomen must be performed<sup>[2,20]</sup>.

If dental instruments reach the digestive tract, they tend to be naturally eliminated without major complications<sup>[10,11]</sup>. However, instruments with larger dimensions, such as triple syringe tips, prostheses, and dental mirrors may not be eliminated, becoming stuck along the esophagus and stomach, making it necessary to perform an endoscopic intervention<sup>[2,16,25]</sup>. Endoscopy may also be needed to retrieve instruments with a complex morphology, such as endodontic files and dental drills, which can perforate and adhere to the mucosa of digestive tract<sup>[15,19,24]</sup>. On the other hand, surgical approaches become indicated when the instruments become stuck in anatomic positions not reachable through endoscopy<sup>[13,24]</sup>. Consequently, major damages to the mucosa, digestive tract, and systemic

health can be avoided. Additional limitations for the use of endoscopy are the time elapsed from the accident and the size of foreign body. Specifically, small foreign bodies ingested a long time ago may reach the intestine and not be visible through endoscopy<sup>[14,16]</sup>.

## CONCLUSION

An effort should be made to avoid breaking dental instruments by preventing their over-use and over-stress. Rubber dams should always be used for hygiene control and to prevent patients from swallowing instruments. When the use of a rubber dam is not possible, dental instruments should be secured with wires to help avoid and accomplish retrieval. All parts of broken instruments must be retrieved immediately following breakage. If ingested broken instrument parts cannot be retrieved, the patient should be referred for a medical opinion.

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## Autotransplantation of a premolar to the maxillary anterior region in young children - how long should the donor root be? A case report

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### Abstract

Autotransplantation of premolars to anterior region after incisor loss due to trauma is accepted as the best restoration procedure with very long follow-ups. There are two main protocols: Premolars with only two thirds of the root or premolars with complete root development. Premolars with two thirds of the root completed remain vital and show complete pulp obliteration while premolars with closed apex require root canal treatment. The problem arises when the child is very young and the root of the donor premolar is developed for only one third. This case report describes the outcome of an autotransplantation of a lower first premolar with only a third of developed root to the anterior region. The donor tooth was extracted with his follicle and placed instead of tooth No. 21. For the first month esthetics was restored with a glass-fibers ribbon attached to tooth No. 11 and composite material. After a month, the crown erupted and was reshaped to mimic an incisor with composite. Orthodontic movement was performed after 5 mo, in order to alleviate the gingival contour. The final restoration was performed after 15 mo. Follow up showed full root development with normal mobility, continuous periodontal ligament and complete pulp obliteration. A multidisciplinary approach and meticulous preparation are necessary for a positive result in autotransplantation of premolars with only a third of root development to the anterior region and this case report show that this method can be performed in very young children.

**Key words:** Autotransplantation; Dental trauma; Donor tooth root length

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**Core tip:** Autotransplantation of a premolar to the anterior region has a success rate of more than 90% if the donor tooth has a developing root and pulp healing occurs. The only negative outcome is total obliteration of the pulp. This case report describes an autotransplantation of a lower first premolar with only a third of root length to the incisor area after a dental trauma that caused root resorption of a permanent upper left incisor, in a 8-year-old boy. Follow up of 15 mo showed full root growth and periodontal healing with normal mobility and obliteration of the pulp. The crown was restored using composite material to resemble the adjacent incisor. This case report shows that even with very short donor root length, autotransplantation to the anterior region can be performed in young children.

Zilberman U, Zagury A. Autotransplantation of a premolar to the maxillary anterior region in young children - how long should the donor root be? A case report. *World J Stomatol* 2015; 4(4): 141-145 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v4/i4/141.htm> DOI: <http://dx.doi.org/10.5321/wjs.v4.i4.141>

## INTRODUCTION

The method of autotransplantation of premolars to maxillary anterior region in order to replace severely traumatized permanent incisors is known for more than 40 years<sup>[1,2]</sup>. There are two main protocols regarding the stage of root development of the donor premolars - full root development<sup>[3]</sup> or half to two thirds root length<sup>[1,4]</sup>. The survival rate of premolars with complete root formation was 100% after 5 years and 72.7% after 10 years<sup>[3]</sup> and the survival rate of premolars with half to two-thirds root formation was 100% after 6-78 mo follow-up<sup>[5]</sup>. and the success rate was 91.3%. Pulp healing of the autotransplanted premolar is related to root development. For premolars with half to two thirds root length pulp healing was observed in 96% of the premolars after 6 mo follow-up<sup>[5]</sup> while for premolars with complete root length pulp healing was observed in only 15%<sup>[5]</sup>, implicating that root canal treatment is necessary after autotransplantation in premolars with full root length and closed apex. The major sign for pulp healing was obliteration of the pulp and normal periodontal ligament<sup>[5]</sup>. The problem is that the minimal age for autotransplantation should be between 9-10 years, when the donor premolar has half-two thirds of root length, while for root length of less than half absence of further root development was observed<sup>[6]</sup>. But sometimes the autotransplantation have to be performed earlier. This case report describes a successful autotransplantation of a lower first premolar with only a third of root length for an upper left incisor in an 8-year-

