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CONTENTS


CHAPTER
1

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ERYTHEMA MULTIFORME: A REVIEW OF CLINICAL MANIFESTATIONS, DIAGNOSIS, AND MANAGEMENT

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Erythema multiforme (EM) is an infrequent, acute, sometimes recurrent, typically self-limiting, immune-mediated vesiculobullous inflammatory and hypersensitivity reaction with varied aetiologies characterised by distinct acrally distributed target-like cutaneous eruptions with or without mucosal involvement (Scully & Bagan, 2008; Trayes, Love, & Studdiford, 2019).

Although it was first described by Bateman (1817), the first characteristic morphological feature of this particular eruption along with its aetiology was defined by Ferdinand von Hebra (1866) with the term "erythema exudativum multiforme". Afterwards, Thomas (1950) recommended that EM with the typical clinical picture with cutaneous involvement described by Hebra (1866) be named as "EM minor", and variants with more severe mucocutaneous lesions as "EM major".

This chapter is aimed to comprehensively review the epidemiology, aetiology, classification, clinical manifestations, diagnosis, differential diagnosis, and man-

agement of EM to enable dentists, who may encounter cases of EM with significant oral involvement, become familiar with the clinical picture for prompt diagnosis and management or referral to a specialist for appropriate management.

Epidemiology

Epidemiological data on EM are scarce mainly because the disease has an acute course and does not have a universally accepted classification. The prevalence of EM is unknown due to the large number of unreported or misdiagnosed cases of minor form that do not require hospitalisation but is estimated to be far less than 1% worldwide (Celentano, Tovaru, Yap, Adamo, Aria, & Mignogna, 2015; Oluwadaisi, Adewale, Mogaji, Oyetola, & Owotade, 2020).

EM, which is more frequent in young adults aged between 20 and 40, may actually be encountered at any age, and children and older adults may also be affected. Although the data on gender predilection are contradictory, EM usually exhibits a slight male predominance. In addition, no racial predominance was reported (Carrozzo, Togliatto, & Gandolfo, 1999; Ayangco & Rogers, 2003).

Aetiology

EM, the exact aetiopathogenesis of which remains unclear, is regarded as an immune-mediated disorder due to Type IV cytotoxic immune reaction triggered by numerous factors and mediated by T-lymphocytes. Although a significant portion of the cases remain idiopathic, a variety of triggering and precipitating factors such as previous viral and bacterial infections and the use of certain drugs have been implicated. Other occasional triggering factors include autoimmune diseases, malignancies, immunisation, radiotherapy, menstruation, pregnancy, chemicals, and food additives (Ayangco & Rogers, 2003; Scully & Bagan, 2008).

Almost 90% of the EM cases may be attributed to infections, usually to Herpes Simplex Virus (HSV) infections in adults and Mycoplasma pneumoniae (M. pneumoniae) infections in children. In fact, it is uncertain how many EM cases initially regarded to be idiopathic are associated with an underlying or subclinical HSV infection (Schofield, Tatnall, & Leigh, 1993; Oluwadaisi et al., 2020). Many pathogens including Hepatitis Viruses, Cytomegalovirus, Epstein-Barr Virus, Varicella Zoster Virus, Human Immunodeficiency Virus, Mycobacterium leprae, and Orf Virus have been correlated with EM (Miranda, Antunes, Nery, Sales, Pereira, & Sarno, 2012; Cieza-Díaz, Campos-Domínguez, Santos-Sebastián, Fer-

nández-Antón Martínez, Ceballos-Rodríguez, Navarro-Gómez, & Suárez-Fernández, 2013; Park, Kang, Seol, Sung, & Kim, 2014; Turnbull, Hawkins, Atkins, Francis, & Roberts, 2014; Ma, Smith, & Gordon, 2015). Recently, an association has also been reported between EM and the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the new coronavirus accused for the Coronavirus pandemic in 2019 (COVID-19) (Jimenez-Cauhe, Ortega-Quijano, Carretero-Barrio, Suarez-Valle, Saceda-Corralo, Moreno-Garcia Del Real, & Fernandez-Nieto, 2020).

Less than 10% of the EM cases are attributed to adverse drug reactions, often to non-steroidal anti-inflammatory drugs, antiepileptics, and antibiotics. As the drug list correlated with the emergence of EM continues to expand with the introduction of novel drug categories, this rate is reported as high as 50% in some studies (Scully & Bagan, 2008; Celentano et al., 2015). Influenza, measles, rubella, varicella, smallpox, mumps, diphtheria, tetanus, Hepatitis B, pneumococcal, meningococcal, and COVID-19 vaccines have also been correlated with EM (Griffith & Miller, 1988; Di Lernia, Lo Scocco, & Bisighini, 1994; Patja, Davidkin, Kurki, Kallio, Valle, & Peltola, 2000; McMahon, Amerson, Rosenbach, Lipoff, Moustafa, Tyagi, Desai, French, Lim, Thiers, Hruza, Blumenthal, Fox, & Freeman, 2021). It has been reported that the reaction may occur within hours in case of re-exposure to the responsible drug.

The main chemokine playing a role in drug-induced EM is tumour necrosis factor alpha (TNF-α), whereas in HSV-associated EM interferon gamma (IFN-γ) is more frequently found (Kokuba, Aurelian, & Burnett, 1999). Further research is required on this mechanism, which has not been fully elucidated.

Recurrent EM cases have been associated with Hepatitis C infection, Coxsackie infection, vulvovaginal candidiasis, complex aphthosis, menstruation, polymorphic light eruption, and high food preservative intake besides HSV and M. pneumoniae infections (Schofield et al., 1993; Wetter & Davis, 2010). Although both Type 1 and 2 HSV infections are cited in the aetiology of EM, HSV-1 has a predominant role in the recurrence of EM (Samim, Auluck, Zed, & Williams, 2013).

Persistent EM cases have been connected with HSV, Epstein-Barr Virus, Cytomegalovirus, Hepatitis C Virus, and influenza virus infections, autoimmune diseases in particular inflammatory bowel disease, underlying malignancies including haematological (lymphoma and leukemia) and solid malignancies (extrahepatic cholangiocarcinoma, gastric adenocarcinoma, and renal cell carcinoma) (Chen, Tsai, Chen, & Hung, 2008; Turnbull et al., 2014).

Genetic susceptibility may also be involved in the development of the disorder, particularly in HSV-related EM cases. Increased susceptibility to recurrent EM with human leukocyte antigen (HLA) associated alleles, especially HLA-B15 (B62), HLA-A33, HLA-B35, HLA-DR53, HLA-DQ3, and HLA-DQB1*0301, and extensive involvement of mucosae with DQB1*0402 has been reported (Khalil, Lepage, Douay, Morin, al-Daccak, Wallach, Binet, Lemarchand, Degos, & Hors, 1991; MacKenzie, Laing, & Smith, 1997).

Classification

Different clinical EM forms are extensively described according to the current classification criteria based on the mucocutaneous findings (presence, morphology, and extent) (Celentano et al., 2015).

EM has been considered by many authors in the category of diseases that includes Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Nevertheless, the differentiation of these conditions from each other is important because of variable aetiology, severity, clinical presentation, management, and prognosis. Although EM is particularly strongly associated with infections such as HSV, SJS and TEN appear to be more commonly triggered by intake of certain drugs. Generally, EM is observed with typical target or atypical raised target lesions commonly on the face, limbs, and trunk. On the other hand, SJS mostly appears with atypical flat target lesions or diffuse purpuric macules on the trunk with more severe systemic involvement and manifestations. Some authors consider that the diagnosis of EM would be appropriate for patients with involvement of less than 10% of the surface area of the body, while more extensive involvement should be defined as SJS or TEN (Auquier-Dunant, Mockenhaupt, Naldi, Correia, Schröder, Roujeau, & Severe Cutaneous Adverse Reactions [SCAR] Study Group, 2002; Farthing, Bagan, & Scully, 2005; Al-Johani, Fedele, & Porter, 2007; Scully & Bagan, 2008).

EM has been subclassified as “EM minor” and “EM major” according to the severity of symptoms and the number of involved mucosal regions. Although both variants share many features, EM major is characterised by the involvement of two or more mucosal membranes, more severe involvement of the mucosae, and systemic symptoms including fever and arthralgia. EM minor usually exhibits minimal or no involvement of mucosal membranes with milder cutaneous symptoms and no associated systemic symptoms (Huff, Weston, & Tonnesen, 1983; Farthing et al., 2005). EM minor was reported in approximately 90% of the patients, while EM major was diagnosed in about 10%. The low number of EM

major cases was attributed to the fact that most patients with extensive skin lesions applied to dermatology clinics and only cases with oral mucosal involvement were referred to oral medicine clinics (Oluwadaisi et al., 2020).

Depending on the evolution of the disease over time, acute, recurrent, and chronic persistent forms of EM are distinguished. In a minority of patients, the disease may recur resulting in a variant described as "recurrent EM". Recurrences may be seen in 22-37% of the cases, seasonal clustering in spring or autumn may be observed, and the clinical severity of the attacks may increase. Studies on patients fitting this subgroup have demonstrated an average of 6 EM episodes each year and a mean disease period of 6-10 years. HSV infection even without the symptoms of an active HSV outbreak may often be associated with recurrent EM, and this relation of HSV with the recurrent EM is reported to vary between 61-100% (Schofield et al., 1993; Wetter & Davis, 2010). The EM variant distinguished by the undisrupted emergence of typical and atypical EM lesions with obvious resistance to therapy is regarded as "Persistent EM". The disorder may persist longer than a year without therapy (Chen et al., 2008; Turnbull et al., 2014).

An inflammatory oral disorder that resembled the typical oral lesions of EM without any cutaneous involvement was described by Kenneth (1968). This EM category, suggested as "oral EM" by many researchers, has been reported in about 40% of the patients. Although the primary oral EM attacks have been indicated to be restricted with the oral mucosa without any cutaneous involvement, more severe EM forms with the involvement of the skin may be observed in the subsequent attacks (Kennett, 1968; Lozada-Nur, Gorsky, & Silverman, 1989). Oral EM is considered as a controversial, not well-recognized, and rare variant of EM because some dermatologists still strongly advocate the idea that the distinguishing appearance and distribution of target cutaneous lesions is a prerequisite for the diagnosis of EM (Oluwadaisi et al., 2020).

Clinical Manifestations

In most patients, EM is a transient condition that resolves spontaneously without long-term morbidity. Rarely, patients experience frequent recurrences, persistence, or serious complications. EM-associated lesions typically develop within 3-5 days (2-17 days after an episode of HSV infection) and usually resolve within 1-2 weeks. However, more severe cases of EM involving the mucous membranes may take 5-6 weeks to resolve (Schofield et al., 1993; Trayes et al., 2019).

EM often presents with lesions of both skin and mucosa but may also exhibit only cutaneous or mucosal lesions. The cutaneous lesions may be in various forms including macules, papules, vesicles, and bullae, and therefore termed "multiforme (many forms)". Cutaneous lesions may either be typical or atypical. Typical three-component "target" or "iris" lesions with three concentric rings of distinct colour variation, often less than 3 cm in diameter, symmetrically distributed on the extensor surfaces of the acral extremities are the characteristic of the disease but may not always be present. Atypical lesions appear as raised, oedematous, palpable lesions with solely two concentric rings of colour variation and an ill-defined border. Typical or atypical lesions may appear on the face, neck, flexor surfaces of the extremities, soles, palms, and/or trunk. Although cutaneous lesions are generally asymptomatic, itching and burning may occur at the eruption site in some cases. EM lesions are more common in sites of physical trauma or current sunburn. Although the lesions on the skin often recover without any complications and do not cause scarring, post-inflammatory hyperpigmentation may remain for a few months after healing, especially in dark-skinned patients (Kennett, 1968; Wetter & Davis, 2010).

Mucosal lesions are encountered in 25-60% of EM patients. Although the oral mucosa is the most frequently involved mucosal site, genital, nasal, and/or ocular mucosal lesions may be observed with or without accompanying cutaneous lesions. Rarely, the involvement may spread to the pharynx, oesophagus, and upper respiratory tract (Pope & Krafchik, 2005). Oral mucosal involvement is observed in approximately 70% of patients with EM. The intraoral lesions tend to be located in the anterior region and the mainly affected areas are the vermilion borders of the lips, labial and buccal mucosa, soft palate, floor of the mouth, non-attached gingivae, and tongue, while the attached gingivae and hard palate are relatively spared. The oral mucosal lesions are characterised clinically by haemorrhagic crusting on the lips and ulcerations of predominantly the non-keratinized mucosae interfering with speech, chewing, and swallowing (Kennett, 1968; Lozada-Nur et al., 1989; Ayangco & Rogers, 2003). In case of ocular involvement, the first finding may be lacrimation and photophobia. The ocular lesions, which can cause scarring and progressive blindness, are of particular concern (Power, Ghoraishi, Merayo-Lloves, Neves, & Foster, 1995). Inflammation and erosion can be detected in other mucosal surfaces including the nasal, urethral, and anogenital mucosae.

Prodromal symptoms including headache, fever, myalgia, and malaise are rare in mild cases, but may be observed in cases where involvement of the mucosae is significant. Respiratory symptoms and cough may be noted in EM cases related

to M. pneumoniae infection (Amode, Ingen-Housz-Oro, Ortonne, Bounfour, Pereyre, Schlemmer, Bequignon, Royer, Wolkenstein, & Chosidow, 2018).

Diagnosis

EM is diagnosed principally based on the patient history and the clinical picture. The history typically including the symptoms of recent infection (e.g.; HSV, M. pneumoniae) or drug intake prior to onset, accompanied by the typical target skin lesions and mucosal lesions helps the diagnosis of EM (Sokumbi & Wetter, 2012; Samim et al., 2013).

Although most of the EM cases do not necessitate additional diagnostic testing, skin biopsies and laboratory tests may be useful in uncertain cases to rule out other inflammatory, vesiculobullous, and dysplastic diseases. The results of the skin biopsies may vary in relation to the period of the lesion and the biopsy site within the lesion. Since the histopathological appearance is non-specific and non-diagnostic, biopsy is recommended for early vesicular EM lesions, not for ulcerated ones. Although the histopathological examination may show some important signs in the perilesional tissue such as intercellular or intracellular oedema, micro vesicular formation, polymorphous nuclear cell infiltration, and necrotic keratinocytes, there are no pathognomonic histopathological features of EM (Samim et al., 2013; Krishnankutty, Chaudhuri, & Ashok, 2018). Direct or indirect immunofluorescence tests are not specific and diagnostic and are not helpful other than in the differential diagnosis of EM and other autoimmune blistering diseases such as bullous pemphigoid (Sokumbi & Wetter, 2012).

No specific abnormal laboratory findings can assist in the diagnosis of EM except in very severe cases with elevated white blood cell count, erythrocyte sedimentation rate, and liver enzymes (Huff et al., 1983; Krishnankutty et al., 2018).

In the differential diagnosis of EM, a variety of mucocutaneous eruptions such as oral lichen planus, pemphigus vulgaris, mucous membrane pemphigoid, SJS, urticaria, fixed drug eruption, systemic lupus erythematosus, hypersensitivity reactions, and different drug reaction patterns should be considered (Kokuba et al., 1999; Ayangco & Rogers, 2003; Samim et al., 2013).

Management

Most of the proposed management options for EM refer to small case series, expert opinions, and limited number of clinical trials (de Risi-Pugliese, Sbidian, Ingen-Housz-Oro, & Le Cleach, 2019).

The management of EM depends on the aetiology and severity of the disease and no single specific treatment modality has been found ideal. Identifying the aetiology of EM is crucial for the success of the treatment. The basis of treatment is eliminating the triggering agent under suspicion. In case of evidence of a recent infection, treatment of the infection, or similarly, if there is evidence that EM is induced by a drug, discontinuation of the drug is the first step in management (Sokumbi & Wetter, 2012; de Risi-Pugliese et al., 2019; Trayes et al., 2019). Different treatment options are recommended for acute and recurrent disease.

In the acute form of the disease, since the lesions typically regress within a few weeks, supportive treatment is aimed at providing symptomatic relief and treatment is rarely needed (Wetter & Davis, 2010; Trayes et al., 2019). Most mild or moderate cases can be treated symptomatically on an outpatient basis, or may require topical corticosteroids or oral antihistamines (Krishnankutty et al., 2018). The use of topical corticosteroids, analgesics, anaesthetics, and antiseptics may be necessary in the management of mucosal lesions (Trayes et al., 2019; Oluwadaisi et al., 2020). In case of suspected ocular involvement, ophthalmologic consultation should be sought to avoid vital future complications (Chang, Huang, Tseng, Hsu, Ho, & Sheu, 2007).

Severe cases having extensive mucosal involvement require hospitalization for systemic corticosteroids (most commonly prednisone at a dose of 40-60 mg daily, tapering over 2-4 weeks) and intravenous repletion of fluids and electrolytes (Krishnankutty et al., 2018; Trayes et al., 2019). Immunosuppressant agents such as cyclosporine, cyclophosphamide, azathioprine, and thalidomide are used alone or sometimes in combination with corticosteroids (Celentano et al., 2015; Krishnankutty et al., 2018).

The most challenging type to treat is recurrent EM due to its resistant nature. Prophylactic systemic antiviral therapy is recommended in recurrent EM caused by HSV infection. The most effective treatment approach has been reported to be continuous or intermittent twice daily oral use of acyclovir (400 mg), valacyclovir (500 mg), or famciclovir (250 mg) for a period longer than 6 months. Recurrence is common after discontinuation of antiviral therapy. In this case, restarting the drug with the lowest effective dose and re-discontinuation after 6-12 months may be attempted. In recurrent EM cases that do not respond to antiviral therapy,

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the dose of the current antiviral agent may be doubled, alternative antiviral agents may be tried, or different agents including immunosuppressives, corticosteroids, antimalarials, and others can be used (Kennedy, Leigh, Ridgway, Wansbrough-Jones, & Brigden, 1981; Tatnall, Schofield, & Leigh, 1995).

Second-line therapies including alternative systemic immunomodulating/immunosuppressive agents and antimicrobial drugs such as hydroxychloroquine, azathioprine, cyclosporine, dapsone, levamisole, thalidomide, mycophenolate mofetil, adalimumab, rituximab, and apremilast are generally reserved for refractory or resistant EM cases that are more difficult to treat (Cherouati, Claudy, Souteyrand, Cambazard, Vaillant, Moulin, Crickx, Morel, Lamorelle, & Revuz, 1996; Davis, Rogers, & Pittelkow, 2002; Chen et al., 2008; Hirsch, Ingen-Housz-Oro, Fite, Valeyrie-Allanore, Ortonne, Buffard, Verlinde-Carvalho, Marinho, Martinet, Grootenboer-Mignot, Descamps, Wolkenstein, Joly, & Chosidow, 2016; Baillis & Maize, 2017; Chen, Levitt, & Geller, 2017; Oak, Seminario-Vidal, & Sami, 2017; Liu, Chen, Hui, Kuan, & Chung, 2018).

Conclusion

Despite the many factors involved, the exact aetiology of EM is still debatable and no specific diagnostic criteria have been established. Treatment is symptomatic and the underlying possible causes should be eliminated. Since EM cases with significant oral involvement may refer to them, dentists should be competent with the clinical picture of EM for differentiation from other vesiculobullous lesions, prompt diagnosis, and appropriate treatment or referral to a specialist for appropriate management.

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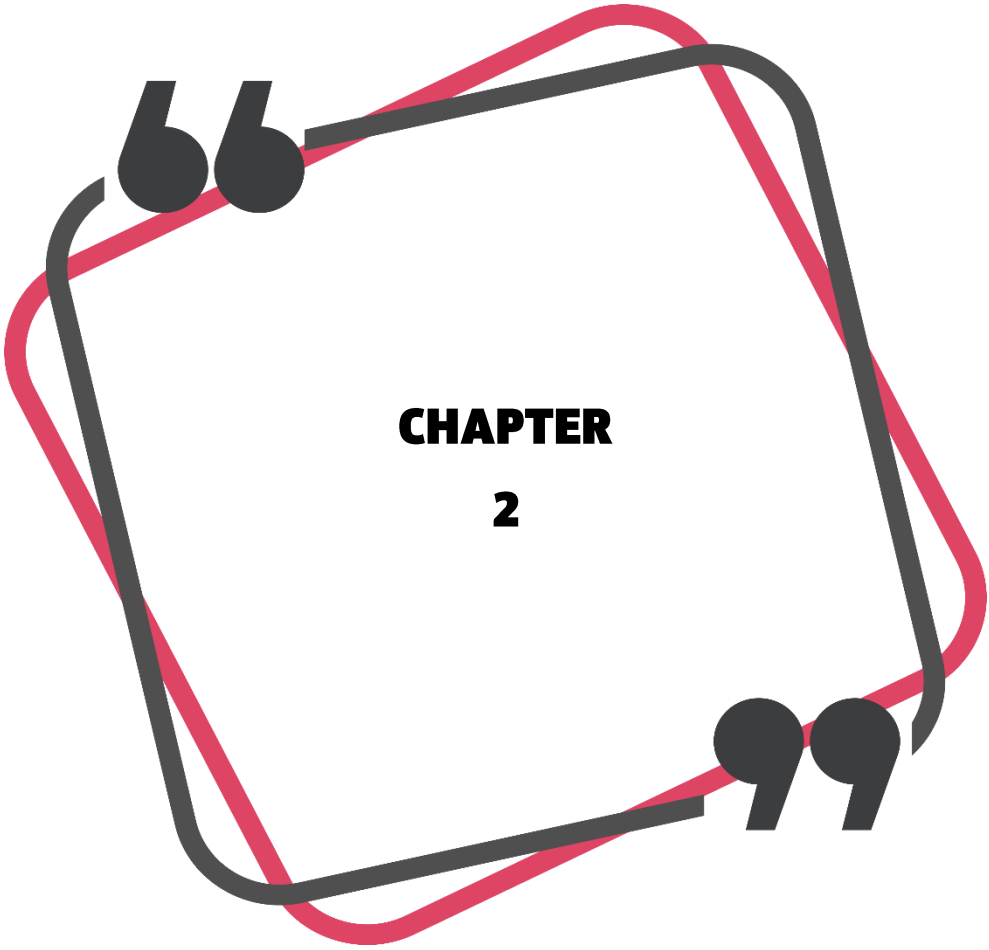
CHAPTER
2

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RETENTION IN ORTHODONTICS

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1. Introduction

At the end of active orthodontic treatment, the treatment applied to ensure the continuity of the obtained tooth and jaw positions is called 'Retention treatment'. The stability of teeth and skeletal structures is insufficient at the end of active treatment. This insufficient stabilization causes the positions obtained at the end of the treatment to return to their former state. This relapse is called an 'orthodontic relapse' (Littlewood et al., 2017). There are different opinions about what this amount should be in order to evaluate the amount of relapse as a relapse. While Booth et al. called dental irregularity of more than 2 mm a relapse (Booth et al., 2008), Steinnes et al. stated that relapses of more than 3.5 mm could be noticed by patients and this amount could be considered as relapse (Steinnes et al.,2017).

At the end of orthodontic treatment, the relapse of the first few hours or a few days after the desimentation of the orthodontic appliances is called 'rapid relapse'. The type of relapse that occurs in the long term due to different factors such as continued growth and development, degenerative periodontal disease, mouth breathing, and bad habits acquired afterward is called 'late relapse' (Thilander 2000; John et al., 2014). Relapse does not occur in every patient who has received orthodontic treatment, and it is very difficult to predict which patients will relapse. For this reason, it is very important to carry out the treatment as if there is a potential for relapse, taking into account the factors that affect the stabilization of the condition obtained at the end of the treatment (Littlewood et al., 2017). Various theories have been put forward regarding the factor that is effective in stabilization at the end of the treatment. After Kingsley revealed that the occlusion achieved at the end of the treatment was the most effective factor on stability (Kingsley 1880), various ideas were reported such as that muscle balance is closely related to stability (Rogers 1922), and that the position of the mandibular incisors on the apical base significantly affects stability (Grieve 1944; Tweed

1952). Since the stabilization of orthodontic treatment may depend on many factors, retention treatment should be planned considering these factors in order to ensure retention. When planning retention treatment at the end of orthodontic treatment; the continuation of craniofacial growth, the reorganization of the gingival and periodontal tissues according to the new condition, the presence of pressures created by the soft tissues, the continuation of bad habits, the occlusion obtained after the treatment, the altered arch form with the treatment, and the presence of the third molar tooth should be evaluated (Profitt et al., 2013):

The individual follows the skeletal growth pattern that exists in his own growth process. Accordingly, the existing skeletal problem will be seen as long as the growth continues. Therefore, the individual's growth pattern should be considered as one of the factors determining relapse when planning retention treatment (Behrents et al., 1989).

The integrity of periodontal structures is impaired due to the movement of the teeth during orthodontic treatment. This irregularity in these periodontal structures has a negative effect on stabilization. It takes time for periodontal structures to be arranged and adapted to their new positions. This period takes 3-4 months for the reorganization of the periodontal ligament, 4-6 months for the reorganization of the gingival collagen network, and more than 232 days for the reorganization of the supracrestal fibrils. These adaptation periods should be considered when planning retention treatment (Retain 1960). Although the possibility of relapse after rotation, which is the movement in which supracrestal fiber tension increases most, is high (Edwards 1968; Southards et al., 1992). It has been reported that the tendency to relapse also increases under alveolar crest loss and root resorption (Sharpe et al., 1987).

If the limits set by the soft tissue are exceeded with orthodontic treatment, the muscle pressure applied by the soft tissues negatively affects the stability and increases the probability of relapse (Moss 1980; Fränkel and Fränkel, 1989). Therefore, if it is planned to change the arch width and length of the individual with active treatment, the change should be within the soft tissue limits (Riedel 1960; Burke et al., 1988). Tongue-lip-cheek pressures caused by functional movements such as chewing, swallowing, and speaking do not cause unwanted tooth movements. Because the duration of the forces occurring during these functions is not sufficient for tooth movement. However, undesirable pressures due to bad habits such as tongue thrusting, lip sucking, and mouth breathing may cause relapse depending on factors such as the frequency, severity, and duration of the forces that occur with these para functions (Proffit 1972; Thüer and Ingervall, 1986). In addition, the movement of the teeth in the mesial direction, depending on the

anterior component of the forces created by functional movements, has been shown to be the reason for the relapse seen in the anterior segment in the late period (Steadman 1961; Southard et al., 1991; Profitt et al.,2013).

The contribution of the final occlusion obtained when the active orthodontic treatment is terminated to stability is very important. Angle argues that if occlusion is ideally achieved after treatment, there is no need for any retention treatment (Angle 1907).

The effect of third molars on stability is controversial. While some researchers argue that the third molars disrupt the alignment of the teeth, especially in the lower anterior region, during and after the eruption, there are also studies that argue that the third molar has no effect on stability (Bergstrom and Jensen, 1961; Shenaman 1968; Björk and Skieller, 1972; Sakuda et al., 1976; Lindqvist and Thilander, 1982). Kahl Nieke et al. reported in their study that the effect of third molars on crowding after retention was statistically significant but clinically insignificant (Kahl-Nieke et al., 1995). Late lower incisor crowding is multifactorial, and factors other than third molars play an important role. The effect of extraction of third molars in preventing lower incisor crowding has not been proven (Kandasamy 2011).

Due to the ongoing skeletal mandibular growth and the negative effects of this growth on the existing tooth positions, the probability of relapse in the lower anterior region is higher than in other regions. In addition, the increased inter-canine distance returning to the pre-treatment state and the inability of the soft tissue to adapt to the situation at the end of the treatment also increase the risk of relapse in the lower anterior region (Angle 1907; Southard et al., 1991; Profitt et al.,2013). Many different factors, such as the type and severity of malocclusion before treatment, inappropriate treatment methods, patient cooperation, and the size of the mandibular incisors, are among the factors that cause relapse (Heiser et al., 2004).

2. Importance of Retention Treatment

Retention treatment is the treatment to ensure the continuity of the ideal positions of the teeth and surrounding tissues obtained at the end of active orthodontic treatment and to prevent relapse. Retention treatment is characterized as the continuation of active orthodontic treatment (Reitan 1960; Moyers 1973).

Retention treatment can be applied as active and passive retention treatment. While various appliances are used in the treatment of active retention, retention

is provided by the occlusal relationship obtained with active orthodontic treatment without the use of any retention device in the treatment of passive retention (Perkün 1973).

Different views have been advocated in order to ensure that the results obtained at the end of active orthodontic treatment are permanent. Besides the researchers who say that occlusion is the most effective factor for stabilization (Hawley 1919; Hellman 1944); Paul Rogers argued that properly functioning muscle activity and muscle balance are the most influential factors for stability (Rogers 1922). Some researchers have also argued that the ideal positioning of the teeth in the basal base ensures the continuity of stability (Lundström 1925; Nance 1947). Studies showing that the preservation of arc width and limited expansion is effective for the continuity of stability have also taken place in the literature (McCauley 1944). In studies examining the effects of lower incisors on stability, it has been reported that the upright position of these teeth in the basal base is an important factor for stability (Grieve 1944; Tweed 1952). There is still no consensus on the duration and type of retention treatment, and physicians usually decide based on their own clinical experience (Profitt et al., 2013).

2.1. Timing of Retention Treatment

Retention therapy should ensure that the tooth positions obtained as a result of active orthodontic treatment remain stable by allowing the reorganization of periodontal and gingival tissues and neuromuscular adaptation. During orthodontic tooth movement, the teeth are in an unstable state due to the expansion of the periodontal ligament and the disintegration of the collagen fibril networks. Therefore, pressures from surrounding tissues can cause changes in tooth positions. Retention therapy is required to prevent these changes (Profitt et al., 2013).

The retention treatment protocol should be determined by considering the malocclusion, the patient's growth pattern, and the treatment technique applied before the treatment (Melrose and Millett, 1998). The type of appliance to be used in the treatment of retention and the duration of use should be determined depending on factors such as the patient's age, malocclusion, duration of treatment, number of teeth moved, tubercle structure of the teeth, the width of the arches, the health of the teeth and surrounding tissues, muscle pressures (Joondeph 1966).

The mainstay of retention treatment is to keep the periodontal structures until they adapt to their new positions and to continue the retention treatment until the

growth is completed (Reitan 1960). It has been shown in studies that the adaptation of periodontal fibers to their new positions requires at least 232 days, so the shortest retention period should be 232 days (Littlewood et al., 2006). Profitt et al. recommend that the retention appliances be used full-time for the first 3-4 months following the end of active treatment, and for at least 12 months thereafter (Profitt et al., 2013). Rossouw and Malik recommend wearing the retention appliance full-time for the first month following the end of active treatment, and then only at night, while Mc Nally et al. recommend wearing the retention appliance full-time for the first 3-6 months following the end of active treatment, and then at night for 12-18 months. (McNally et al., 2003; Rossouw and Malik, 2017). There are also researchers who advocate lifelong retention to avoid relapse (Parker 1989). Depending on the duration of retention treatment, the type of malocclusion, and the treatment method, it can be specified into 3 different groups: Cases that have undergone crossbite treatment (anterior crossbite treatment/lateral crossbite treatment), cases requiring serial extraction or single tooth extraction, cases with impacted teeth and cases where the canines are in the infra position require limited-term retention treatment at the end of active treatment. Cases requiring medium-term retention can be counted as Class I protrusion-non-extraction cases, Class I and class II extraction cases, Class I or class II deep bite cases, and cases with supernumerary or ectopic teeth. Cases with maxillary expansion, polidiastema cases, cases involving severe rotations, cases with median diastemas, cases with cleft lip and palate, and cases where the mandibular incisors are proclined more than 2 mm are cases that require continuous retention (Graber and Vanarsdall, 2000).

2.2. Appliances Used in Retention Treatment

Following the active orthodontic treatment, the most important factors determining which retention protocol will be applied are; initial malocclusion of the patient, age of the patient, growth pattern, occlusion achieved at the end of the treatment, and patient cooperation (Joondeph 1966).

Various appliances, including removable and fixed, can be used in the treatment of retention. As removable appliances; Hawley, Wraparound, Elastic Wraparound, Van der Linden retainer, Sarhan all retainer, Spring aligner, Coregg appliance, Osamu retainer, Essix with vacuum clear plates are used. In cases with growth modification, part-time use of functional appliances or headgear is recommended to prevent relapse. Lingual retainer wires are used as fixed retention appliances (Rodriguez et al., 2007; Profitt et al.,2013). Retainer types frequently used

by orthodontists today are, Hawley appliances, vacuum-formed clear plates, and fixed lingual retainer wires (Wong and Freer, 2004; Keim et al., 2008; Singh et al., 2009; Renkema et al., 2019).

A retention appliance should allow physiological tooth movements, allow functional occlusion, be biologically compatible with tissues, be easy to manufacture and repair, prevent relapse, and be aesthetic (Collet 1998).

2.2.1. Removable Retention Appliances

2.2.1.a. Hawley Appliance

The Hawley appliance was designed by Charles Hawley as an active treatment appliance in the 1900s and has been transferred to the present day by making various modifications to it. Although it is generally used in the maxillary arch, it can also be used for the mandibular arch (Hawley 1919). The Hawley appliance consists of 2 parts: the acrylic part and the holding elements part. The acrylic part is the part that contacts the lingual of the teeth and covers the soft tissue. This part, which is in the structure of methyl methacrylate, should be prepared with a thickness of 1.5-2 mm in the upper jaw and 2-2.5 mm in the lower jaw and well polished. The retaining elements consist of a vestibule arch, usually prepared from 0.020-0.036 inch round stainless steel wire, passing through the buccal surfaces of the anterior teeth, and the drop clasp between the two premolars and Adams clasps gripping the first molars (Figure 1). Since the Hawley appliance does not cover the occlusal surfaces of the teeth, it allows physiological tooth movements of the maxillary and mandibular posterior teeth and ensures the establishment of posterior occlusion. This appliance can be used as a long-term retention appliance in cases of overbite by adding the anterior bite plane to the maxillary plate, and in open bite patients by adding a block to the posterior bite. The disadvantages of this appliance are that its use is dependent on patient compliance, it is not aesthetic, and the wires passing through the occlusal surfaces prevent occlusion (Rodriguez et al., 2007).

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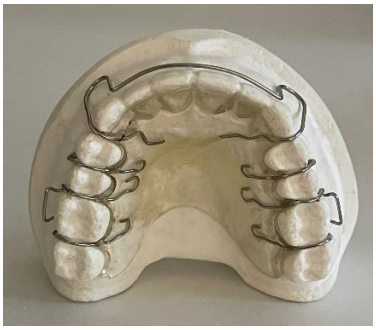

Figure 1. Hawley Appliance

2.2.1.b. Wraparound (Clip-on) Appliance

The vestibular arch in the Wraparound appliance is extended from the distal to the posterior region of the first molars and sometimes even the second molars (Figure 2). Since this appliance does not have drop/knob clasps that provide retention, the risk of reopening the extraction space in extraction cases is eliminated. The Wraparound appliance is generally used to prevent the opening of the extraction space in extraction cases, as a splint in teeth with periodontal destruction, and to close the minimal gaps left after the bands are removed in the posterior teeth. It is less aesthetic and less comfortable compared to the Hawley appliance (Joondeph 1966; Profitt et al., 2013).

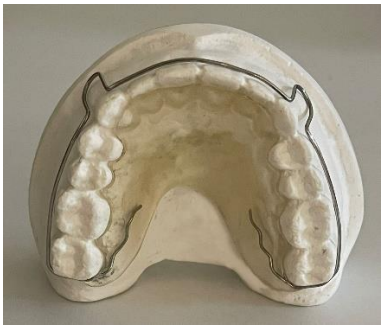

Figure 2. Wraparound (Clip-on) Appliance

2.2.1.c. Vacuum-Formed Thermoplastic Appliances

This type of retention appliance is a vacuum-formed transparent thermoplastic appliance (Figure 3). These appliances are frequently preferred by patients because they are transparent and thin. It is also frequently preferred by physicians because it is easy to clean, easy to manufacture, and inexpensive (Sheridan et al., 1995; Jäderberg et al, 2012; Johnston and Littlewood, 2015). Today, they are the

most commonly used appliances for the maxillary arch. The disadvantages of clear aligners are that they prevent the interdigitation of teeth because they cover the occlusal surface of the teeth, they are not successful in overbite control compared to the Hawley appliance, they are recommended to be renewed once a year due to discoloration over time, and their use depends on patient compliance (Proffit et al., 2013).

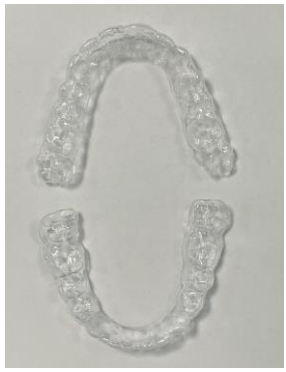

Figure 3. Vacuum-Formed Thermoplastic Appliances

2.2.1.d. Positioner

Positioner appliances are used in the treatment of retention as well as at the end of active treatment (Kesling 1945). These appliances are generally used as finishing appliances in open bite patients, as they provide intrusion of the posterior teeth and extrusion of the anterior teeth, and they are also preferred because they direct the mandible to posterior rotation in patients who are prone to relapse as a result of Class III treatment. They can also be used to maintain the position of the mandible until fixed orthodontic treatment after functional appliances in patients with Class II malocclusion due to growth patterns. This appliance contributes to the recovery of gingival hardness and color by continuously stimulating the tissue (Degirmenci and Ozsoy, 2009). Due to its bulky structure, it is difficult to use in long-term use and in patients with nasal airway obstruction. The flexible structure of the appliance creates a disadvantage in preventing the relapse of teeth with corrected rotation and preventing incisor crowding after treatment (Kesling 1945; Bennett 2006).

2.2.1.e. Moore Appliance

This appliance, which is used to prevent the opening of the extraction spaces as a result of the treatment carried out by tooth extraction in the mandibular arch,

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can be considered as the mandibular arch version of the Wraparound appliance (Proffit et al., 2013).

2.2.2. Fixed Retention Appliances

Fixed retention appliances are retainers in the form of bonded wires. They are also called 'lingual retainers' because they are usually prepared by bonding to the palatal and lingual surfaces of the anterior teeth (Proffit et al., 2013) (Figure 4). There is no need for patient cooperation in this type of retainer. Therefore, they are often preferred in cases where retention is required for a long time. Proffit et al. reported that fixed retention appliances should be used to prevent the reopening of interdental spaces closed with orthodontic treatment, to prevent the recurrence of lower incisors due to late jaw growth, to protect the spaces prepared for prosthetic treatment, and to protect the extraction spaces closed at the end of tooth extraction. (Proffit et al., 2013). It should be kept in mind that in cases with first premolar extraction in which fixed lingual retainers are extended to the second premolar, the wire may break due to occlusal forces and this may pose a risk of relapse (Zachrisson 2015).

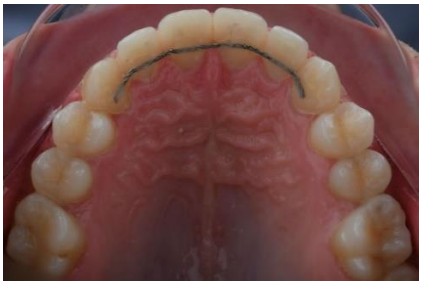

Figure 4. Lingual retainer

The mechanical properties of the wire to be used in the use of fixed retainers are of great importance. Fixed lingual retainer wires are divided into several generations according to their materials and sections (Değirmenci et al., 2009): 1st generation wires are round wires with a thickness of 0.025-0.036 inches, in blue elgiloy (CoCrNi) or stainless steel structure. 2nd generation wires are triple helix wires with a thickness of 0.032 inches in stainless steel construction. 3rd generation wires are wires that are in the structure of 0.032-inch stainless steel or 0.030-inch gold. 4th generation wires are 0.0215-inch five-stranded coaxial wires. 5th generation wires are 0.032-inch thick wires in blue elgiloy (CoCrNi) structure. Polyethylene fiber or glass fiber-reinforced composite retainers, which are highly

biocompatible, transparent, aesthetic, and easy to adapt, are also used as an alternative to stainless steel retainers (Karaman et al., 2002; Rose et al., 2002). Although these wires can be used as an alternative to stainless steel wires in patients with metal and nickel allergies, the biggest disadvantages are their high cost and more sensitive technique (Sobouti et al., 2016). As a result of long-term studies, it has been reported that the optimal fixed retainer wire is a 0.0215-inch thick five-helix wire. This wire has enough elasticity coefficient to allow physiological movement of the teeth (Zachrisson 2007).

Fixed lingual retainer wires can be applied by fixing only on the canine teeth or to all anterior teeth between the canine and the canine (Bearn 1995; Hegde et al., 2011; Pazera et al., 2012) . Retainer wires, which are attached only to canine teeth, are hygienic and therefore have less risk of periodontal problems and caries (Zachrisson 2007). Their biggest disadvantage is that they are not sufficiently successful in preventing incisor crowding because they are not attached to anterior teeth (Störmann and Ehmer, 2002). Studies have shown that retention wires attached to all anterior teeth between the canine and the canine are more effective in preventing incisor crowding (Watted et al., 2001). Retainer wires applied to all anterior teeth between the canine and the canine are used in cases with poly diastema and median diastema treatment, cases with mandibular incisor extraction, and cases with severe rotation correction (Zachrisson 1983) (Figure 5).

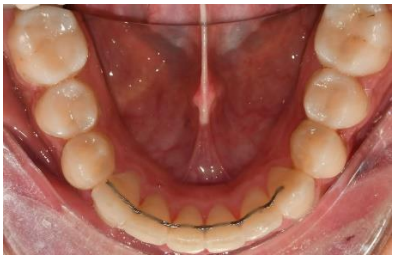

Figure 5. Retainer wires applied to all anterior teeth between the canine and the canine

Fixed lingual retainer wires can also be prepared directly in the mouth or indirectly on dental models (Karaman et al., 2003; Zachrisson 2007). In the indirect method, the retainer wire, which is passively adapted lingually on the dental model, is carried into the mouth with a silicone key or vacuum-shaped clear plates and cemented onto the teeth with composites (Ferguson 1988; Corti 1991). In this method, although the time spent with the patient is shorter than the direct application, it requires preliminary preparation in the laboratory, which creates a disadvantage (Karaman et al., 2003; Corti 1991).

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In the study, the success rates of direct and indirect bonding techniques were compared and no significant differences were found in the success rates. However, more undesirable movements were observed in the group that fixed with the direct technique compared to the group that fixed with the indirect technique. It is thought that the cause of these unwanted tooth movements is due to the plastic deformation that occurs during the adjustment of the wire in the clinic (Egli et al., 2017).

The biggest advantage of fixed lingual retainer wires is that they do not require patient cooperation. These wires are aesthetic because they are cemented only to the lingual or palatal surfaces of the teeth. They do not fix all the teeth in the arch as a whole and this contributes to the formation of interdigitation by allowing physiological tooth movements (Sadowsky et al., 1997; Zachrisson 2015). The biggest disadvantage of fixed lingual wires is that the intraoral procedure takes time and requires precision. Some researchers argue that these wires increase plaque accumulation and should only be applied in people who do not have periodontal problems (Heier et al., 1997; Atack et al., 2007). However, some researchers have reported the use of these wires as an advantage due to their periodontal splint function in patients with periodontal problems (Dahl and Zachrisson 1991).

The most common failure of retainer wires is the separation of the wire from the tooth surface. This situation is generally observed between the first 3-6 months after cementation (Iliadi et al., 2015). During the cementation of the retainer wire, failure to provide insulation, less composite application, and moving the retainer wire cause the retainer wire to separate from the tooth surface, and stress fractures can also be seen in the wire (Zachrisson 2007).

3. Auxiliary Methods That Contribute To Retention

3.1. Overcorrection

It is thought that possible relapse can be tolerated by overcorrection during orthodontic treatment (Van Leeuwen et al., 2003). Correction of rotations by overcorrection is an example of overcorrection since periodontal fiber tension in the derotation of rotated teeth increases the likelihood of relapse (Reitan 1967; Surbeck et al., 1998).

3.2. Interproximal Reduction

With the interproximal reduction process, which is the abrasion process made from the mesial and distal enamel surfaces of the teeth, the point tooth contacts are turned into superficial large contact areas. This process helps retention by contributing to compensation for the loss of arc length that may occur over time (Boese 1980). It is recommended that the stripping process, which is applied as an alternative to the retention treatment, should be performed in 3 stages: The first abrasion should be applied immediately after the lower incisor leveling, the second abrasion should be applied immediately after the removal of the brackets, and the third abrasion should be applied by adjusting the timing according to the amount of mandible growth and the change in the lower anterior arch form (Boese 1980).