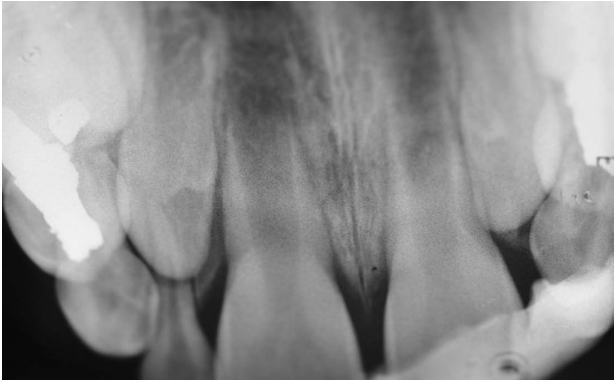
old boy with a follow-up of 15 mo.

## CASE REPORT

OB, a 7-year-old boy arrived to the pediatric dental unit at Barzilai medical center two days after a head trauma at school. The avulsed upper left central incisor was kept in dry condition and was re-implanted 3 h after the trauma at a different hospital. The tooth was splinted to the adjacent teeth with composite (Figure 1). Two weeks after the trauma, the splint was removed and the pulp canal was filled with calcium hydroxide paste. At follow-up visit after 3 mo the root was resorbed and mobility of 2 mm was observed. A split with glass-fibers ribbon was performed (Figures 2 and 3). After 12 mo and four more traumas to the tooth, the option of autotransplantation was described to the child and the parents. Under general anesthesia, tooth No. 21 was extracted (Figure 4), and germ of tooth No. 34 was exposed from the buccal aspect, without damaging tooth No. 74 (Figure 5). The premolar was extracted with the full follicle and reimplanted rotated and infra-occluded at the site of tooth No. 21, and kept in place with cross-over sutures (Figures 6 and 7). For esthetic reasons tooth No. 21 was restored using fiber-glass ribbon attached to tooth No. 11 and composite material (Figure 8). Ten days after the auto-transplantation, the sutures were removed. A month after the surgery the composite and the glass-fiber ribbon were removed and the crown of tooth No. 21 was reconstructed on top of the erupted premolar and splinted to tooth No. 11 with glass-fibers ribbon (Figure 9). Two months after surgery root development was observed. Five months after surgery, forced eruption of the autotransplanted tooth was performed in order to bring the gingival margin at the same height as tooth No. 11. The brackets were removed 4 mo later (Figure 10). At the last follow-up visit, 15 mo after the surgery, the root was completed, the mobility was similar to tooth No. 11, and the pulp was obliterated completely. A new composite restoration was performed for better esthetic (Figures 11 and 12).

## DISCUSSION

Autotransplantation of premolars to the anterior region subsequent to trauma have several advantages in comparison to other modalities, especially for young children. A tooth transplant keeps the alveolar margin at optimal height and facilitates continuous growth of the maxillary complex. It also keeps the buccopalatal dimension of the alveolar bone in the very esthetic region. The transplanted tooth allows also orthodontic movements, necessary for gingival margin reconstruction. For premolars with half to three fourth root formation, pulp and periodontal healing was reported in 80% of the cases after 14 years<sup>[7]</sup>. Complete pulp obliteration, followed by continuous root formation was



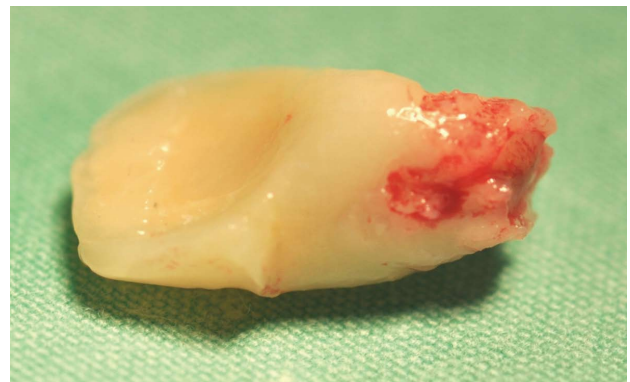
**Figure 1** Two days after the avulsion and re-implantation of tooth number 21. A composite splint is in place (November 2012).