3.3. Fiberotomy

Although it is said in the literature that the periodontal fibers adapt to their new positions after 232 days, Retain applied rotational movements on animals and revealed that the free gingival fibers remained in tension even after 232 days of reinforcing treatment. In this study, the researcher stated that the tendency to relapse of rotated teeth arises as a result of the tension of the fibrils and that surgical cutting of the fibrils will eliminate the possibility of relapse (Reitan 1959). The fiberotomy procedure, which was introduced by Edward in 1970 and named as 'circumferential supracrestal fiberotomy' by Campbell et al., is the process of cutting inter gingival, transseptal, transgingival and semicircular fibers by placing a scalpel blade in the gingival groove and is performed at the end of the treatment (Edward 1970; Campbell et al. al., 1975). Fiberotomy is indicated in the moderately and heavily rotated teeth with severe crowding and is contraindicated in patients with poor oral hygiene with high bacterial plaque involvement, chronic gingivitis, chronic periodontitis, and patients with less attached gingiva (Kahl-Nieke 1996).

3.4. Frenectomy

Frenectomy is a surgical procedure that involves reshaping the gingival papilla, in which the labial frenulum is positioned apically. Frenectomy, which is applied to preserve the condition obtained after the closure of the maxillary median diastema and to prevent the reopening of the cavity, is a very effective procedure (Edwards 1977; Sullivan et al., 1996).

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4. Conclusion

With orthodontic treatment, it is aimed to provide an ideal function and aesthetics by rearranging the dental and skeletal structures that have deviated from the ideal. Maintaining this ideal situation is as important as reaching the ideal situation. Ensuring this continuity is possible with a well-planned retention treatment. Therefore, retention treatment is as important as active treatment. While evaluating the case to be treated, the retention treatment to be applied when the active treatment is finished should be planned. Since it is unpredictable which case will relapse, each case should be treated as if it has a potential for relapse. Minimizing the potential for relapse is possible by planning the appropriate retention treatment, as well as using the retention appliances as described by the patient's physician. In this respect, it is very important for the physician to inform the patient about the importance of retention treatment and their responsibilities in this regard, as well as plan the correct retention protocol.

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CHAPTER
3

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A GENETIC OVERVIEW OF TEMPOROMANDIBULAR DISORDERS

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Introduction

The temporomandibular joint (TMJ) is a complex joint of the human body that has a role in its functions, including chewing, speaking, and swallowing. These joints connect the mandible to the skull via ligaments, muscles, and ligaments. The TMJ consists of an articular disc in the articular cavity, the glenoid fossa of the temporal bone, and the mandibular condyle. The joint cavity is filled with synovial fluid. TMJ is a unique joint in terms of its structure. It is unique because it provides two main movements for one mandibular condyle. It is important for opening and closing the mouth and chewing (1). Because the TMJ is structurally and functionally different from other joints, it is susceptible to being affected (2). Temporomandibular disorders (TMDs) are a broad term that includes the jaw muscles and/or other appendages (3)**.** It is the most common cause of extra-dental pain. Findings range from mild discomfort to limitations in jaw function. TMD is a complex and multifactorial disease to which many factors contribute. The multifactorial feature of TMD suggests that different genetic loci may be involved in its development and course, contributing to minor effects and interacting with environmental exposures that may determine its course. This review will detail various aspects of TMD, including its genetic mechanisms.

Epidemiology

TMD is a disease that negatively affects the quality of life. It has been estimated that every 100 million working adults in the United States cause 17.8 million annual losses due to TMD (4). It has been shown that the average health expenditures of TMD patients are 1.6 times higher than those of those without TMD

(5). The prevalence of TMD, which is a common disease, is quite high at 31% in adults and 11% in children (6). TMD is approximately 1.5 times more common in women than men (7). The onset of TMD is between the ages of 18 and 44 (7).

Etiology

The causes of TMDs are complex and multifactorial. Etiology includes biological, environmental, social, emotional, and cognitive factors. Psychological factors as well as causes such as malocclusion and trauma have been blamed for the etiology of TMD (8). Identification of etiological factors is important for treatment selection in TMD (9).

TMD Genetics

Due to the multifactorial nature of TMD formation, genetic risk factors have been the subject of research. There are many differences in pain sensitivity among individuals. About half of the difference can be explained by genetic influences (10). In addition, psychosocial factors that modulate pain sensitivity are also genetically involved (11). Some of the previous studies on TMD showed that there was no significant difference in the prevalence of myofascial pain in monozygotic and dizygotic twins (12). But Plesh et al. stated that TMD is hereditary with a 27% probability for twin siblings (13). In many studies, such as the Orofacial Pain Prospective Evaluation and Risk Assessment Study (OPPERA) conducted for this purpose, it has been shown that single nucleotide polymorphisms have an effect on the biological pathways of pain perception (14).

Single nucleotide polymorphisms

Mutation, which is one of the types of genetic variation, characterizes variants that occur in less than 1% of the population. The more common polymorphisms are single nucleotide polymorphisms (SNPs), occurring in more than 1% of the population (15). At the DNA level, polymorphism can be a single base pair change or it can consist of multiple fused pairs and frequent sequences. SNPs may exert functional effects on disease-associated genes. The introduction of technologies such as microarray-based genotyping and next-generation sequencing has provided new methods for examining genetic variants (16). Genetic variants are important for understanding the pathogenesis of diseases, response to

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treatment, and, as a result, individual medicine. There are many polymorphisms that have been shown to be associated with TMD in studies.

Genetic Polymorphisms in TMD

Adrenergic receptor beta 2 gene polymorphisms

β2-Adrenergic receptors (ADRB2) are superfamily members of G protein-coupled receptors. ADRB2 regulates smooth muscle relaxation by mediating catecholamine-induced activation of the adenylate cyclase signaling cascade (17). When variants that affect these gene-mediated responses are combined with environmental factors, they may predispose to TMD pain. ADRβ2 functional differences have been associated with psychiatric and psychological disorders (18). The human ADRβ2 gene is located on chromosome 5q31-32 (19). There are several polymorphisms in this gene. If TMD pain is associated with hyperfunction of the ADRβ2 gene, an ADRβ2 antagonist may be useful in the treatment of the majority of these patients (20). The ADRB2 (rs1042713) variant AA genotype was associated with the absence of myofascial pain (21).

Estrogen Receptor 1 α

Estrogen, which regulates various physiological functions such as cell growth, reproduction, differentiation, and development, is a steroid hormone. It acts on estrogen receptors (ER) and the peripheral and central nervous systems (CNS) for their functions such as inflammation and central pain pathways (22). Estrogen also regulates the production of proinflammatory cytokines in monocytes and macrophages, such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) (23). Landi et al. showed that men and women with TMD who are in the luteal phase of the menstrual cycle have higher serum estradiol levels than healthy controls (24). The ER encoded by the ESR1 gene has been reported to be associated with TMD (25). ER-a is found in intracellular cartilage tissue, intra-articular osteocytes, and mandibular condylar fibrocartilage (26).

Serotonin transporter gene

TMD often accompanies other conditions with psychosomatic symptoms such as sleep disturbance, headache, fatigue, and depression (27). Study results also show that besides TMD, conditions such as irritable bowel syndrome and fibromyalgia are dysfunctional in their pain and sensory processing systems. One of the

neurotransmitters associated with TMD pain is serotonin (5-hydroxytryptamine, 5-HT). Clinical and animal studies have shown that serotonin and noradrenaline reuptake inhibitors are beneficial for the treatment of fibromyalgia (28). Polymorphisms in 5-HT-related genes may be associated with 5-HT neuronal dysfunction. The human serotonin transporter gene (5-HTT) is found on chromosome 17q11.1-q12.1. It regulates 5-HT activities. There is a 44-bp insertion/deletion polymorphism known as 5HTTLPR in the 5-HTT gene. It has two forms, the long allele (L) and the short allele (S). The short allele has lower transcriptional activity than the long allele (29). 5HTTLPR genotypes were associated with different serotonin uptake rates in lymphoblastoid cell cultures (29). In a study investigating the relationship between TMD myalgia and 5-HTT gene polymorphisms, it was determined that TMD patients had more long alleles (30). The higher transcriptional activity of this allele may result in a lower concentration of 5-HT in the extracellular space. However, in a study conducted on the Syrian population, no relationship was found between polymorphism in the promotor region of the 5-HTT gene and TMD risk (31). Another polymorphism associated with serotonin activity is a polymorphism of the serotonin receptor 2A in T102C. Those with the homozygous C allele have been shown to be at increased risk of developing TMD with the homozygous T allele (32).

Catecholamine-O-methyltransferase gene

The difference in pain in patients with TMD is a subject that has been extensively studied (33). Although genetic and environmental factors have an effect on pain perception, their mechanisms are not completely clear. The heritability of nociceptive and analgesic sensitivities in mice is estimated to be 28%- 75% (34). It has been reported that catecholamine-O-methyltransferase (COMT) gene polymorphisms lead to differences in TMD pain perception. COMT is an enzyme that metabolizes catecholamines (35). Abnormalities in catecholamine physiology are associated with decreased COMT activity. This leads to elevations in catecholamines that induce persistent pain (36). The COMT gene is localized at 22q11.21. The gene encodes two forms of the enzyme, membrane-bound and soluble COMT. The association of six SNPs in the COMT gene, which is common in the human population, with pain in TMD was investigated. Michelotti et al. reported that COMT rs 165656 and rs 4646310 variants were associated with TMD in Italian patients (37). In a different study, the rs165774 A/A genotype and A allele carriers were found to be associated with increased TMD risk compared to the G/G genotype (38).

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Tumor necrosis factor-alpha

It has been reported that pro-inflammatory cytokines are higher in the serum of patients with TMD compared to healthy controls (39). TNF-α (tumor necrosis factor-alpha) is an important immune regulatory cytokine (located at 6 p21.31). TNF-α stimulates a variety of other cytokines, mediating the inflammatory cytokine cascade (40, 41). In the event of infection or injury, immune and non-immune cells, as well as trigeminal ganglion-associated neurons, release TNF-α into the TMJ. This cytokine causes inflammation and pain in TMJ patients (42). TNF-α is thought to play a role in the development of TMD by stimulating joint inflammation due to its multifaceted effect. This leads to an increase in pain perception around the trigeminal ganglion and degeneration of the TMJ in cartilage and bone tissue (43). TNF-α inhibitors improve physical function by decreasing the likelihood of joint damage. For this reason, it is used in patients with rheumatoid arthritis, which causes chronic pain and joint pain, including TMJ pain (44). In a study evaluating data from six studies, the majority of TMD patients were found to be women (44). They discovered that the TNF- α 308G/A A allele and the A/A genotype are associated with increased TNF-α levels (45).

Vitamin D receptor

Vitamin D, a steroid prohormone, is an essential fat-soluble vitamin for the body. It is important for the musculoskeletal and cardiovascular systems, as well as for calcium and phosphate metabolism and for maintaining blood levels of these minerals (46). According to the results of a systematic review, serum vitamin D levels may be generally lower in patients with TMD (47). The same result was obtained in another study (48). Vitamin D synthesized in the skin is converted to its active form in two stages and binds to the vitamin D receptor (VDR) (49). Multiple allelic variants are found at the *VDR* gene locus, located at 12q13.11. Some studies have shown that *VDR* polymorphisms are associated with osteoarthritis (50), and osteophytosis of the lumbar spine (51). Therefore, the relationship between VDR polymorphisms and TMD has also come to the fore. In our previous study, we also found that serious vitamin D deficiency was more prevalent in the TMD patients than the controls (52). In addition, the carriers of the VDR Bsml variant bb genotype and b allele had an increased risk of disc displacement in TMD patients.

Conclusion

TMD is a common orofacial pain state originating outside the tooth. TMD symptoms have a negative impact on patients' quality of life. Being multifactorial, genetic factors play a role in the formation of TMD. Genetic polymorphisms and genetic mutations may lead to a change in activity in TMJ inflammation. The elucidation of the molecular structure of TMD will lead to the introduction of new treatment options.

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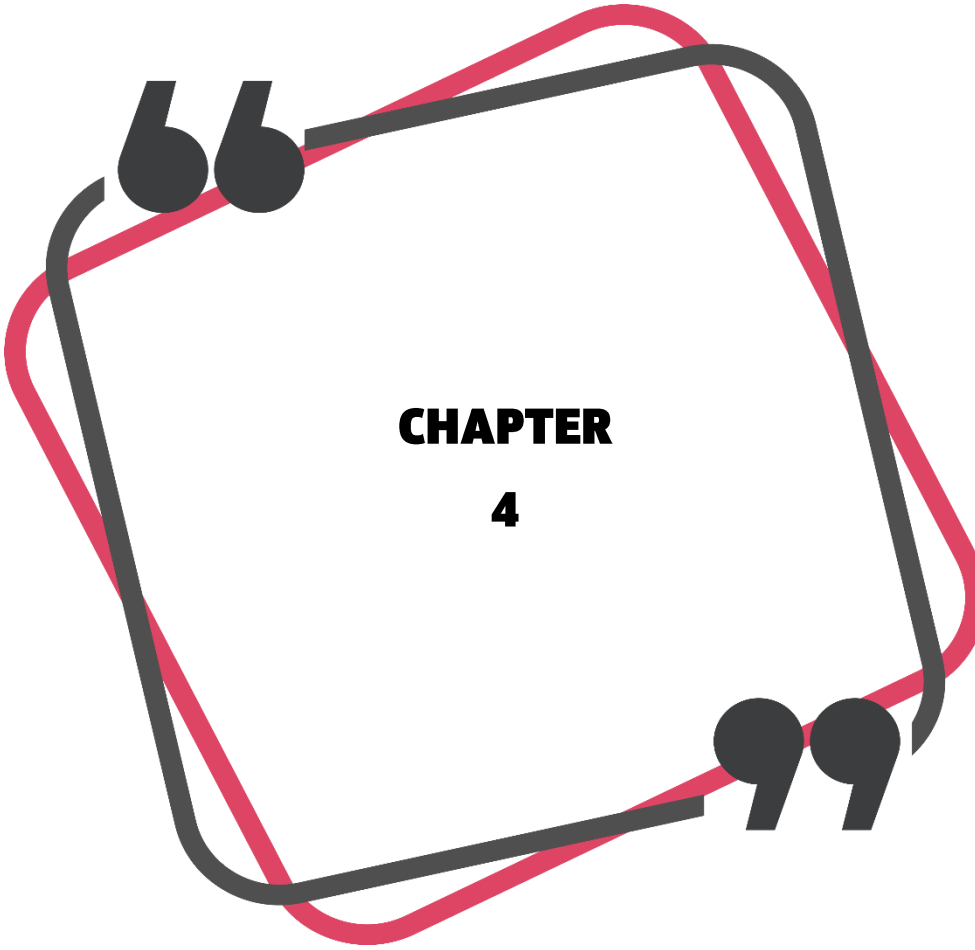
CHAPTER
4

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ALVEOLAR BONE RESORPTION

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Alveolar bone resorption (ABR) refers to alterations in the alveolar crest that occur after tooth removal and continue long after the extraction cavity has recovered. One of most crucial aspect of this process of recovery is the residual bone architecture of the maxilla and mandibula undergoes remodeling throughout the rest of patient's life (Virdi, M. (Ed.), 2012). It is a continuous, gradual, and irreversible process. The rate of decrease of the alveolar crest is greatest in the first 3 months and thereafter gradually slows down (Winkler, 2002).

Bone loss process persists at a lesser rate throughout life, leading in the loss of different amounts of jaw tissue and eventually the patient becomes a 'dental cripple' (Virdi, M. (Ed.), 2012). Residual crest height decrease throughout the course of the individual's life, this reduction occurs at various rates in different patients and even at different periods in the same patient. Bone loss in the eden-

tulous ridge develops with or without dentures and is caused by a variety of interrelated factors specific to the individual patient (Atwood, 1962). The ongoing process of reducing remaining ridges following tooth extraction establishes a dynamic basis for implant placement and prosthetic tooth replacement (Winkler, 2002).

Residual alveolar ridge remodelling

A cascade of inflammatory mediators is activated immediately after tooth extraction, resulting in the creation of a blood clot, which is the initial stage in the ultimate closure of the extraction site. The clot then organizes and eventually is replaced by granulation tissue towards the alveolar socket's periphery and base. New bone development is visible after seven to ten days, with osteoid matrix appearing as non-calcified bone spicules. Mineralization proceeds coronally from the alveolar socket base, and two-thirds of the socket is filled in 5 to 6 weeks (D'Souza, 2012). The ensuing bone rebuilding happens in two stages: an early and somewhat rapid phase that may be seen in the first three months, and a later gradual, moderate yet constant resorption that lasts a lifetime. During the first stage, new bone production occurs, with loss of the alveolar crest height and nearly two-thirds of the ridge width reduced, these alterations persist during the first ten to twelve weeks (Kreisler, Behneke, Behneke, Hoedt, 2003). Studies showed that the resorption, 3-7 months after extraction, in the buccal/lingual sites was (0.9-3.6 mm) whereas in the mesial/distal sites was (0.4–0.5 mm). Mesial/distal bone levels are maintained by the existence of adjacent teeth, which is one explanation for this pattern (Baron, Aldini, Fini, Giardino, Calvo Guirado, & Covani, 2008; Aimetti, Romano, Griga, & Godio, 2009).

When the vertical dimensional variations at the buccal and lingual bone walls were measured, 3–7 months after extraction the buccal plate resorption (0.9-3.6 mm) was larger than the lingual plate resorption (0.4–3 mm). The bundle bone idea can explain this pattern of resorption (Iasella et al., 2003; Barone et al., 2008; Aimetti et al., 2009). The buccal plate's vertical bone wall height resorption ranged from 11- 22% six months after extraction (Lekovic, Kenney, Weinlaender, Han, Klokkevold, Nedic, & Orsini, 1997; Camargo, Lekovic, Weinlaender, Klokkevold, Kenney, Dimitrijevic et al., 2000; Pelegrine, da Costa, Correa, & Marques, 2010).

While the horizontal bone loss was a range of (2.46-4.56 mm) after 6 months, investigations only offered information about horizontal resorption at the alveolar crest level; no information was available regarding the degree of horizontal bone

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loss at a distance from the alveolar crest (Lekovic, Kenney, Weinlaender, Han, Klokkevold, Nedic, & Orsini, 1997; Iasella, Greenwell, Miller, Hill, Drisko, Bohra, & Scheetz, 2003; Pelegrine, da Costa, Correa, & Marques, 2010). According to Kerr et al., a relative decrease in horizontal ridge reduction was observed, which showed most bone loss was at the coronal third and least bone loss at the apical third of the alveolar ridge (Kerr, Mealey, Noujeim, Lasho, Nummikoski, & Mellonig, 2008).

At three months, there was a 32% drop, and at six months, the horizontal dimension had decreased by 29-63%. This showed that the ridge width may resorb to at least 50% of its original width after six months. All studies point to tissue loss being more significant on the buccal wall than from the lingual or palatal wall (Araujo & Lindhe, 2005; Baron, Aldini, Fini, Giardino, Calvo Guirado, & Covani, 2008; Schropp, Wenzel, Kostopoulos, & Karring, 2003). Between six and twelve months, a portion of the new bone undergoes further remodeling, resulting in a further decrease of the alveolar ridge width to about half. The pace of resorption then reduces to the minor stages, however, because it occurs throughout a person's life, there is a large drop in bone volume noted in elderly people (D'Souza, 2012; Cawood & Howell, 1988).

Factors affecting resorption of the residual alveolar ridge

It has been proposed four major aspects that contribute to alveolar bone loss: anatomic, prosthetic, metabolic, and functional factors (Atwood, 1971; Kelly, E., 1972). Numerous researchers have attempted to analyze changes in the morphology of the remaining alveolar ridge utilizing lateral cephalograms, panoramic radiographs or diagnostic casts as standardized measures since then (Campbell, 1960).

There are many mechanisms influencing alveolar bone resorption;

1- Localised mechanical stress

It has been clinically demonstrated that the use of improper removal denture cause localized mechanical stress on the residual bone affects the rate of alveolar bone loss. (Nishimura, Hosokawa, Atwood, 1992; Kribbs, 1990).

2- The anatomical considerations

The residual crest's size and shape have a significant impact on bone resorption since the well-formed broad ridges exhibit less resorption than the narrow ridges do, because the broad ridge receives less force per unit area. Furthermore,

the bone types have a significant impact on the rate of bone resorption (Atwood, 1962).

3- Stress and strain effect

The force exerted on the bone influences its remodeling, which can be caused by habits as parafunctions such as bruxism (Atwood and Coy, 1971); and prosthesis misuse including wearing removable dentures constantly, having an unstable occlusion, immediate denture and using dentures that aren't properly made. Patients with complete dentures had more mandibular resorption than maxillary resorption (Campbell, 1960; Feng X McDonald and Jay 2011; Kirby, Meghji, Nair, White, Reddi, Nishihara et al., 1995).

4- Periodontal disease

Periodontal disease is the term used to describe the inflammatory reactions to bacterial buildups or dental plaque on the teeth, that take place in the structures around the teeth. The bacterial buildups trigger the body's inflammatory reaction. The breakdown of alveolar ridge and loss of tissue attachment to the teeth are caused by a persistent and progressive bacterial infection (Shanb, Youssef, 2014).

5- Metabolic and systemic factors

Post-menopausal osteoporosis has been found to have a connection with alveolar bone resorption (Atwood, 1971; Carlsson, 2004). The inability of post-menopausal older women to form new bone tissue is linked to a decrease in estrogen, which explains their much higher rate of bone resorption (Shanb, Youssef, 2014). Despite the fact that in those circumstances, the rate of bone loss can be controlled by treating the reasons with medications that raise bone mineral density such as bisphosphonates, RANKL inhibitors, SERMs-selective, estrogen receptor modulators, hormone replacement therapy and calcitonin (Yeh & Rodan, 1984). Furthermore, light weight bearing exercise has been shown to reduce the detrimental consequences of bone resorption (Wical and Swoope, 1974).

Because alveolar bone resorption has such a wide range of clinical manifestations, it is reasonable to believe that several factors all play a role in determining the ultimate rate and extent of bone loss in an individual (Atwood, 1971). Age, race, the existence of systemic disorders such as osteoporosis, dietary condition (particularly calcium and vitamin D) (Tallgren, 1972) and the length of time the patient has been edentulous all have a significant impact on the rate of bone resorption (Atwood and Coy, 1971).

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6- Inflammatory mediators' role:

Many researchers believe that certain inflammatory mediators, prostaglandins, have a role in increasing the rate of residual ridge resorption. Yeh and Rodan (1984) discovered that when osteoblastic cells were exposed to recurrent mechanical stressors in vitro, prostaglandin E2 production increased significantly.

Anatomic Consequences of Edentulism

Throughout life, there is an intimate association between the tooth and the alveolar bone. According to Wolff's law, bone changes in response to applied pressure. When the function of bone is altered, the internal architecture and exterior configuration undergo significant change (Murray, & Drachman, 1969; Wolff, 1986).

Bone requires stimulation to keep its shape and density (Roberts, Turley, Brezniak, 1987). According to Roberts and colleagues, a 4% pressure to the skeletal structure conserves bone and keep the appropriate balance between the processes of bone's loss and formation. Compressive and tensile pressures are transmitted to the surrounding bone by teeth. After a tooth removal, the absence of stimulation to the leftover bone produces a reduction in trabeculae and bone volume in the region, resulting in a loss of exterior width and subsequently height of the bone mass (Roberts, Turley, Brezniak, 1987).

There is a 25% drop in bone width and a 4 mm decrease in height during the first year after extractions for an immediate denture. In a 25-year research, continuous bone loss was discovered; when the bone loss of the maxilla was compared to the mandible, the mandible had a fourfold larger loss (Tallgren, 1966).

Prostheses lead to bone loss as well as removable dentures accelerate bone resorption rather than stimulating and maintaining bone. Masticatory force is transmitted to the bone surface, not the entire bone, decreased blood flow and overall bone mass loss consequently. This crucial problem has been noticed, but conventional dentistry hasn't addressed it till lately. When a patient wears a poorly fitted prosthetic, bone loss increases (Marcus, Joshi, Jones & Morgano, 1996).

Alveolar bone is not the only part of bone that can resorb in the upper or lower jaw; the basal bone can also do, particularly in the posterior part of the lower jaw where excessive resorption can be seen (Gruber, Solar, Ulm, 1996).

Classification of edentulous ridge

An edentulous ridge classification is crucial because it makes describing the remaining alveolar ridge easier and improves assist communication between clinicians; help choosing the best surgical prosthetic approach; provide a neutral starting point from which to assess and analyze various treatment modalities and aid in selecting interceptive measures to protect the alveolar process (Cawood & Howell, 1988).

Cawood et al, 1988, conducted a randomised cross-sectional investigation that resulted in the development of an edentulous jaw classification (Figure 1-4). They created a diagnostic classification of these modifications after observing variations in the upper and lower residual processes' form:

Type I: Dentate

Type II: Just after extraction.

Type III: Appropriate in height and width, with a perfectly rounded crest form.

Type IV: Knife-edge crest shape, acceptable in height but insufficient in width.

Type V: Flat crest shape, insufficient hight and width.

Type VI: Depressed crest shape with partial basilar loss.

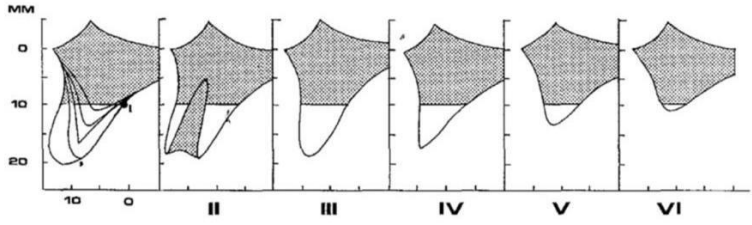

Figure 1: Classification of anterior maxilla

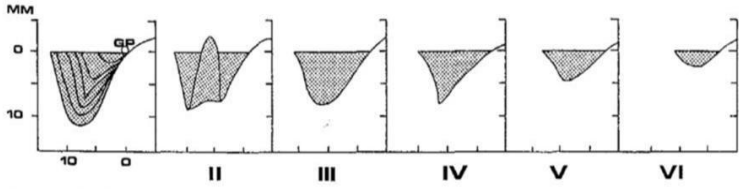

Figure2: Classification of posterior maxilla

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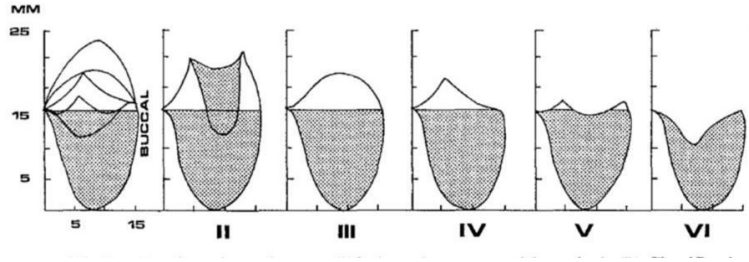

Figure 3: Classification of anterior mandible

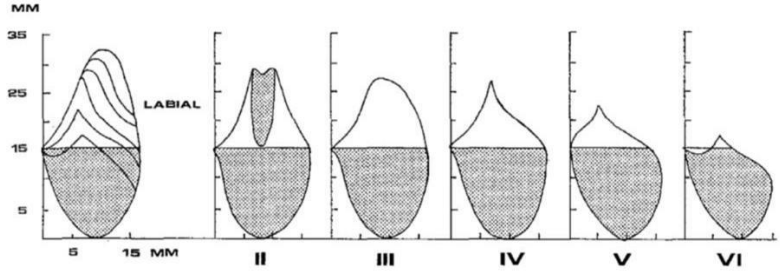

Figure 4: Classification of posterior mandible

They also discovered that the basal bone's form does not dramatically change, unless it is exposed to adverse local influence, as the overloading of poor fitting dentures. Additionally, the alveolar bone exhibits a consistent pattern of considerable form change along both the horizontal and vertical sides (Schropp, Wenzel, Kostopoulos & Karring, 2003)

Evaluation of alveolar bone resorption

Many scholars evaluated the alterations in the remaining alveolar bone's shape with various techniques, including lateral cephalograms, orthopantomograms radiographic, diagnostic molds as standardized assessments.

The method utilized to measure bone resorption was orthopantomograms. This sort of image is prone to magnification and distortion changes, but these issues were minimized once we knew how magnification-level our orthopantomogram was at (Kreisler , Behneke , Behneke , d´Hoedt, 2003).

Because it has confirmed a minimum of distortion and overlapping, and because the measurements it displays are consistent with the actual size, CBCT is used to detect bone loss (Acar ,Kamburoglu, 2014).

Additionally, CBCT provided 3D views that are required for the diagnosis of bone deformities, tumors, width bone resorption, etc. All CBCT devices offer axial, coronal, and sagittal multi-sections views without distortion (de Faria Vasconcelos, Evangelista, Rodrigues, Estrela, de Sousa, Silva, 2012).

It has been noticed that the lower jaw's mean loss in ridge height was double compared to the upper jaw after one year of tooth removal. Mandibular ridge is more likely than the maxillary ridge to sustain larger functional stresses transferred through the dentures. Furthermore, the mandible has a reduced surface area and the lower basal seat has a less favorable form (Lammie, 1956; Tallgren, 1967).

Maxillomandibular resorption patterns

1) Maxillary Arch:

With gradual bone resorption, the upper front ridge resorbs upward and backward. The ridge at the front nasal spine, conversely, remains generally stable. The upper posterior crest resorbs upward and inward, gradually diminishing. The incisive papilla is a crucial anatomical point. It can serve as a guideline for proper positioning of the central incisors in the edentulous upper ridge. The incisive papilla is unaffected by crest resorption and maintains a rather stable location on the upper edentulous arch. Typically, the natural incisors are 8 to 10 mm anterior to the incisive papilla (Landa, 1973).

Inadequate bone mass may cause incorrect implant angulation or even obstruct implant insertion (Dietrich, Lippold, Dirmeier, Beneke, & Wagner, 1993; Buser, Brägger, Lang, Nyman, 1990). The safe and accurate placement of implants may be hindered by bone loss in edentulous patients. Sometimes there isn't enough bone to firmly anchor the implants in place (Cordaro, Amadè, & Cordaro, 2002). Alveolar rebuilding is necessary in these situations because a sufficient amount of bone mass is required to ensure long-term stability of the implant. Sometimes, implant insertion without grafting techniques results in a rehabilitation that is less aesthetic because of the increased inter-arch space or the unfavorable location and angulation of the implants (van Steenberghe, Naert, Bossuyt, De Mars, Calberson, Ghyselen, & Brånemark, 1997).

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Rehabilitation of the edentulous maxilla with implants is frequently hampered by poor bone quality and quantity. Restoring bone volume and ridge shape and height for implant insertion is possible by surgical ridge augmentation (Atwood, 2001). Several grafting techniques have been documented to generate enough bone volume for implant insertion in atrophic maxilla, including bone onlays, Le Fort I osteotomy with interpositional bone grafts, and maxillary sinus lifting (Buser, Dula, Hirt, & Schenk, 1996; Mellonig & Nevins, 1995).

2) Mandibular Arch:

The front ridge of the mandible resorbs downward and forward. Unlike the maxilla, the mandibular posterior ridge resorbs downward and outward, becoming increasingly broader. The highest point on the lower crest becomes associated with the genial tubercles when there is extensive resorption in the lower alveolar bone (Winkler, 2002).

Alveolar ridge abnormalities can be caused by trauma, developmental problems, tooth extraction with preexisting periodontal disease, tooth extraction followed by bone resorption, these abnormalities may lead to inadequate bone mass for dental implant insertion and poor aesthetics (Buser, Brägger, Lang, & Nyman, 1990). Prosthetic teeth are often positioned incorrectly, the achieving of esthetics is challenging, since natural teeth have never filled these areas (Buser, Dula, Hirt, Schenk, 1886). The interarch space increases as bone loss advances. This increase will necessitate further augmentation, grafting, or both before implants are inserted. Inadequate site development can lead to unfavorable crown/root ratios, which can affect implant success (Allen, Gainza, Farthing, & Newbold, 1985; Mellonig JT, Nevin, 1995). Successful implants can be created if the prosthetic teeth are positioned in the same location of the lost natural teeth. So to perform successful implant placement, the clinician needs to be aware of how natural teeth relate to the alveolar ridge and the processes of resorption after teeth loss (Frank Feuille, Knapp, Brunsvold, & Mellonig, 2003).

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CHAPTER
5

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PAIN AND DENTAL ANXIETY

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Fear of dentistry is a widespread issue that may be upsetting for both the public and the dentists (Newton & Buck, 2000). Dentists and dental practitioners should be aware that the patients can have preconceptions and worries, and they should offer high-quality medical care to help them feel less anxious (Panda, Garg, & Shah, 2015). People who are anxious often exaggerate the severity of unpleasant emotions like hesitation and discomfort. Prediction is based on experience and may be less prone to bias because of worry when an adverse event has been directly experienced (van Wijk and Hoogstraten, 2005). A vicious cycle of worry, panic of ache, and delaying treatment is more likely to occur in persons who are inclined to react fearfully to pain (van Wijk and Hoogstraten, 2005).

Pain

Pain is an uncomfortable sensory and emotional experience associated with actual or potential tissue injury. It is the most typical symptom of disease or injury that prompts individuals to seek guidance and treatment from medical and dental professionals. It has a profound impact on many aspects and due to how frequently it occurs it is a significant health issue and financial problem (Bonica, 1983).

For the patient, pain in the face and mouth has unique emotional, biological, and psychological significance. In addition, the most common pain in the body is probably acute orofacial pain, which frequently accompanying with acute pathologic conditions in teeth and related structures. Furthermore, referred and chronic pains are frequently felt in maxilofacial area (Sessle, 1987).

Dental pain

The teeth contain a unique sensory nervous mechanism by which they recognize sensations in pathological circumstances. Additionally, dental neurological cells may have other characteristics that set them apart from other bodily tissues.

There are 3 mechanisms have been proposed to explain dental pain:

(1) The neural theory suggests that pain receptors in the dentin immediately react to outside stimulus; noxious temperatures are directly transmitted by teeth afferent fibers.

(2) The hydrodynamic theory, according to which nerve terminals close to the dentin can sense fluid movement within the dentinal tubules; and

(3) The odontoblast transducer theory, according to which odontoblasts could act as pain receptors.

The central nervous system receives oral nociception as a result of the activation of dental primary afferents. In each one of assumed mechanisms, the central nervous system receives oral pain sensation as a result of the stimulation of teeth afferent neurons. The neuroanatomical characteristics of nerve terminals and dental pain receptors, as well as the cellular and molecular mechanisms underlying dental nociception, have undergone tremendous advancement in recent decades. A deeper comprehension of the molecular mechanisms behind dental pain would extremely boost the progress of medicines which focus on toothaches (Chung, Jung & Oh, S. B, 2013).

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Pain in temporomandibular disorders (TMD)

Peripheral mechanisms, which may be triggered by excessive temporomandibular joint (TMJ) loading, produce pain by mechanically stimulating nociceptors, upregulating the release of neuropeptides and inflammatory mediators, and/or inducing local hypoxia (Cairns, 2010).

Degenerative alterations to the joint are frequently accompanied by severe pain and dysfunction; some patients with no discomfort will have a considerable anterior disc displacement, whilst other patients with severe pain will not show any signs of degenerative change (Tanaka, Detamore & Mercuri, 2008)

Painful TMJs may cause central nervous system neurons to become more sensitive over time, which lowers TMJ pain thresholds and may also provide a neurological mechanism for the emergence of pain and increased sensitivity to pain in people with TMD (Campi, Jordani, P, Tenan, Camparis & Gonçalves, 2017)

Pain in the TMJ also seems to make the defensive reflexes of the jaw muscles stronger (Furquim, Flamengui & Conti, 2015).

Assessment of pain

It is impossible to accurately determine the pain felt by an individual. Since pain is a complex phenomenon and a personal experience, it can only be evaluated indirectly. For this reason, different methods have been developed for the evaluation of the pain (Güzeldemir, 1995; Eti-Aslan, 2002).

Pain assessment methods with subjective criteria

Single criteria :

Visual Analogue Scale (VAS), Verbal Descriptor Scales (VDS), Face Expression Scale (FS), Numerical Rating Scale (NRS), Simple Word Scale, Dermatomal Pain Drawing, Analogue Chromatic Continuous Scale (ACCS), Card Classification Methods (Keele, 1948; Güzeldemir, 1995; Xavier, Torres & Rocha, 2006; Breivik, Borchgrevink, Allen, Rosseland, Romundstad, Breivik Hals, Kvarstein & Stubhaug, 2008; Cordts, Grant, Brandt & Mears, 2011).

Multiple criteria :

Dartmounth Pain Questionnaire (DPQ), McGill Pain Questionnaire (MPQ), Haven-Yale multidimensional pain chart; (West Haven-Yale Multidimensional Pain Inventory; WHYMPI), Reminder pain assessment card (Memorial Pain Assesment Card), Pain perception profile (PPP), Countermethod comparison

(Cross-Modalify Matching; CMM), Short pain chart(Wisconsin Brief Pain Inventory; BPI) (Keele, 1948; Güzeldemir, 1995; Xavier, Torres & Rocha, 2006; Breivik, Borchgrevink, Allen, Rosseland, Romundstad, Breivik Hals, Kvarstein & Stubhaug, 2008; Cordts, Grant, Brandt & Mears, 2011).

Objective criteria pain assessment methods

Behavioral and electroencephalographic evaluations, physiological, biochemical and neurological measurements, neuropharmacological methods (Keele, 1948; Güzeldemir, 1995; Xavier, Torres & Rocha, 2006; Breivik, Borchgrevink, Allen, Rosseland, Romundstad, Breivik Hals, Kvarstein & Stubhaug, 2008; Cordts, Grant, Brandt & Mears, 2011).

Visual Analogue Scale (VAS)

It is a straight line, mostly 10 cm long, with horizontal and vertical lines, starting with "No Pain" and ending with "Unbearable Pain" (Figure 1). Graphic Evaluation Scale; It is the split version of the VAS and the identification words. The graphic evaluation scale is not much preferred (Clarke & Spear, 1964; Güzeldemir, 1995; Xavier, Torres & Rocha, 2006; Breivik, Borchgrevink, Allen, Rosseland, Romundstad, Breivik Hals, Kvarstein & Stubhaug, 2008; Cordts, Grant, Brandt & Mears, 2011).

How to fill out a VAS should be explained very well to the patient. The patient determines the severity of the pain by marking the appropriate place on this line. The distance between the onset of no pain and this point is measured as “cm” and the values are recorded. The accuracy of the VAS is difficult to prove (Clarke & Spear, 1964; Güzeldemir, 1995; Xavier, Torres & Rocha, 2006; Breivik, Borchgrevink, Allen, Rosseland, Romundstad, Breivik Hals, Kvarstein & Stubhaug, 2008; Cordts, Grant, Brandt & Mears, 2011).

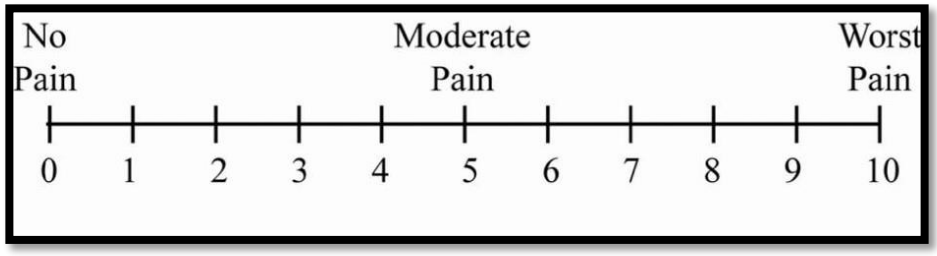

Figure1: Visual Analogue Scale (VAS)

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Advantages of VAS:

One of the most commonly used methods in the evaluation of pain is VAS (Isik, Unsal, Kalayci & Durmus, 2011; Özveri Koyuncu, Zeytinoğlu & Çetingül, 2013).

- As a result of comparisons with other methods in the evaluation of pain severity, it has been seen that VAS has sufficient effectiveness.
- It has been stated that VAS is an easy-to-understand and easy-to-apply method by individuals over the age of 5 years.
- Evaluations with VAS allow statistical analysis.
- Compared with the verbal pain rating, it has been shown to have sufficient sensitivity in the assessment of treatment effects.
- The measurement is repeatable.
- It has been a successful evaluation method for treatment outcomes in many studies (Clarke & Spear, 1964; Güzeldemir, 1995; Xavier, Torres & Rocha, 2006; Breivik, Borchgrevink, Allen, Rosseland, Romundstad, Breivik Hals, Kvarstein & Stubhaug, 2008; Cordts, Grant, Brandt & Mears, 2011).

Disadvantages of VAS:

- Markings can be made randomly by patients, which may affect the evaluation results.
- Psychological conditions or incompatibility of patients may prevent the VAS from being reliable.
- When evaluating pain, the time intervals to be evaluated should be well planned. Differences that may occur over time may lead to misconceptions. To avoid this, evaluations should be made at regular intervals.
- Seeing the previous pain value may lead to a different evaluation of pain intensity during the next marking.
- Older patients may have problems with adaptation, coordination and inability to perceive the VAS line (Clarke & Spear, 1964; Güzeldemir, 1995; Xavier, Torres & Rocha, 2006; Breivik, Borchgrevink, Allen, Rosseland, Romundstad, Breivik Hals, Kvarstein & Stubhaug, 2008; Cordts, Grant, Brandt & Mears, 2011).

Anxiety

Anxiety is a feeling of apprehension brought on by the expectation of a threatening event or circumstance (15). Despite all the technical advancements in dentistry, dental anxiety, which is referred to as fear, worry or tension in a dental environment, is a fairly prevalent occurrence and prevents many patients from

receiving the necessary dental care (Appukuttan, 2016; Sadi, Finkelman, & Rosenberg, 2013).

The effect of dental anxiety on the patient's life quality:

Fear of dentists and dentistry is a widespread issue that may be upsetting for both the general public and dentists (Newton & Buck, 2000). The effects of fear and avoidance on patients' oral health are evident. When dental care is put off for a long time, the patient's oral health may undergone in a bad state whereby many interventions are needed including as extractions, endodontic treatment and surgical operations. (De Jongh , Adair, & Meijerink-Anderson, 2005). Many individuals of different ages and socioeconomic levels suffer from dental anxiety, which frequently leads to poor oral health through avoidance of dental therapy, sporadic attendance at dental appointments or uncooperative behavior. (Wardle, 1982; Aartman, 1998; Moore, Birn, Kirkegaard, Brødsgaard & Scheutz, 1993).

Previous studies have demonstrated that dental anxiety is most likely to manifest in childhood and may be brought on by an early negative dental experience or by vicarious learning, in which children are exposed to others' negative personal experiences or stereotypical views about dentistry through family members or peers (Locker, Liddell, Dempster & Shapiro, 1999; Locker, Shapiro & Liddell, 1996; Milsom, Tickle, Humphris & Blinkhorn 2003; Ten Berge, Veerkamp & Hoogstraten, 2002).

Additionally, it's thought that dental anxiety, once it's acquired, can last into adulthood (Locker, Liddell, Dempster & Shapiro, 1999). High dental anxiety in children increases the likelihood of delaying, reschedule or skip appointments, which raises the incidence of oral disease, which can even persist into puberty (Buchannan & Niven, 2002). It can cause people to avoid dental treatment in spite of being in need of it and it prevents people from receiving the proper dental treatment and increases the chance of having poor oral health (Vassend, Willumsen, Hoffart & 2000; Pohjola, Lahti, Vehkalahti, Tolvanen & Hausen, 2007; Eli, Weir, Williams, Roberts & Browne , 2005). Compared to non-anxious patients, individuals had fewer filled teeth and more missing teeth and they were four times more likely to need immediate treatment for pain or a dental infection (Locker & Lidell, 1992). Anxious patients' avoidance of treatment has been associated with a deterioration in their quality of life (Ng SK & Leung, 2008).

The aetiology of dental anxiety depends on the age of onset. Severe dental anxiety is founded on a number of factors, including the effect of the familial and social factors, worry, ache, and negative experiences. The cause is typically a bad

dental experience in childhood, but in adults, general anxiety states are more likely to be to blame. (Locker, Liddell, Dempster & Shapiro, 1999; Bergdahl & Bergdahl, 2003).