**Figure 2** Three months after trauma. Note complete root resorption of tooth number 21 (December 2012).



**Figure 3** Splint with glass-fibers ribbon as temporary treatment till the surgery.



**Figure 4** Tooth number 21 after extraction. Note the resorption lacunae.



**Figure 5** Exposure of the donor germ, tooth number 34 from the buccal, while tooth number 74 covered by a stainless steel crown remained stable and functioning in the mouth.



**Figure 6** Donor tooth extracted with its entire follicle, before transplantation.

positively related to autotransplant viability. Clinical variables for transplanted premolars were found to be similar to the natural incisors when the mean age of surgery was 11 years<sup>[8]</sup>. A slight increased mobility was observed but the crown-root ratio and the distance between the CEJ and alveolar bone crest was similar to the adjacent incisor after a mean follow-up period of 4 years<sup>[8]</sup>. The size of the apical foramen, as long as the apex is not closed, seems not to be a very important factor for successful revascularization and ingrowth of

new tissue after transplantation in dogs<sup>[9]</sup>. Resorption of the root was higher in reimplanted teeth with more than three-quarters or apex-closed stages. The authors described that teeth with root length of less than one-half had a higher probability of having arrested root growth, but no description was given to the type of the donor tooth, and the higher failure rate was observed during the first year after transplantation. Other esthetic and restorative options for missing permanent upper centrals at young age include removable flipper with acrylic tooth or orthodontic device with bands on the molars and acrylic tooth on orthodontic wire, till



Figure 7 Donor tooth transplanted to the anterior region instead of tooth number 21.



Figure 8 Final X-ray after autotransplantation and fiber-glass and composite bridge.



Figure 9 Crown restoration of the donor tooth after a month and splint to tooth number 11.



Figure 10 End of the orthodontic stage.



Figure 11 Follow up 15 mo after autotransplantation. Note root development, pulp obliteration and continuous periodontal ligament.



Figure 12 Clinical views of the 15 mo and last composite restoration.

after the puberty growth is completed and an intra-osseous implant can be placed. The main problems with the removable or orthodontic appliances are the accumulation of plaque, the compliance of the child and his family and the possibility of losing the removable appliance or dislodgement of the orthodontic bands. Moreover, the alveolar bone will be resorbed till the insertion of the implant causing a marked discrepancy in gingival contour between the implant and the adjacent incisor. Auto-transplantation results in favorable growth

of the alveolar bone and reconstruction of the gingival contour. Successful tooth transplantation offers almost ideal esthetics, arch form and dentofacial development. A transplanted tooth diminishes the extent of resorption of newly formed alveolar bone and provides functional stimulation. Periodontal healing is usually completed after 8 wk and is affected mainly by infection at the host site due to improper postoperative control of supragingival plaque.

The case report showed that for young patients, premolars with only one third of root length can be considered suitable for autotransplantation in the anterior



region after loss of incisors due to trauma. Fifteen months follow-up showed complete root length formation, obliteration of the pulp, favorable crown/root ratio and mobility similar to the adjacent incisor. Orthodontic movement was performed in order to reconstruct a similar gingival margin and the reconstruction of the crown was performed using composite material. The final clinical result was highly accepted by both the patient and the parents. More follow-up is needed, but this case shows that autotransplantation of premolars to the anterior area can be performed even in young children.

## COMMENTS

### Case characteristics

An 8-year-old boy with no significant medical history, with an upper left central incisor with total root resorption after avulsion and unsuccessful re-implantation.

### Clinical diagnosis

Esthetic replacement of the lost upper permanent incisor is needed.

### Treatment

Removable orthodontic appliance with an acrylic tooth, fixed orthodontic appliance with an acrylic tooth, autotransplantation of a premolar, till implant insertion and crown restoration can be performed. Autotransplantation of a lower first premolar with only a third of root length was performed.

### Related reports

Success of autotransplantation of premolars to upper anterior region was related to the length of the donor tooth root. Better success rate were observed with root length of half-two thirds.

### Experiences and lessons

Autotransplantation of a premolar to replace a lost upper permanent incisor can be performed very early when the root length is only a third. This method results in a very esthetic and long lasting restoration that can be performed in very young children after dental trauma.

### Peer-review

Excellent written, the weaknesses are that the method is common knowledge with very high successful rate but this case report remind the audience of this possibility to restore missing permanent incisor after dental trauma.

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