Dental anxiety measurement methods:

Utilizing standardized questionnaires, the Anxiety Scale is likely the most popular and widely used for determining the level of dental anxiety (Corah, 1969). Nevertheless, according to the international classification system of psychiatric disorders (DSM-IV), anxiety relating to dental procedures is considered to reach a clinically important level (i.e., specific phobia) when a number of specific diagnostic parameters are met. (De Jongh, Adair & Meijerink-Anderson, 2005). There are numerous distinct assessment techniques available for this purpose (Aartman and Van Everdingen, 1996). Previous longitudinal and experimental research have used measures with appropriate psychometric qualities, such as the Dental Anxiety Scale (DAS)/ Modified Dental Anxiety Scale (MDAS), Children's Fear Survey Schedule-Dental Subscale (CFSS-DS), and Modified Child Dental Anxiety Scale (MCDAS) (Folayan, Ufomata, Adekoya-Sofowora, Otuyemi & Idehen,2003; Hosey, Asbury, Bowman, Millar, Martin, Musiello, et al.,2009;Alexopoulos, Hope, Clark, McHugh and Hosey, 2007).

To empower physicians to make referrals and to allow suppliers to schedule for the individuals with high levels of anxiety referred to secondary healthcare, a valid measurement is wanted at the level of the service organization. However, it should be emphasized that younger children may need assistance in order to understand a few of the elements and forms on tests like the MCDAS and CFSS-DS. Younger patients may benefit with the MCDAS's facial version, while very young children will still require assistance (Porritt, Buchanan, Hall, Gilchrist & Marshman, 2013).

MDAS:

On a scale of 1 to 5, the MDAS asks participants to rate their degree of anxiety in relation to five dental circumstances (1 = not anxious to 5 = extremely anxious).

The questions are:

1. How anxious would you feel if you had dental procedures tomorrow?

2. How anxious would you feel if you were waiting in the reception area?

3. Describe your level of anxiety in relation to having a tooth drilled.

4. How anxious would you be about getting your teeth cleaned and polished?

5. How nervous would you feel about receiving an injection of local anesthetic?

The lowest score is 5 and the highest is 25.

The MDAS's creators defined "clinical cut-off points" as scores between 15 and 18 which indicated moderate anxiety and 19 and higher which indicated severe anxiety with a high chance of dental phobia (Figure 2) (Humphris, Morrison & Lindsay,1995).

The MDAS has been demonstrated to have acceptable psychometric qualities, outstanding validity, and reliability (Coolidge, Arapostathis, Emmanouil, Dabarakis, Patrikiou & Economides, 2008; Humphris & Hull, 2007; Newton & Edwards, 2005).

Items	Modified dental anxiety scale (MDAS) anxiety questionnaire	
1	If you went to your dentist tomorrow, how would you feel?	1. Not anxious
2	If you were sitting in the waiting room, how would you feel?	2. Slightly anxious
3	If you were about to have a tooth drilled, how would you feel?	3. Fairly anxious
4	If you were about to have your teeth scaled and polished, how would you feel?	4. Very anxious
5	If you were about to receive a local anesthetic injection in your gum, how would you feel?	5. Extremely anxio

Figure 2: List of Modified Dental Anxiety Scale (MDAS) anxiety questionnaire

Regarding to perform measurement dental anxiety in children, the scale must cover the reliability and validity method (Al-Namankany, De Souza and Ashley, 2012).

Children's Fear Survey Schedule - Dental Subscale (CFSS-DS) and Modified Children Dental Anxiety Scale (MCDAS) are two psychometric measures that are most frequently used with kids. These two scales are believed to be reasonably straightforward and inexpensive when compared to other indexes (Cuthbert and Melamed, 1982; Cianetti, Paglia, Gatto, Montedori, Nardone, Pagano, et al., 2016). MCDAS was created by Humphris et al. and included eight questions regarding dental procedures, including dental examinations, polishing, injections, fillings, extractions, and general anesthesia and sedation (Figure 3) (Humphris, Wong and Lee, 1998).

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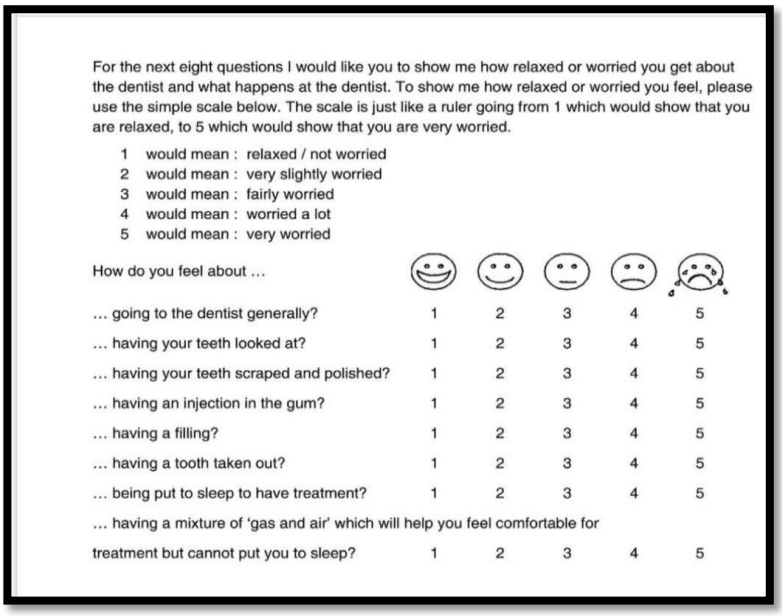

For the next eight questions I would like you to show me how relaxed or worried you get about the dentist and what happens at the dentist. To show me how relaxed or worried you feel, please use the simple scale below. The scale is just like a ruler going from 1 which would show that you are relaxed, to 5 which would show that you are very worried.

1 would mean : relaxed / not worried
2 would mean : very slightly worried
3 would mean : fairly worried
4 would mean : worried a lot
5 would mean : very worried

How do you feel about …					
… going to the dentist generally?	1	2	3	4	5
… having your teeth looked at?	1	2	3	4	5
… having your teeth scraped and polished?	1	2	3	4	5
… having an injection in the gum?	1	2	3	4	5
… having a filling?	1	2	3	4	5
… having a tooth taken out?	1	2	3	4	5
… being put to sleep to have treatment?	1	2	3	4	5
… having a mixture of 'gas and air' which will help you feel comfortable for treatment but cannot put you to sleep?	1	2	3	4	5

Figure 3: Faces version of the Modified Child Dental Anxiety Scale (MCDAS)

Relationship between perceived pain and dental anxiety:

Sanikop S. et al. (2011) designed a study to assess the link between dental anxiety and patients' sensations of discomfort during scaling. After scaling, pain levels were measured using a VAS and a seven-point anxiety questionnaire. There were no statistically significant variations in the mean VAS scores for the various age and gender categories over the all study group, which was 17.3 ± 13.8. Whereas the average score for anxiety was 11.66 ± 4.17. There were no statistically significant differences in this between the various age groups, however this was significantly higher in women (P = 0.005). As well as the VAS showed a statistically significant link with the overall anxiety score (P<0.001). Scaling was discovered to cause very little pain for the patients. They were fearful because they anticipated suffering and women were more fearful than males (Sanikop, Agrawal, & Patil, 2011).

Relationship between pain expectation and dental anxiety:

Klages U. et al. (2006) found that patients with high anxiety sensitivity anticipated more emotional affective Pain Scale (SPS), Sensory Pain Scale (SPS), and numerical pain rating (NPR) than Anxiety Status Inventory (ASI)-low scorers. Patients who performed well on the DAS had greater expectations of emotional pain and pain intensity. In individuals with dental anxiety, the correlation between anxiety sensitivity and predicted affective pain and pain intensity was greater. According to expected variances, high anxiety-sensitive individuals within the subset of heightened dental fear anticipated higher emotional pain, as measured by APS ($t = 2.80$), and pain intensity, as measured by NPR ($t = 3.29$, both $P < 0.01$), than their low anxiety-sensitive counterparts (Klages, Kianifard, Ulusoy & Wehrbein, 2006).

However, the findings show that individuals who are extremely sensitive to anxiety suffered greater pain throughout treatment than did people who scored low on the ASI scale. Higher affective pain and pain severity were felt by patients with significant dental scare than by their counterparts. The DAS and ASI's connection with the NPR turned out to be significant. This interaction shows that in the patients with DAS-high score compared to the DAS-low score group, the effect of anxiety sensitivity on pain intensity was higher. Assessment of comparison showed that the variation between high and low anxiety-sensitive individuals were significant only among DAS-high group ($t=4.08$, $P<0.001$). The experienced affective quality of pain showed a similar statistical trend for an interaction, with an error probability of 0.06. According to planned variances, the variations in emotional pain between the patients with ASI high scores and low scores were significant within the higher dental phobic group ($t=3.89$, $P<0.001$), but it was not observed in the group of paitents with a low score of fear. Additionally, markedly anxiety-sensitive individuals (within greater dental fear group) suffered from more sensory pain ($t=2.96$, $P < 0.01$) (Klages, Kianifard, Ulusoy & Wehrbein, 2006). Individuals with elevated pain sensitive in the high fear subset displayed a congruence between predicted and actual pain. The findings can be attributed to the strong impact of pain sensitivity on the level of pain felt by patients who are afraid (Klages, Ulusoy, Kianifard & Wehrbein, 2004).

Rachman & Arntz proposed that exposure to a treatment offers a chance to disprove incorrect pain expectations. The principles of successive approximation to the most intense frightening stimuli are the foundation of desensitization and exposure therapy (Rachman & Arntz, 1991).

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Treatment for dental anxiety and pain phobia may involve gradual exposure to uncomfortable dental treatments in order to show that pain overestimations can be corrected (Vlaeyen, Geilen and Peter, 2001). Clinicians should take pain and anxiety associated with dental operations into consideration, as anxiety heightens uncomfortable sensation and makes it more resistant to treatment. The three optimal circumstances in dentistry and maxillofacial surgery are to prevent acute nociceptive pain, prevent the formation of terrible experiences, and to manage anxiety for dental procedures (Sakamoto & Yokoyama, 2018).

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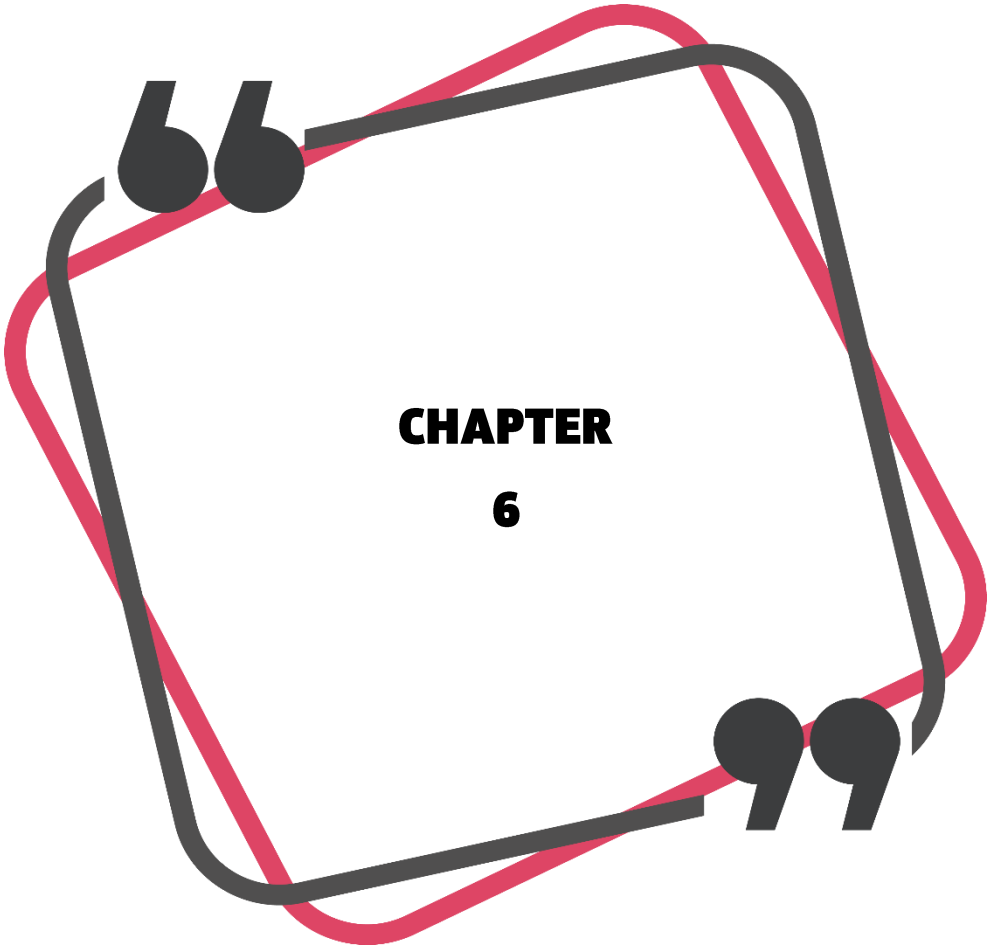
CHAPTER
6

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TOOTHPASTE: OVERVIEW

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1.HISTORY OF TOOTHPASTES

Archaeologists have discovered a lot of proof that dental hygiene has been practiced by humans for thousands of years. For cleaning teeth, several methods were utilized, including chewing sticks, tree branches, and bird feathers (Fink, 2018). The Egyptians are thought to have created a tooth powder around 5000 BC that included pumice, myrrh (resin), powdered and burned eggshells, and ox hoof ashes (Fink, 2018). According to estimates, the tooth cream that is created by combining this powder with water as it is being used is mostly utilized to eliminate residue (Lippert, 2013). Later, about 1000 BC, the Persians enhanced this tooth cream with honey, gypsum, burned oyster and snail shells, spices, and other ingredients. 1000 years after the Persians, the Greeks and Romans improved this formula by adding abrasives such as ground bones and oyster shells (Fink, 2018; Lippert, 2013).

Unlike today's toothpastes, ancient toothpastes have high abrasiveness, high cost and bad taste (Lippert, 2013). The first recorded tooth powder (rock salt, mint, rice flowers, and pepper) was developed by the Egyptians in the 4th century AD.In the ninth century, Iraqi musician Ziryab, who worked in many fields, developed a toothpaste (Carew, 1991). The exact ingredients of this toothpaste are unknown, but it has been reported to be functional and pleasant in taste (Fink, 2018).

Towards the end of the eighteenth century, borax powder (sodium borate) was added to tooth powder to make it foamy. At the beginning of the nineteenth century, glycerin was added to turn the powder into a paste, to give it a pleasant taste

and to prevent the paste from drying out. At about the same time, the use of strontium, which is thought to strengthen teeth and reduce sensitivity, has been suggested (Fink, 2018; Lippert, 2013).

Toothpastes continued to evolve from the traditional soap and abrasive model in the early 1900s to new "modern" toothpastes that included the addition of chemicals such as calcium fluoride and later sodium fluoride. 1914 is an important year in the history of toothpastes in terms of introducing the idea of toothpaste containing sodium fluoride (Lippert, 2013). It is interesting that a researcher named Gottlieb in 1947 reported that the drugs used in the treatment of tooth sensitivity showed a caries-protective effect (Gottlieb, 1947). Shaner and Smith reported that the use of 2500 ppm sodium fluoride twice daily reduced acidogenic microorganisms in human saliva (Shaner & Smith, 1946). While it is not known exactly when fluoride toothpaste was first sold, as a result of Dr. Joseph Muhler's research at Indiana University, the first fluoride containing toothpaste was released into the american market under the name Crest by the Procter & Gamble company in 1955 (Lippert, 2013).

At the annual meeting of the American Dental Association (ADA), Thomas Hill defined tooth-cleaning agents that contain bactericidal, bacteriostatic, enzyme-inhibiting or acid-neutralizing effects, helping to reduce caries and periodontal diseases, as therapeutic toothpastes (Emslie, 1980). Even a hundred years after the invention of the first modern toothpaste, the only effective method of maintaining good oral hygiene is cleaning the teeth with a brush and paste. The development of toothpastes is not yet complete. The biggest challenge to overcome is the generally poor intraoral persistence of active agents, and most importantly fluoride (Lippert, 2013).

2. FLUORIDE TOOTHPASTES IN OUR COUNTRY AND IN THE WORLD

Despite the prevalence of dental caries in the world, with the discovery of methods and agents used to prevent dental caries, this increase has started to show a reverse momentum in some developed countries. Removing dental plaque by using a toothbrush and fluoride-containing toothpaste not only prevents dental caries, it helps improve periodontal health. Effective toothpastes containing fluoride have not been easy to formulate. Initial attempts to add sodium fluoride to toothpaste were unsuccessful (Bibby, 1945). The first successful attemp at adding fluride to toothpaste was reported 10 years after, and the first fluoride toothpaste was introduced in 1955 (Muhler, Radike, Nebergall, & Day, 1955). These reports

led to the acceptance of fluoride toothpastes in 1964 by the American Dental Association (ADA) and the Council on Dental Treatment. In the early 1970s, a rapid increase in market share began to be observed. The World Health Organization has played an important role in informing governments and health officials around the world of the great benefits of the appropriate use of fluoride. While many countries have clarified policies on fluoride use, many have not (Whelton, Spencer, Do, & Rugg-Gunn, 2019).

Toothpastes may contain fluoride in various chemical forms, mainly sodium fluoride (NaF), sodium monofluorophosphate (Na_2FPO_3), amine fluoride ($C_{27}H_6OF_2N_2O_3$), stannous fluoride (SnF_2), or combinations and doses thereof. Fluorine ions, especially at low pH, can enter the bacterial cell, reduce the acid production in the plaque and prevent microbial growth. When evaluated in terms of dentistry practices, tooth brushing with fluoride toothpastes should be applied at least twice a day and for 2 minutes in order to prevent tooth decay and periodontal diseases. When applied with the right technique and the right dose, it can remineralize the teeth which is the strengthening of the enamel whith the use of antimicrobial effects (Griffin, Regnier, Griffin, & Huntley, 2007; O Mullane et al., 2016).

The maximum allowable dose of fluoride compounds used as oral hygiene products is calculated to be 0.15% (1500 ppm), fluoride. Fifteen mg/kg of sodium fluoride has been fatal to humans. Between 1989 and 1994, approximately 10,000 suspected cases of excessive fluoride intakes were reported in the USA. In infants and children up to 6 years of age, the consequences of exposure to dental products used at home are generally not serious. Of these 10,000 cases, only 2,000 were found to be toothpaste-related, and it seems very unlikely that toothpaste containing the recommended dose of fluoride in young children will cause fluorosis. Therefore, it has been shown as a result of various studies that fluoridation of water or the doses of fluoride used in toothpastes does not have a risky effect on general health (Comber, Deady, Montgomery, & Gavin, 2011; Dey & Giri, 2016). It is stated that fluoride toothpastes on the shelves in our country contain 1000 -1450 ppm fluoride, which is generally accepted as a safe and preventive level of caries. It is suggested that 1000 ppm fluoride toothpastes can be used in lower amounts (0.125-0.25 g) for children aged 1-6 (Toumba et al., 2019). When adults brush their teeth with 0.25 grams (lentil size) of fluoride toothpaste twice a day, at least 182.5 grams of toothpaste is used. The World Health Organization recommends four toothbrushes and 6 tubes of toothpaste for consumption per year. This requires the use of a new toothbrush every 3 months and a tube of toothpaste every two months. Although annual toothpaste consumption per capita

in Turkey has increased in the last 5 years, it is still behind developed countries with a 110 grams (Akar, 2014). As in our country, the prices of toothpastes are quite high in many developing countries. The World Health Organization approves the development of affordable toothpastes (S. Jones, Burt, Petersen, & Lennon, 2005). Government policies and regional trade policies need to be transformed to eliminate taxation of global branded fluoride toothpastes. Local production of affordable fluoride toothpastes should be encouraged. Multinational toothpaste manufacturers should be asked to offer different pricing, which reduces the cost of toothpaste with cheap packaging for poor countries.

3.TOOTHPASTE CONSUMPTION AMOUNT, BRUSHING FREQUENCY AND BRUSH CHANGE FREQUENCY IN OUR COUNTRY AND IN THE WORLD

While the development of dental caries and gingival diseases can easily be prevented with regular oral hygiene practices, it is surprising that the rates are so high. The reasons for this may be the inability to perform oral hygiene habits with sufficient efficiency, the inability to transform oral hygiene education into a behavior or the inaccessibility of oral health products.

The Turkish Dental Association (TDA) reported that only 70% of the households in Turkey have toothpaste, and the amount of toothpaste consumption in 2010 was approximately 110 grams (gr), which is about ¼ of the USA and European countries[19]. While the annual consumption of toothpaste is 480 gr in England, this value is 270 gr in Italy and 155 gr in Spain (ATASEVER, 2015). Although the annual consumption of toothpaste, which was 65 g in 2002, has increased in our country, the amount has not increased as much as it should be when compared to the change in the population. Although the annual per capita toothbrush consumption has increased from 2002 (0.33) to 2010 (0.94), this parameter is also far below the required figure. In order to deform the bristles and prevent possible bacterial colonization, the American Dental Association (ADA) reported that toothbrushes should be replaced every 3-4 months (Karibasappa, Nagesh, & Sujatha, 2011).

As can be determined from the amount of consumption of toothpaste and toothbrushes, the habit of brushing teeth in Turkey is also lower than it should be. In the study published by the Turkish Dental Association (TDA) in 2014, it was determined that the rate of those who brush their teeth twice a day is 48.4%, followed by those who brush once a day with 26.8%. Although the recommended frequency of brushing is twice a day, individuals who develop this behavior are

less than half the population (Shetty & Gusani, 2018). In studies involving 7600 individuals in Nigeria and 1600 individuals from South America, it was reported that 50% of the participants brushed their teeth twice a day, similar to the situation in our country (Gómez et al., 2018; Olusile, Adeniyi, & Orebanjo, 2014). In a study in which the toothbrushing habits of individuals in Italy were questioned, 70% of a total of 2200 individuals aged between 18-98 brush their teeth once a day (Villa et al., 2012).

With the correct use of oral hygiene products, the development of dental caries and periodontal disease can easily be prevented, and the effects of possible pathogens such as bacteria, viruses and fungi can be reduced. Thus, the integrity of the overall body health can also be maintained. Transforming the use of oral hygiene products into a behavior will benefit both the individual and the society.

4.WHAT IS IN THE CONTENT OF DENTIFRICES? WHAT ARE THEY USED FOR?

Tooth brushing is the basis for the protection of our oral and dental health, both socially and individually. If the teeth can be cleaned effectively with a toothbrush and toothpaste and plaque control can be achieved, complex dental treatments that may be requierd can be prevented. It is possible to mechanically remove plaque with a toothbrush. Toothpaste plays an important role in the control and treatment of many dental diseases and conditions. Tooth decay, dentin hypersensitivity, gingivitis, halitosis can be given as examples. In addition, manufacturers have added different therapeutic agents to the content of toothpastes in order to remove tooth discoloration. For all these purposes, toothpaste formulations are prepared by mixing active and inactive ingredients in different proportions. The active ingredients of toothpastes are defined by the Food and Drug Administration (FDA) as ingredients with a specific therapeutic effect. Inactive ingredients include other substances that make up the structure of the toothpaste.

Toothpastes have three important functions. These:

1. Effectivly removing dental plaque thanks to the abrasives and detergents it contains

2. Polishing the teeth to better reflect light and give them an excellent aesthetic appearance

3. It can be look at as a carrier of remineralizing agents such as fluorides, and some therapeutic agents with desensitizing or whitening properties (Shen, Rawls, & Esquivel-Upshaw, 2021).

5.CONTENTS OF TOOTHPASTE

5.1.Inactive Components

5.1.1.Structural Inactive Components

5.1.1.1 Abrasives

Abrasive substances contained in toothpastes are; calcium carbonate, dicalcium phosphate, hydrous or anhydrous sodium metaphosphate, silica, aluminum oxide, calcium pyrophosphate, alumina and pumice. It is preferred that these abrasives are insoluble in liquid, inert, non-toxic and white in color. Abrasives are important in removing the bacterial plaque from the teeth quickly and effectively, as well as removing the discoloration that occurs on the teeth (Lobene, 1968). The relationship between the cleaning power of toothpaste and its abrasive effect is weak. For this reason, the abrasive features of toothpastes are being reduced by adding different substances to toothpastes or by changing the ratios of the existing content (Wulknitz, 1997).

5.1.1.2 Humidifiers

They are non-toxic agents added to the content of toothpaste to prevent moisture loss and hardening. It may also have sweetening effects. Commonly used ones are; glycerin, sorbitol, propylene glycol and mannitol (Forward, James, Barnett, & Jackson, 1997).

5.1.1.3 Detergents(Surfactants)

One of the main purposes in the production of toothpastes is to clean the teeth. For this reason, detergents are added in order to increase the cleaning efficiency by adding foaming properties to their contents. The soaps, which were present in the first toothpastes, were quickly replaced by detergents due to their irritating properties to the mucous membranes, their bad taste, and their incompatibility with other agents such as calcium(Forward et al., 1997).

5.1.1.3.1 Sodium Lauryl Sulfate(SLS)

Anionic surfactant is the most common agent with detergent effects. It has a stable structure. Due to its low surface tension, it allows the toothpaste to flow easily from the tooth surface (Forward et al., 1997). It is added to toothpastes at a rate of 1-2%. It is a foaming agent with an antimicrobial effect. It kills microorganisms, lowers surface energy and denatures proteins (Joiner et al., 2008).

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5.1.1.4 Binders

The agents that function in controlling the stability and consistency of toothpastes are binders. Among them, the most commonly used are carrageenan, alginate, sodium carboxymethylcellulose, magnesium aluminum silicate, sodium magnesium silicate and colloidal silica. They are the structures that allow the toothpaste to be easily dispersed in the mouth, to be easily squeezed out of the tube, and to remain on the toothbrush properly (Forward et al., 1997).

5.1.1.5 Protectives

Benzoate is added to toothpastes as a preservative and has an inhibitory effect on the growth of microorganisms (Forward et al., 1997; Moran, Claydon, Addy, & Newcombe, 2005).

5.1.2 Sensory Inactıve Components

5.1.2.1 Sweetener

The agents added to toothpastes as sweeteners are sodium aspartame, saccharin, sodium cyclamate and acesulfame-K. These agents are not metabolized by cariogenic microorganisms and give flavor without creating cariogenic acid attacks. Apart from these, xylitol, sorbitol and isomalt are also counted among the sweetening agents added to toothpastes (Fejerskov, Nyvad, & Kidd, 2015). Apart from sweeteners, flavoring substances such as menthol, mint, anise, lemon, eucalyptus are used in toothpastes.

5.2.Actıve Components (Theraputıc Agents) And Clinical Indications

5.2.1 Anti-Caries And Remineralisation Agents

5.2.1.1 Fluoride

Fluoride compounds have been used in toothpaste formulations for many years due to their caries-preventing effects. The most common of these are; sodium fluoride and sodium monofluorophosphate. Apart from these, amine fluoride and stannous fluoride are also included in the structure of toothpastes (Cury, Tenuta, Ribeiro, & Paes Leme, 2004). The most important determinant of fluoride efficacy is its concentration in toothpaste. In order to be more understandable for consumers, the amount of fluoride in the total mixture is presented in parts per

million (/ppm). Today, the total amount of fluoride in toothpastes is limited to 1500 ppm.

5.2.2 Other Remineralization Agents

5.2.2.1 Calcium Phosphate Compounds

As the main component of hydroxyapatite crystals, the concentration of calcium phosphate in saliva and plaque does not directly affect the demineralization and remineralization processes (Li, Wang, Joiner, & Chang, 2014).

5.2.2.2 Beta-Tricalcium Phosphate(b-TCp)

Studies show that when used together with fluorides, tricalcium phosphate increases enamel remineralization and causes the formation of more acid-resistant minerals (Li, Wang, Joiner, & Chang, 2014).

5.2.2.3 Dicalcium Phosphate Dihydrate(DCpD)

DCPD is the precursor form of apatite that transforms into fluoropatite in the presence of fluoride (Walsh, 2009). Studies have shown that toothpastes containing DCPD increase the level of free calcium ions in dental plaque, and this level is maintained for up to 12 hours after brushing compared to conventional toothpaste formulations (Hemagaran & Neelakantan, 2014).

5.2.2.4 Casein Phosphopeptide- Amorphous Calcium Phosphate (CPP-ACP)

Developed by Reynolds from milk protein, this agent stabilizes amorphous calcium phosphate by converting it into CPP-ACP complexes, thereby forming CPP, Ca^{+2},Zn^{+2}, Fe^{+2}, It binds ions such as Se^{+2} (Reynolds, 2009).

5.2.2.5 Bioactive Glass

Bioactive glass; It is in the bioactive material class due to its calcium, sodium, phosphate and silicate content (J. R. Jones, 2013). Earl et al. showed that bioactive glass particles accumulate on the dentin surface and osbtruct the dentinal tubules in a structure similar to hydroxyapatite (Earl, Leary, Muller, Langford, & Greenspan, 2011). NovaMi® is a bioactive glass containing 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5. When Novamin particles come into contact with water or saliva, they rapidly release sodium ions, providing a localized pH increase in that area, and ion accumulation occurs to form a hydroxyapatite layer (Greenspan, 2010).

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5.2.2.6 Nano-Hydroxyapatite

Nanohydroxyapatite particles (n-HAP) are similar to the apatite crystal structure of tooth enamel. Li et al. He reported that n-HAP particles with a size of 20 nm close the nano-defects on the acid-eroded enamel surface, making it more resistant to acid attacks (Li et al., 2014). According to teh research of Huang et al. it was stated that nanohydroxyapatite functions as a calcium-phosphate reservoir, providing supersaturation of minerals, reducing enamel demineralization and increasing remineralization (Huang, Gao, Cheng, & Yu, 2011).

5.3. Agents That Prevent Plaque And Gingival Inflammation

Properties expected from agents that prevent plaque formation which are included in the structure of toothpastes are strong antimicrobial effect, broad spectrum against bacteria and fungi, chemical stability in the mouth, adhesion to tissues and active release, non-toxic properties, biocompatibility, no side effects, and not causing taste loss (Canan & Özalp, 2013). Triclosan is a non-ionic antimicrobial agent with hydrophilic and hydrophobic properties. It has a broad-spectrum effect against both gram-positive and gram-negative microorganisms and fungi. Compatible with fluoride and detergents in toothpastes. Specifically, it shows its effect by damaging the bacterial cytoplasmic membrane by inhibiting the enzyme enoyl-reductase, which provides type 2 fatty acid synthesis of the bacteria. (McMurry, Oethinger, & Levy, 1998).

Toothpastes with herbal and natural ingredients are also available in the market and there is a lot of research on their effectiveness. Some of the herbal ingredients used in toothpastes are sanguinarin extract, propolis, rosary tree, clove, aloe vera, green tea and miswak tree (Janakiram, Venkitachalam, Fontelo, Iafolla, & Dye, 2020). According to the systematic review and meta-analysis of Janakiram et al., herbal toothpastes were found to be more effective than non-herbal toothpastes, but did not show any superiority over fluoride toothpastes (Janakiram et al., 2020). This research also states that with the available evidence, herbal ingredients are insufficient to replace the formulations of traditional oral care products. Apart from these, toothpastes containing charcoal have also been produced. Regarding such toothpastes, which are claimed to be free of fluoride, ecological, herbal, natural and pure, Brooks et al. reported in a literature review that they found insufficient evidence to support the antibacterial, antifungal, anticaries, and teeth whitening effects of charcoal-based toothpastes (Brooks, Bashirelahi, & Reynolds, 2017).

5.4. Agents That Reduce Calculus Formation

Dental calculus is formed by the calcification of the plaque on the tooth surface. Toothpastes that reduce tartar formation generally prevent accumulation in the supragingival region. Tetrapotassium, disodium and tetrasodium pyrophosphates, zinc salts (zinc citrate, zinc chloride, etc.), tricolosan/copolymer and sodium hexametaphosphate fulfill their functions by inhibiting the formation of crystals during tartar deposition and have been used for many years (Panagakos et al., 2005).

5.5.Agent Used In Dentin Hypersensivity

Potassium salts are added to toothpastes used in the treatment of dentin hypersensitivity. When 5% potassium nitrate, 3.75% potassium chloride, and 5.5% potassium citrate are added to toothpastes, they show a desensitizing effect by blocking nerve conduction. Strontium ions have been used to precipitate on the tooth surface and provide tubular obstruction. Strontium chloride was included in the structure of toothpastes for a while, but this mixture was not used for a long time (Jacobsen & Bruce, 2001). Stannous fluoride, aluminum, potassium, ferric oxalates and fluorides are active ingredients in use for this purpose (Rosin, Kramer, Bradtke, Richter, & Kocher, 2002). Apart from these agents, calcium sodium phosphosilicate, tricalcium phosphate, CPP-ACP, bioactive glass and nanohydroxyapatites are added to the content of toothpastes due to their dentin hypersensitivity relieving properties as they have tubule-block effects.

5.6. Whitening Agents

Whitening toothpastes contain abrasives, chemicals and agents that give their optical properties. The abrasives are; silica, calcium carbonate, dicalcium phosphate dihydrate, calcium pyrophosphate, aluminum, perlite and sodium bicarbonate. The chemical agents include; hydrogen peroxide, calcium peroxide, sodium citrate, sodium pyrophosphate, sodium tripolyphosphate, sodium hexametaphosphate and papain. Blue covariate is added to whitening toothpastes to impart their optical properties (Joiner, 2010). A low percentage of hydrogen peroxide (around 1%) has been added to whitening toothpastes. The mechanism of action is the formation of oxygen bubbles which leads to the whitening of the tooth surface (Casado et al., 2018; Joiner, 2010).

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6.TOOHPASTE IN DENTIN HYPERSENSIVITY

Dentin hypersensitivity is a chronic disease that is common in dental practices and is difficult to treat. Sensitivity is exposed dentin tissue on the tooth surfaces; It is a short-term and sharp pain that increases in intensity depending on the response to thermal, tactile, osmotic, chemical or evaporative stimuli (Zeola, Soares, & Cunha-Cruz, 2019). Various methods are used in the treatment of dentin sensitivity. These include methods such as ensuring individuals brush their teeth with a correct technique, making occlusal adjustments to their teeth, regulating their diets, and applying desensitizing agents and toothpastes, laser devices, adhesive agents, and adhesive restorations (Ozlem, Esad, Ayse, & Aslihan, 2018).

Toothpastes used in dentin hypersensitivity according to their content:

6.1 Toothpastes containing potassium

After 1980, toothpastes containing potassium chloride and potassium citrate were introduced to the market. Potassium ions are thought to treat dentin sensitivity by diffusing along the dentinal tubules, altering the membrane of the interdental nerves and reducing their excitability (Orchardson & Gillam, 2006). In a clinical study, the desensitizing effects of agents containing fluoride varnish and potassium nitrate were compared and, both materials were able to relieve the pain caused by sensitivity in the prepared teeth, but in the clinical follow up performed 1 week after the crown cementation, it has been reported that the material containing potassium nitrate was more effective (Orchardson & Gillam, 2006). In different clinical studies, the use of potassium-containing mouthwash and toothpaste after 4 and 8 weeks of use has been found to be more effective than fluoride, strontium chloride and herbal toothpastes (Hall, Sufi, Milleman, & Milleman, 2019).In different studies, the effectiveness of potassium-containing toothpastes in the treatment of dentin sensitivity was compared with placebo after 6, 8, or 12 weeks of use, and the desensitizing effect of potassium-containing toothpastes was found to be high (Bae et al., 2015; Wara-aswapati et al., 2005).

6.2 Toothpastes containing strontium

Toothpastes containing strontium do not have a polarizing effect on nerves, unlike those containing potassium nitrate, but the material does affect the dentinal tubules. When applied to the tooth surface, strontium ions replace calcium ions,

forming strontium crystals in the dentinal tubules, and thus exert a desensitizing effect (Clark & Levin, 2016).In an in situ study, it was found that strontium acetate can occlude dentinal tubules to a depth of 5 μm, and dentin sensitivity can be treated with its use (Clark & Levin, 2016).However, there are different opinions about the efficacy of this agent in studies. Bae et al., in their meta-analysis in which they included 4 separate clinical studies containing strontium, found that the efficacy of strontium-containing toothpastes in the treatment of sensitivity was similar to that of the placebo saptamışlardır (Bae et al., 2015). In another meta-analysis study, it was reported that toothpastes containing only strontium did not have a desensitizing effect, but toothpastes containing both strontium and potassium had a reducing effect on dentin sensitivity. In this study, it was reported that the desensitizing effect of toothpaste containing strontium and potassium was due to potassium (Young, Wang, Mason, & Sufi, 2017).

6.3 Toothpastes containing stannous fluoride

These toothpastes prevent dentin sensitivity by blocking dentinal tubules by forming insoluble residue on the teeth surfaces from ions that are soluble in the mouth (Majji & Murthy, 2016). In six different studies examining the effect of stannous fluoride toothpastes in the treatment of dentin sensitivity, the effect of these toothpastes was compared with the use of a placebo. It has been determined that the pain caused by dentin sensitivity decreases with the use of pastes for 2 weeks, 6 weeks or 8 weeks (Clark & Levin, 2016; Schiff, Saletta, Baker, Winston, & He, 2005). In three different clinical studies comparing the efficacy of toothpastes containing potassium and stannous fluoride with a placebo, stannous fluoride was found to be more effective than the placebo in the treatment of dentinal sensitivity (Clark & Levin, 2016; Sowinski et al., 2001).

6.4 Toothpastes with Calcium Sodium Phosphoslicate

In toothpastes, Calcium phosphoslicate prevents dentin sensitivity by a similar mechanism with the combination of strontium acetate and arginine-calcium carbonate (Chen, Parolia, Pau, & Celerino de Moraes Porto, 2015). When toothpastes containing calcium sodium phosphoslicate are taken into the oral cavity, sodium ions are replaced by hydrogen ions and calcium and phosphate ions are released from the paste. These minerals precipitate in the dentinal tubules and provide occlusion of the tubule (Chen et al., 2015). In four different clinical stu-

dies comparing the effect of calcium sodium phosphoslicate-containing toothpastes with a placebo on dentin sensitivity, it has been reported that the use of these pastes for 4-6 weeks reduces dentin sensitivity (Chen et al., 2015; Litkowski & Greenspan, 2010; Pradeep, Agarwal, Naik, Bajaj, & Kalra, 2012).

6.5 Toothpastes Containing Arginine

It has been reported that arginine is a natural amino acid in saliva, acting together with calcium carbonate and phosphate ions to form plugs in dentinal tubules (Young et al., 2017). In two different clinical studies, arginine-containing toothpastes were found to be more effective than placebo in preventing dentin sensitivity (Que et al., 2010; Sharif, Iram, & Brunton, 2013). In both studies, it was determined that the pain caused by dentin sensitivity decreased immediately after the use of the paste and after 8 weeks of continuous use. This suggested that arginine-containing toothpastes may exert their effect in the short term (Low, Allen, & Kontogiorgos, 2015).

6.7 Toothpastes containing nanohydroxyapatite

It has been reported in studies that nanohydroxy apatite provides remineralization in enamel and dentin tissue, and also reduces dentin sensitivity (Low et al., 2015). Nanohydroxy apatite (nHAP) acts as a calcium-phosphate reservoir, and by applying the material topically to the dental tissue, the tooth surfaces are saturated with these minerals and a residue is formed on the surface. Thus, microvoids in the dentin tissue are easily filled (van Loveren, Schmidlin, Martens, & Amaechi, 2018). In the study of Wang et al. in which they evaluated the desensitizing effect of toothpaste containing nanohydroxy apatite, toothpaste containing pro-arginine and fluoride varnish using an air stimulus, it was reported that the most effective toothpaste in preventing dentin hypersensitivity was pastes containing nanohydroxyapatite after approximately three months of use (Wang et al., 2016).

6.8 Toothpastes containing amorphous calcium phosphate

In in vitro studies, it has been reported that toothpastes in this group have a desensitizing effect by forming a residue on dentin surfaces and dentin tissue and occlusion of open tubules (Abdollahi & Jalalian, 2019). In two different clinical studies comparing the efficacy of toothpastes containing amorphous calcium phosphate with a placebo on dentin sensitivity, it was found that the use of these

pastes for 8–12 weeks did not contribute to the reduction of sensitivity (Hooper, W'inston, Bowman, & Sharma, 2009; Hu et al., 2018).

7.WHITENING TOOTHPASTES

With the increase in aesthetic expectations, the majority of patients who apply to clinics are those who are not satisfied with the color of their teeth and demand whitening (Epple, Meyer, & Enax, 2019). Many manufacturers have launched many over the counter (OTC) products as an alternative to office and/or at home teeth whitening procedures used in the treatment of these discolorations. OTC whitening products come in the market as powders, gels, mouthwashes, chewing gums, strips and toothpastes. Interest in OTC products is increasing due to their easy accessibility, ease of use without dental supervision, and lower cost.

7.1 Content And Effect Mechanism

Whitening toothpastes have different ingredients and, therefore, different mechanisms of action. They differ from traditional toothpastes in their abrasive particle differences (type, size, abrasiveness) and peroxide content. While toothpastes contain abrasives, surfactants, calcium chelators, enzymes and polymers color pigments to remove stains or prevent stain build-up; Peroxide-containing pastes, on the other hand, claim to have the ability to change the color of the tooth (bleaching) (Hoic et al., 2004).

7.2 Abrasives

The effectiveness of abrasives that play a role in removing stains; depends on particle size, shape, hardness, distribution, concentration and the load applied during brushing. Frequently used abrasives are; hydrated silica, calcium carbonate, calcium phosphate, calcium pyrophosphate, alumina, perlite and sodium bicarbonate (Vaz et al., 2019). These abrasives remove stains on coronal surfaces, leading to the perception of change in tooth color (Vaz et al., 2019). There are conflicts in the literature on the abrasiveness of toothpastes with different ingredients; This is explained by the presence of chemical, optical and abrasive agents in whitening products by themselves or in many different combinations. In addition to all of these, the pH value also plays a role in determining the abrasive capacity of the toothpaste (Simões et al., 2020).

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7.3 Whitening Agents Such As Peroxide And Sodium Chloride

Hydrogen peroxide (HP) dissolves chromogen molecules and stains on the tooth surface through phosphate salts that react with sodium citrate. The formulation factors and limitations of peroxide agents make it difficult to add peroxide-based agents to pastes. Whitening toothpastes contain a lower concentration of whitening agents than in-office whitening products. The HP concentration used in these pastes ranges from 5.3 to 6.5%, and they are recommended to be used twice a day for 14 days (Sulieman, Addy, MacDonald, & Rees, 2004). In studies, it is recommended that a whitening toothpaste containing 2.8% HP should be used three times a day for about 7 weeks (3 minutes of brushing each time), and a toothpaste containing 0.7% HP should be used for 9-10 weeks (Kim et al., 2020).

7.4 Surfactants

In recent years activated carbons has begun to attract attention for its ability to absorb stains, chromophores and pigments responsible for the discoloration of teeth (Vaz et al., 2019). Toothpastes containing charcoal powder on the market typically contain a controlled heated and oxidized active charcoal powder (Greenwall, Greenwall-Cohen, & Wilson, 2019). Bentonite clay and activated carbon help achieve a cleaner tooth surface by locking in the plaque, bacteria and stained material in the recessed structures of the tooth. It has been reported that the use of activated carbon toothpaste after a professional tooth cleaning delays staining (Greenwall et al., 2019). Particulate hydroxyapatite [$Ca_5(PO_4)_3(OH)$], which is the biomimetic active ingredient, is thought to be advantageous over whitening agents such as alumina and perlite, with its mechanical similarity to human enamel crystals and non-abrasiveness (Epple et al., 2019; Fabritius-Vilpoux, Enax, Herbig, Raabe, & Fabritius, 2019).

7.5 Enzymes And Polymers

Whitening toothpastes containing oxidant enzymes chemically change the pigments on the tooth surfaces and reduce the intensity of the color change by acting chemically (Joiner, 2010). Recently, crospovidone polymer, which is based on plazdone or povidone, has been added to toothpastes, but its ability to remove external stains has not yet been clearly evaluated.

7.6 Color Pigments

An improvement in whitening toothpastes is the use of color transition from yellow to blue to create a change in perception of whiteness. Optical modifying toothpastes, which form a translucent layer on the tooth surface with pigments such as blue covariate, change the interaction of light with the tooth surface, causing the surface to appear brighter and whiter instantly (Joiner, 2010). Although it is stated that toothpastes containing blue covariate show a significant difference compared to pastes without it, it is observed that the amount of blue covariate in the paste also has an effect on the color change after brushing (Tao et al., 2017).

8. HERBAL TOOTHPASTES

8.1 Why Herbal Toothpaste?

Concern about exposure to antimicrobial chemicals through consumer and food products is increasing day by day. The inclusion of antiseptics, disinfectants, detergents, and preservatives in consumer products for oral hygiene (toothpaste and mouthwash) has increased over time to reduce microbial contamination and the incidence of pathogen-related disease (Freires & Rosalen, 2016).

8.2 Herbal Extracts Contained In Herbal Toothpaste

Formulations containing plant extracts and natural ingredients used in dental clinical studies are mouthwashes (47.5%), toothpastes+ (7.3%), oral patches (7.3%), and gels (Freires & Rosalen, 2016). The carbohydrates, amino acids, fatty acids, minerals, vitamins, enzymes and phytochemicals they contain provide the effectiveness of these natural substances. In addition to these, oleoresins make up the functional basic components. The active ingredients they contain can be divided into two; volatile ones are volatile substances that give distinctive taste and aroma, such as sesquiterpene (plant pigments, flavones) and monoterpenoid hydrocarbons. Non-volatile ones are phenol-like structures that vary in unbranched alkyl chain length. All these components constitute the antimicrobial properties of plant extracts. If we examine these plant extracts and natural substances in more detail (Hussain, & Razvi, 2019)

- Aloe vera: Contains saccharides, anthraquinones, gibberellin, cholesterol, uric acid, lignins, triglycerides, steroids, salicylic acid and beta-sitosterol. Treatment of conditions and diseases such as periodontal surgery, aphthous ulcer, lichen planus, chemical burns, alveolitis, gingival abscesses, leukemia and AIDS-

related gingival problems, glossitis, geographic tongue and burning mouth syndrome, candidiasis, desquamative gingivitis, vesiculobullous diseases and xerostomia used for the purpose (Farman et al., 2020).

- Chamomile (Matricaria recutita): It contains substances such as chamazulen, a-bisabolol, luteolin and related sesquiterpenes, quercetin and apigening. It is used in gum diseases and in the treatment of ulcers in the mouth (Taheri, Azimi, Rafieian, & Zanjani, 2011).

- Ginger (Zingiber officinalis): Its components include substances such as gingerol, shagol, zingiberen, carotene, ascorbic acid, terpenoids. Ginger has been reported to be used to relieve toothache and to treat oral thrush (Azizi et al., 2015). In addition, it was found to be as effective as fluoride toothpastes on the remineralization of early caries lesions in the enamel tissue of the tooth (Gocmen et al., 2016).

- Green tea (Camellia sinensis): Polyphenol contents in green tea include catechin, gallocatechin, epicatechin gallate, epicatechin. It has been reported that it is used in the treatment of periodontal diseases and reduces tissue loss in dentin against erosive attacks (Sultan, Zafar, Shahab, Najeeb, & Naseem, 2016).

- Thyme (Thymus vulgaris): Its main components are phenols, carvacrol and thymol. Ointment obtained from thyme, goldenseal and myrrh is used in the treatment of oral herpes. It has also been reported to be used in the treatment of herpes, halitosis, and candidiasis (Taheri et al., 2011).

- Turmeric (Curcuma longa): Turmeric contains several bioactive components, including a number of monoterpenes and sesquiterpenes, such as zingiberen, β-turmerone, and curcumin. Its color and coloring properties are due to curcuminoids. It is used in the treatment of tooth decay, gingivitis, bad breath and lichen planus. It has been observed that when aching teeth are massaged with finely ground and roasted turmeric powder, pain is reduced and existing swelling is reduced (Nagpal & Sood, 2013).

- Miswak (Salvadora persica): Miswak is obtained from the Arak tree and is used as a traditional toothbrush to maintain oral hygiene in many countries. Miswak extract has also been found to be effective as antiplaque and antigingivitis agents in toothpastes (Gupta, Agarwal, Anup, Manujunath, & Bhalla, 2012).

- Peppermint (Mentha piperita): Peppermint leaves have some chemical components, such as an essential oil made of menthone and menthol. One of the traditional uses of peppermint oil is to apply it to relieve toothache by simply dipping a cotton ball into the oil and rubbing it on the tooth or placing it in the

cavity (Taheri et al., 2011). It is used in most of the traditional toothpastes because of its taste and breath-freshening properties.

- Lavender (Lavandula angustifolia): Reduction in stress and anxiety levels has been reported when inhaled or administered orally. It is used in dental treatments to reduce patients' anxiety (Lehrner, Marwinski, Lehr, Johren, & Deecke, 2005).

Tea tree oil (Melaleuca alternifolia): Tea tree is a plant native to Australia (Arweiler, Donos, Netuschil, Reich, & Sculean, 2000). The method of use is to apply tea tree oil directly to the inflamed gums and provide temporary relief. Mouthwash with tea tree oil is used to soothe inflammation in the mouth, it has been reported that it can be used in the treatment of oral candidiasis (Francisconi et al., 2020). It has been reported that it can be applied for irrigation to remove necrotic pulp tissue during endodontic treatment (Filoche, Soma, & Sissons, 2005).

- Sage (Salvia officinalis): It consists of main components such as essential oil, thujone, cineole and camphor. The use of sage in the treatment of sore throat, intraoral inflammations and gingivitis is common (Taheri et al., 2011).

9. WHAT IS ON THE MARKET SHELVES?

Today, with the developing technology, the increase in the aesthetic expectations of individuals and the interest in natural products has led to an increase in the variety of products in toothpastes. For example, in the 21st century, patients' have the ability to protect their own teeth for many years as a result of increasing awareness of dental care which has led to an increase in tooth wear and tooth sensitivity problems. This has resulted in the development of toothpastes for such problems. Likewise, the search for natural products has led to the addition of herbal-based agents to the content of toothpastes. As a result of the use of coloring agents such as tea, coffee and cigarettes in daily life and the desire of patients to have whiter teeth, toothpastes that offer optical whiteness or remove discoloration on the tooth surface thanks to the agents it contains have been put on the market.

The choice of toothpaste is affected by many factors, such as the socioeconomic status of the individual, the advertising promotion of the product, its accessibility, packaging, taste, content, recommendation by the dentist or the environment (Sarker, Yousuf, & Monzoor, 2013).

When these factors are considered, it is seen that the role of the dentist in the selection of toothpaste is not in the right place. Unfortunately, the recommenda-

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tion of the physician is not included as one of the main factors in toothpaste selection. Unless physicians prescribe the right product in line with their patients' needs, the choice of toothpaste will continue to be affected by other factors. Since there are so many products on the shelves, even we dentists have a hard time remembering the names of these toothpastes and knowing their contents, as a result of this it is very difficult for the public to choose the right one from these products by looking at the shelves. For this reason, toothpastes should be prescribed by the physician in consideration with what the individual needs. Otherwise, only products with evaluations such as packaging and price will be taken.

As a result, dentists should follow the developments related to toothpastes, know the content and mechanism of action, and prescribe the right product according to the needs of their patients. Thus, the positive effect of toothpaste, which is the biggest supporter of preventive dentistry, will be benefited at the highest level.

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CHAPTER
7

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DENTAL PLAQUE DIAGNOSIS AND IMAGING METHODS

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INTRODUCTION

Biofilm; is a polymicrobial community with a complex structure, surrounded by a polysaccharide matrix produced by microorganisms that can communicate with each other and different microorganisms (Chaudhary, Jyoti, Shrivastava, & Tomar, 2020; Donlan & Costerton, 2002). Microbial dental plaque is a true biofilm formed by bacteria embedded in a matrix of extracellular bacterial polymers, saliva and gingival exudate products (Hepdeniz & Seçkin, 2017). Combining previous theories from dental plaque hypotheses, D. Marsch proposed the Extended Ecological Plaque Hypothesis (Laurisch, 2021). According to this theory, the oral microflora alters according to the effect of environmental conditions which increases the cariogenicity of the dental plaque. Dental plaque must be removed from the teeth due to its cariogenic potential. When the microbial dental plaque is not removed from the dental surfaces, the plaque matures, the complexity of the flora increases with additional microorganisms, and finally the calculus formation occurs with the precipitation of the inorganic salts (Rabin et al., 2015; Sharma, Misba, & Khan, 2019).

Diagnosis and imaging of microbial dental plaque is of great importance in terms of providing oral hygiene education to patients and thus improving public

oral health. Plaque staining methods, plaque indexes and imaging methods are used in the diagnosis of dental plaque.

Dental Plaque Staining

Dental plaque is traditionally detected by clinicians by visual inspection or with the help of an explorer. Because dental plaque is a colorless formation, it is difficult to determine when its amount is small. However, since it is also a staining formation, it can be made visible with the help of plaque staining agents (Becker, Becker, & Berg, 1984; Lang, ØStergaard, & Löe, 1972). Among the plaque staining agents, basic fuchsin, erythrosine, mira-2 ton, Tri Plaque ID Gel are widely used.

Basic fuchsin, which is low in water and well soluble in ethyl alcohol, is applied to the tooth surface with a cotton or applicator to dye the microbial dental plaque, or the bacterial plaque is stained by rinsing the solution in the mouth.

Erythrosine added to the composition of basin, pharmaceuticals and cosmetic products, has been used as a microbial dental plaque staining agent for years.

Mira-2 Ton contains lactose, magnesium citrate, menta arvensis plant, silica and food coloring in the structure of plaque dye and does not contain erythromycin. It reveals mature plaque in blue and new plaque formations in pink. A tablet is placed on the patient's tongue and the patient is asked to chew the tablet, or it is applied to the tooth with the help of a cotton pellet, spread in the mouth with saliva and the patient is asked to spit it out (Lang et al., 1972).

Tri Plaque ID Gel (GC Corp., Tokyo, Japan) stains teeth in 3 different colors, red, purple and light blue. Areas painted in red indicate newly formed low-risk plaque, while the areas painted in purple indicate the mature plaque. It contains ethyl alcohol, glycerol and sucrose (Brostek & Walsh, 2014). It also shows the acid-producing mature plaque areas indicated in light blue due to the sucrose content (Figure 1).

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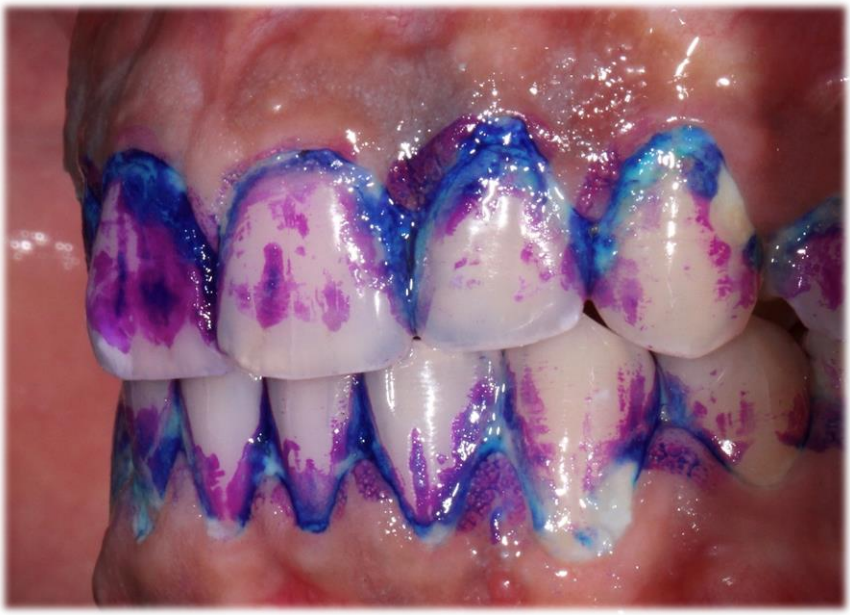

Figure 1: Different colorations depending on the plaque density on tooth surfaces after staining dental plaque

The application of dental plaque staining agents is a non-invasive method, and is important to aid the detection of the plaque in the early period of formation and the motivation of the patient's oral hygiene.

Dental Plaque Indices

An index can be used to determine the level or severity of a disease or the etiology. Dental plaque and debris indices have been developed to measure the presence of the microbial dental plaque. Moreover, the indices are used to track changes in patient's periodontal health, compare the incidence of the diseases, and test the level of improvement for the treatment modalities (Fischman, 1986). Although there are currently several plaque indices, the most commonly used indices in clinical practice are the Ramfjord Plaque Index, the Sillness-Löe Plaque Index, the Quigley Hein Plaque Index, the Turesky Plaque Index, the Approximal Plaque Index, the Simplified Oral Hygiene Index, and the O'Leary Plaque Index (Carranza, 2019).

One of the first plaque indices developed in history is the Ramfjord Plaque Index. In this method, selected six teeth are colored with a specific solution that reveals the plaque (Ramfjord, 1959). Each tooth is divided by imaginary demarcation lines and plaque deposition is scored as 0 (no plaque), 1 (slight plaque on interproximal and gingival surfaces of the tooth, but not all), 2 (plaque is present on all the interproximal and gingival surfaces but covers less than half of the entire crown), or 3 (plaque is present on more than half of the crown and extending to all the interproximal and gingival surfaces) (Table 1).

Table 1: Ramfjord Plque Index (Ramfjord, 1959)

0	No dental plaque
1	Slight plaque on interproximal and gingival surfaces of the tooth, but not all
2	Dental plaque is present on all the interproximal and gingival surfaces but covers less than half of the entire crown
3	Dental plaque is present on more than half of the crown and extending to all the interproximal and gingival surfaces

According to the Sillness-Löe Plaque Index, individual scoring is performed for the mesial, distal, vestibule and lingual surfaces of the tooth, and the total value found is divided by 4 to determine the total score of the related tooth (Table 2). The total of the scores of the teeth are divided by the total number of teeth included and the mathematical average value is taken to determine the plaque score of the patient (Brown & Löe, 1993).

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Table 2: Sillness-Löe Plaque Index (Brown & Löe, 1993)

0	No dental plaque
1	It is in the form of a thin film layer on the gingival margin, which is not visible but can be determined by a dental probe.
2	It is in the form of a moderately visible film layer on the gingival margin. The plaque is not visible in interproximal areas.
3	A large plaque layer can be observed on the gingival margin. Dental plaque is also visible in interproximal areas.

According to the Quigley Hein Plaque Index, buccal and lingual surfaces are divided into 3 parts by an imaginary line, and scores from 0 to 5 are given according to the level of plaque accumulation on the tooth surface. All the scores are summed and divided by the number of tooth surfaces scored to determine the total plaque index score of the patient (Kornman & Wilson Jr, 2003). Another modification developed by Turesky et al. including both buccal and lingual surfaces of all teeth (Turesky, 1970). These indices evaluate the area which is visually covered by the dental plaque, but not the amount of dental plaque as the Sillness-Löe Plaque Index does (Table 3).

Table 3: Quigley Hein and Turesky Plaque Indices (Kornman & Wilson Jr, 2003; Turesky, 1970)

Score	Quigley ve Hein	Turesky
0	No dental plaque	No dental plaque
1	Spots on the gingival margin	Seperate plaque spots on the gingival margin
2	Definite plaque line on the gingival margin	A thin band of continuous plaque on the gingival margin
3	In the gingival triad of tooth surface	A band of plaque less than 1/3 of the crown and wider than 1 mm
4	On the 2/3 of tooth surface	Plaque covering at least 1/3 but less than 2/3 of tooth surface
5	More than 2/3 of tooth surface	Plaque covering 2/3 or more of tooth surface

The Approximal Plaque Index (API) is a modification of the Quigley-Hein Index. After staining the microbial dental plaque, the interdental effected areas are examined. The tooth surface is marked as 'Yes (+)' if the dental plaque is present, and as 'None (-)' when it is absent. The API evaluation is based on the percentage values and the approximal plaque index value is calculated by percentage (%).

According to the amount of plaque formation;

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100 to 70%: Inadequate oral care

70 to 35%: Moderate oral care

35 to 25%: Very good oral care

25% and less: Indicates optimal oral care.

The Simplified Oral Hygiene Index evaluates 6 teeth (such as anterior and posterior teeth) instead of examining all (Kornman & Wilson Jr, 2003). The teeth are numbered as 16, 26, 11, 31, 36, 46.

The O'Leary Plaque Index observes the plaque formation on all mesial, distal, buccal and lingual surfaces of the tooth. The staining of the plaque is performed and then the tooth surface is recorded on the index chart as '+' in the presence of plaque and '-' when there is no plaque. The degree of exposure to the dental plaque is determined by percentage (%).

The formula used to determine the percentage is:

PI = (Number of areas with plaque/number of areas measured) x 100

Dental Plaque Imaging Methods

Although the visibility of microbial dental plaque increases after staining with the plaque staining agents, the diagnosis of dental plaque on the lingual surfaces is difficult for the clinician. In addition, patients can see the dental plaque on the buccal surfaces of their stained teeth by a mirror, while it is difficult to explain the plaque accumulation on the lingual surfaces of the teeth. The plaque staining process also aims to educate the patients regarding the oral hygiene by showing the stained tooth surfaces in details simultaneously. Accordingly there are imaging methods that can facilitate the clinical diagnosis of the dental plaque. The devices used for such imaging are professional dental photography and mobile dental photography devices (MDP), specialized LED light sources, intraoral 3-dimensional (3D) scanners, Quantitative Light Induced Fluorescence-Digital (QLF-D), and FluoreCam.

Dental Photography Devices

Following the staining of the dental plaque, intraoral photographs of the patient can be taken by using a professional digital macro camera or a mobile camera

with dental photography equipment (Figure 2 and 3). The MDP device consists of a camera of a smart phone in combination with a specialized dental photography lightning unit which is called the MDP device. Intraoral photography shooting is performed by placing the smart phone on the MDP device (Hardan & Moussa, 2020). The twin continuous led light sources on the right and left sides of the MDP help illuminate the patient's mouth (Figure 3). Through this technique, the level of brightness for the buccal surfaces of the anterior teeth is good, while it is generally not sufficient for the posterior photography especially for the lingual surfaces of teeth (Figue 4). Therefore, it is necessary to use additionalcheek retractors and a dental intraoral mirror to take such intraoral photographs in good quality.

Specialized LED light sources help to visualize the dental plaque in detetection mode (Figure 5,6).

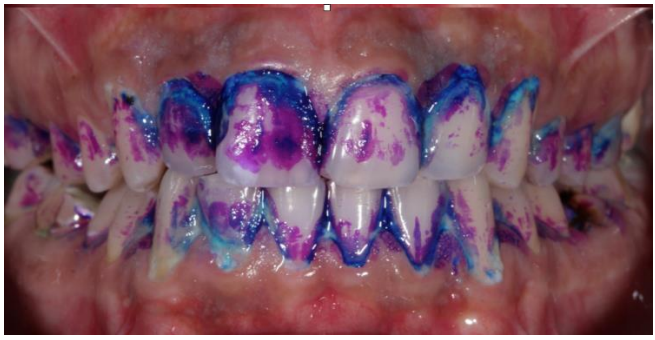

Figure 2: Intraoral image taken by a professional digital camera setup after staining dental plaque (Canon 700D ISO: 400, F:22, Av: 1/125; Canon 100 mm macrolens, Yong Nuo twin flash)

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Figure 3: Mobile dental photography device

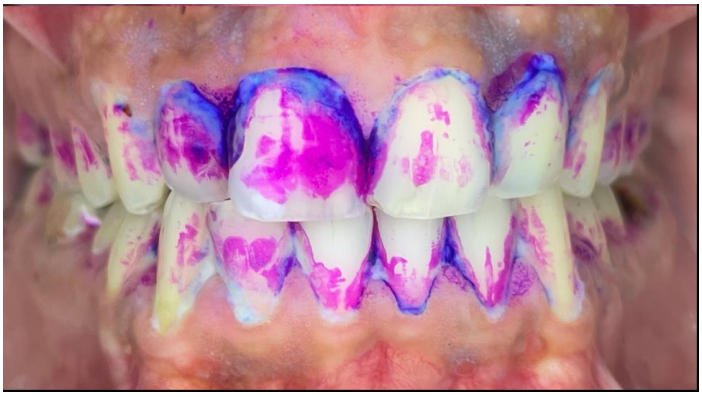

Figure 4: Intraoral image taken with MDP integrated smart phone after staining the dental plaque

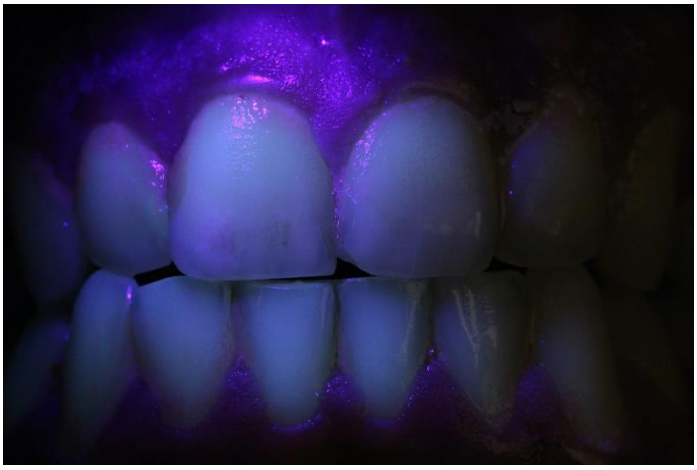

Figure 5: Intraoral image taken by a professional digital camera setup and a curing light source in Detection Mode (GC D-Light Pro, GC Corp., Tokyo, Japan) before staining dental plaque

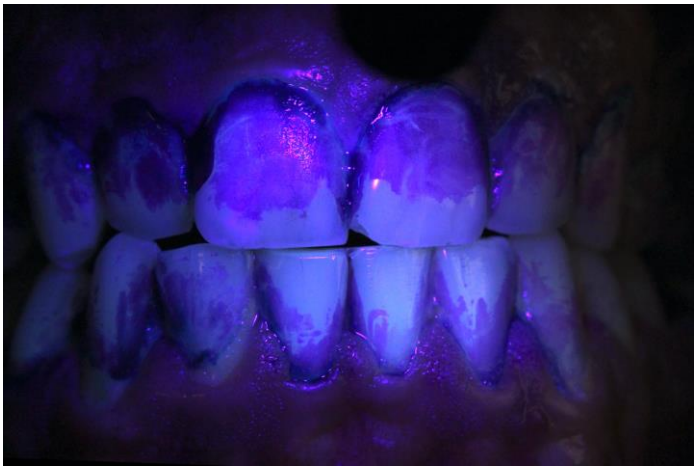

Figure 6: Intraoral image taken with a digital camera (Canon 700 D; ISO:1600, F: 11, Av: 1/125) and a light source (GC D-Light Pro, GC Corp., Tokyo, Japan) after staining dental plaque

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Intraoral 3D Scanners

The development of the dental computer aided design (CAD) systems have enabled the 3D imaging of the teeth and the provisional design of the planned restorations in a computer software program through the recorded intraoral data. Intraoral scanners have allowed the clinician to view the recorded multiple intraoral images of the patients in 3D in just a very short chair-time (Logozzo et al., 2011). The mechanism of the dental intraoral scanners is that, the intraoral camera of the scanner (wand) sends linear lights to the teeth resulting in light distortions. The two-mirror system of the scanners allows the teeth to be viewed from two different planes (facial, dorsal) with the scanner. The light reflected back in different angles to the wand are recorded by the CCD camera and collected as the individual data. During the process, multiple and overlapping images are also transferred to computer software program. After the image processing with the recorded data, the virtual intraoral model of the patient can be viewed in three dimensions on the screen. Today, almost all intraoral scanners can be used in non-contact mode without touching the teeth (Commer, Bourauel, Maier, & Jäger, 2000; Hurt, 2012; Sehrawat et al., 2022). Regarding the dental plaque imaging, following the staining of the plaque, the 3D modeling generated by the multiple intraoral images taken by the intraoral scanner can also be used effectively (Figure 7). The most important advantage of this method is the ability to view the most difficult areas, lingual and palatal surfaces and also the distal surface of the 3rd molar through the computer screen by both the patient and the clinician (Doi et al., 2021). A recent thesis study was conducted comparing dental plaque scoring of intraoral scanners with clinical and different imaging methods (Meşeli & Tağtekin, 2022).

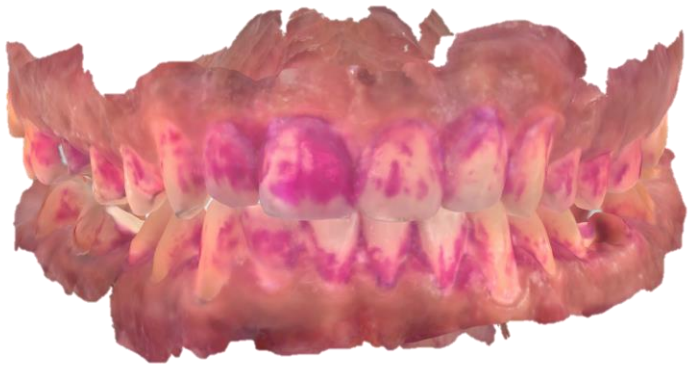

Figure 7: Intraoral 3D model frontal image by an intraoral scanner (iTero Elements 2, Align Technologies, San Jose, California) after staining the plaque

Quantitative Light Measuring Fluorescence-Digital (QLF-D)

Quantitative Light Measuring Fluorescence-Digital (QLF-D, Inspektor Research Systems, Amsterdam, The Netherlands) was developed mainly to diagnose the initial carious lesions. The working principle is based on the the autofluorescence of the dental hard tissues which may alter due to the alterations of the mineral content in time (Kim, 2013; Shi, Tranaeus, & Angmar-Mansson, 2001). QLF also quantitatively detects the red fluorescence (RF) emitted by the microorganisms present in dental plaque. In addition to this, it can detect the red fluorescence produced by endogenous porphyrins produced by late colonizing oral bacteria in dental plaque (Angmar-Månsson & Ten Bosch, 2001; De Jong et al., 1995; Karlsson, 2010). While most planimetric methods require the use of plaque staining agents to reveal dental plaque, QLF-D does not require the application of a plaque staining agent (Lee, Choi, Mah, & Pang, 2018). Regarding the clinical application, intraoral images of the patient are collected by an intraoral camera and analyzed by a computer software program.

FluoreCam

The FluoreCam System (Daraza Corporate Headquarters, Indiana, USA) is a dental imaging system including an intraoral camera and a specific computer software program to quantitatively detect the early carious lesions as well as the

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white spot lesions on enamel surface (Figure 8, 9). The working mechanism is similar to the QLF device. The tip of the FluoreCam intraoral camera has a window that is fixed to the focal point of the camera. By bringing the tip of the device closer to the tooth and pressing the button on it, the fixed image can be recorded and analysed.

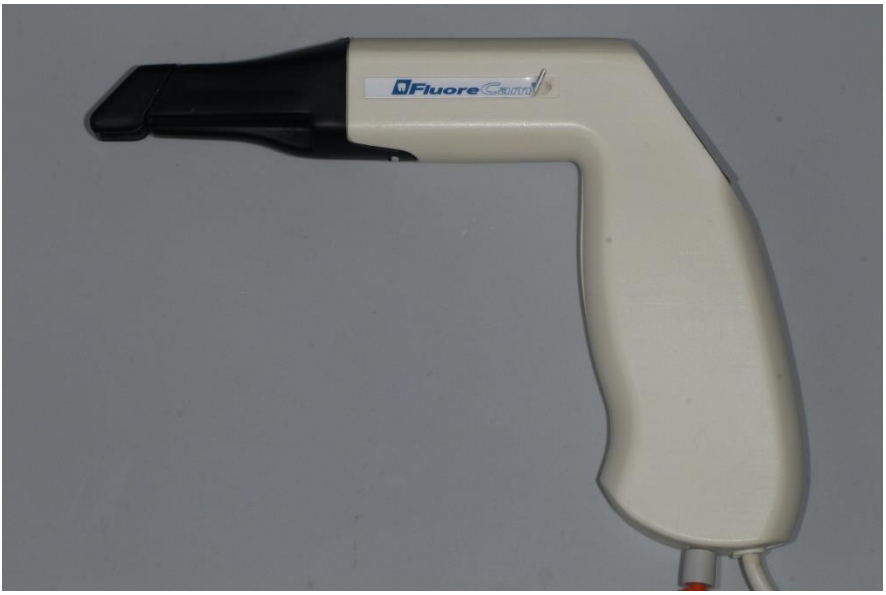

Figure 8: Intraoral camera of FluoreCam

Figure 9: Intraoral image capturing with FluoreCam

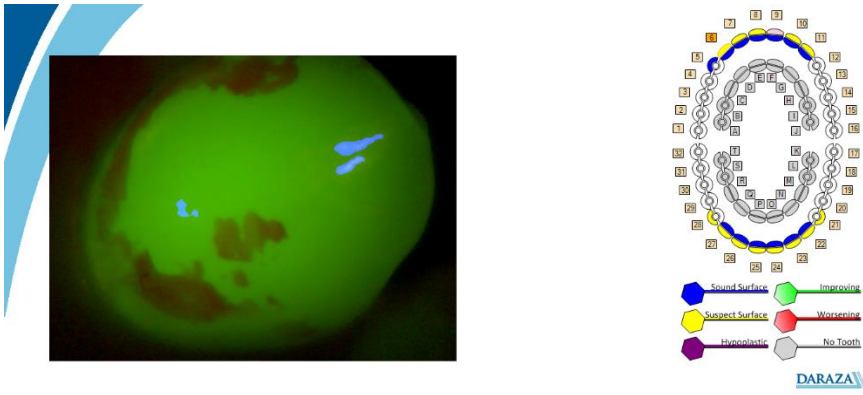

Figure 10: Fluorescence image of right upper canine taken with FluoreCam after plaque staining

The FluoreCam system uses the Fluorescence Enamel Imaging (FEI) approach to measure the health of enamel tissue. The basic idea of this approach stems from the chemical and physical properties of tooth enamel. As the enamel tissue is highly mineralized and semi-transparent, the high mineral content allows it to show fluorescence, while its semi-transparent nature allows different enamel densities to emit fluorescence at different levels. As a result, the density of enamel tissue can be determined by measuring the fluorescence emitted by the tooth

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when exposed to a certain wavelength with FEI technology (Durmus et al., 2017; Kiristioglu, Yanikoglu, Alkan, & Tagtekin, 2021).

Although the FluoreCam is primarily used to detect quantitative changes basicly in enamel tissue, it can also be used as an auxiliary method for dental plaque imaging (Figure 10).

All photographs and images were taken at Department of Restorative Dentistry, Marmara University, Istanbul, Turkey. Intraoral photographs were taken by a proffesional digital camera (Canon EOS 700D, Japan) (ISO: 400, F:22, Av: 1/125), macro lens (EF 100 mm 1:2.8 L IS, Canon Inc., Japan), twin flash (Yong Nuo YN24EX, China).

CONCLUSION

It is vital to diagnose dental plaque at early stages and accordingly to give the oral hygiene education to the patients in terms of public and dental health. In addition to traditional methods in the diagnosis of the dental plaque, the application of a plaque staining agent and the use of the recent intraoral imaging methods may provide a more accurate diagnosis to guide a proper treatment plan. It is possible to collect the intraoral images of a patient by the dental plaque imaging methods which are also effective on the evaluation of the final outcome of the applied treatment. Additionally, the visualization and presentation of the current oral hygiene to the patient is a very effective clinical tool to increase the awareness and the motivation of the patient.

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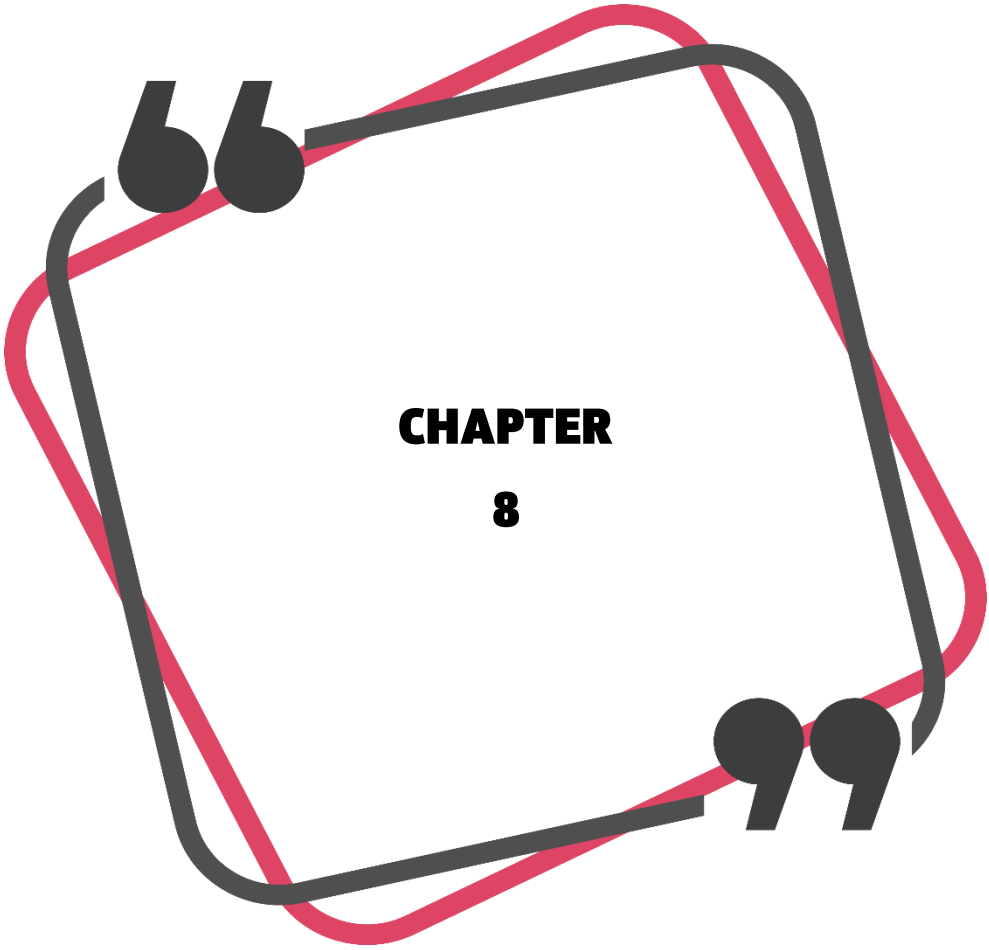
CHAPTER
8

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THE MANAGEMENT OF TRANSVERSE MAXILLARY DEFICIENCY WITH RAPID MAXILLARY EXPANSION

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Introduction

The constituent bones of the craniofacial system undergo changes in growth direction and rate during development, which are influenced by both genetic and environmental factors. Genetic factors are linked to heredity, while environmental factors are related to muscle attachments, functional activity, and growth of neighboring skeletal structures (Starnbach et al., 1966). Skeletal anomalies that arise from genetic, functional, or environmental factors can lead to malocclusions in the transverse, sagittal and vertical planes by adversely affecting development of the maxilla (Graber LW et al., 2022).

Transverse maxillary deficiency (TMD), also known as narrow maxilla or maxillary hypoplasia, is a significant malocclusion that adversely affects facial growth and the integrity of dentoalveolar structures (Consolaro & Consolaro, 2018; McNamara, 2000).

Transversal maxillary deficiencies are frequently observed as posterior crossbite, which can occur as a result of skeletal, functional, or dental origin (Graber LW et al., 2022; Haas AJ, 1965).

Maxillary Growth, Remodelling, and Maturation

The maxilla undergoes postnatal development exclusively through intramembranous ossification. Due to the absence of cartilage replacement, the growth of the maxilla occurs through two primary mechanisms: bone apposition and surface remodeling. Additionally, the growth of the cranial base contributes to the advancement of the maxilla in a forward direction (Latham, 1970; Proffit WR et al., 2019).

The development of the face is characterized by its progressive emergence from beneath the cranial structure. As a result, the maxilla undergoes significant

forward and downward movement relative to the cranium and cranial base during growth. This is achieved through a combination of growth in the cranial base and sutural growth. Since the maxilla is attached to the anterior aspect of the cranial base, forward displacement of the maxilla occurs due to growth of the cranial base. Notably, cranial base growth is critical for the maxilla's anterior growth until the age of six. (Proffit WR et al., 2019).

According to implant studies, Björk (Björk, 1955) has reported that sagittal growth of the maxilla occurs as a result of sutural apposition in the palatine bone, and periosteal apposition at the maxillary tuberosity.

In the vertical development of the maxilla, several different factors are influential. These include bone appositions in the orbital walls and the hard palate, accompanied by resorptive changes in the nasal cavity. The upper jaw moves downward and forward due to the changes occurring in these areas (Björk & Skieller, 1977).

The median palatine suture is an important contributor to the transverse growth of the maxilla and retains its functionality until the completion of growth and development (Björk, 1955; Björk & Skieller, 1977; Korn & Baumrind, 1990; Krebs, 1959).

The growth of the hard palate length from ages 13 to 15 is attributed to transverse suture growth and apposition at the posterior margin of the palate. Sutural growth ceases after this age, while apposition continues for a few more years. The morphology of the transverse suture changes postnatally from a broad and slightly sinuous suture at birth to a typical squamous suture with the palatine part covering the maxillary part. During puberty, the suture becomes slightly sinuous again. This change affects the vertical growth of the hard palate, particularly the lowering of the anterior part. Transverse growth of the midpalatal suture persists until ages 16 in females and 18 in males. The process of the median suture's development is classified into three phases based on its morphology. Initially, during the first stage, the suture appears short, broad, and Y-shaped. Subsequently, during the second stage, it develops a more curved shape, and finally, during the third stage, the interdigitation becomes so intricate that it would necessitate fracturing the interlocked processes to separate the two halves of the maxilla.(Figure 1) (Melsen, 1975).

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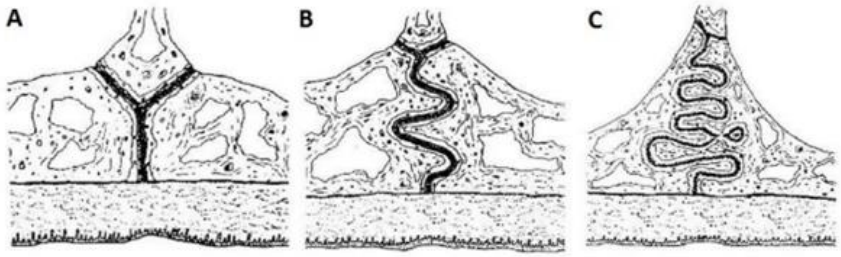

Figure 1: Increasing interdigitation of the midpalatal suture (Melsen, 1975).

Transverse Maxillary Deficiency

Transverse maxillary deficiency (TMD), also referred to as maxillary hypoplasia, has detrimental effects on both facial growth and dentoalveolar structures. TMD is mostly characterized by a posterior crossbite, a deep and narrow palate, crowding of the maxillary teeth, and large buccal corridors. In addition to these, it may contribute to functional changes, particularly respiratory difficulties, such as the development of prolonged mouth breathing, nose breathing difficulties, and sleep apnea syndrome. TMD may also contribute to respiratory difficulties, such as sleep apnea syndrome, as a result of the development of prolonged mouth breathing, occurred from nose breathing difficulties (Andrucioli & Matsumoto, 2020; Graber LW et al., 2022; Nowak et al., 2015; Proffit WR et al., 2019).

Transverse maxillary deficiency (TMD) is one of the most prevalent malocclusions, often occurring as a solitary condition or in combination with other malocclusions (Betts et al., 1995). It is characterized by a reduction in the transverse distance of the maxilla and is commonly referred to as transverse deficiency (TMD) (Pogrel et al., 1992). The correction of a skeletal or dentoalveolar transverse deficit must be a primary therapeutic goal in orthodontic treatment (Ballanti et al., 2010).

Transversal maxillary deficiency commonly presents as a posterior crossbite, a term used to describe the abnormal buccolingual (labiolingual) relationship between the upper and lower teeth in centric occlusion (Moyers RE, 1988; Zegan et al., 2015).

Posterior crossbite can occur if the width of the maxilla and/or maxillary dental arch is narrower than that of the mandible and/or mandibular dental arch. This can happen on one side of the mouth or both sides and can occur at any point

from the eruption of the primary teeth to the establishment of the permanent dentition. Additionally, the condition may either develop or improve over time (Heikinheimo et al., 1987; Kurol & Berglund, 1992; Thilander et al., 1984). It is also evaluated whether the deviation from ideal occlusion is primarily due to dentoalveolar, skeletal problems, or a combination of both. In most cases, posterior crossbite is a combination of both dental and skeletal factors, with one aspect being more dominant than the other. The extent of dental or skeletal involvement varies depending on the individual case, and a thorough examination and diagnosis are required to determine the appropriate treatment plan (Graber LW et al., 2022).

A posterior crossbite can be classified as either skeletal, dental, or functional (Dean JA, 2021; Proffit WR et al., 2019). The crossbite is classified as dental in cases with adequate palatal width. In contrast to that, the cases with inadequate palatal width are considered as skeletal (Figure 2) (Proffit WR et al., 2019).

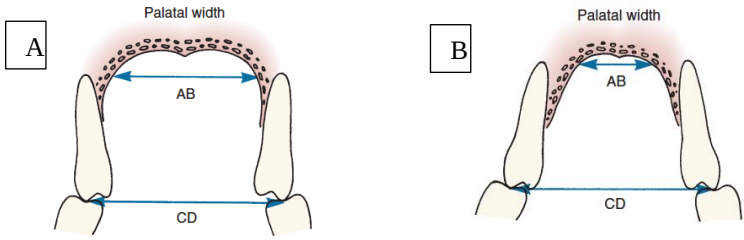

Figure 2: A) Dental crossbite with adequate palatal width, **B)** Skeletal crossbite with inadequate palatal width (Proffit WR et al., 2019).

Skeletal Posterior Crossbite

In skeletal crossbite, a disharmony in the craniofacial structures is observed. This disharmony may arise from asymmetrical growth of the upper or lower jaw or a disparity in their widths. This phenomenon can have an impact on the overall occlusal function and esthetics of the patient, necessitating appropriate diagnosis and management (Moyers RE, 1988). In instances where a bilateral palatal crossbite is due to a constricted palatal vault, it would be regarded as a skeletal problem (Graber LW et al., 2022; Proffit WR et al., 2019).

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According to Betts et al. (Betts et al., 1995) posterior crossbite is not solely restricted to dental anomalies but frequently associated with an underlying skeletal issue. Skeletal crossbite can result from various maxillomandibular discrepancies such as a narrow maxilla and normal mandible, normal maxilla and wide mandible, and narrow maxilla and wide mandible.

Skeletal posterior crossbites are characterized by significant basal discrepancies between the maxilla and mandible, often resulting in a full bilateral crossbite with marked maxillary constriction. During closure, occlusal midlines typically coincide with the facial midline, and no functional deviations are observed. The underlying skeletal dysplasia can be further complicated by other factors such as maxillary tooth crowding, anterior open bite, and environmental factors that may hinder normal growth patterns (e.g., cleft palate, severe airway issues) (Dean JA, 2021). According to Kurol and Berglund (Kurol & Berglund, 1992), there is a relatively low prevalence of skeletal posterior crossbite among children, with only 4 out of 86 cases presenting as full bilateral crossbites.

Dental Posterior Crossbite

Dental posterior crossbite results from the palatally inclined position of upper teeth and is not affected by the size or shape of the basal bone or palatal width (Graber LW et al., 2022; Moyers RE, 1988).

Dental posterior crossbites are characterized by localized displacement of individual teeth, resulting in atypical eruption and alignment in a crossbite configuration. The most affected teeth are the permanent maxillary first molars or premolars (Dean JA, 2021).

Functional Posterior Crossbite

Functional posterior crossbites are caused by transverse occlusal interference between the maxillary and mandibular arch widths, resulting in a lateral shift of the mandible during closure. Functional posterior crossbites are characterized by a unilateral crossbite in centric occlusion, often involving multiple posterior teeth on one side while maintaining normal buccolingual occlusion on the opposite side. The deviation is also visible in the lower midline and chin, which appear to shift toward the crossbite side. While the occlusion appears to be unilateral, functional posterior crossbites exhibit cusp-to-cusp transverse contacts on both sides, accompanied by a narrow maxillary arch that is incapable of completely enclosing the lower dentition during the initial contact (Dean JA, 2021).

Ingervall and Thilander (Ingervall & Thilander, 1975) termed the displacements resulting from premature contacts in children as lateral forced bite. Nerder et al. (Nerder et al., 1999) indicated that the forced guidance causing lateral shift occurs due to neuromuscular guidance of the lower jaw resulting from premature tooth contacts.

Incidence

Transverse maxillary deficiency is a common malocclusion in orthodontics with a prevalence estimated to be between 2.7% and 23%, as reported by several studies (Basciftci FA et al., n.d.; da Silva Filho et al., 1991; Kutin & Hawes, 1969; Lindner & Modeer, 1989; Sandikçioğlu & Hazar, 1997; Tausche et al., 2004; Thilander et al., 1984).

Thilander et al. (Thilander et al., 1984) investigated the efficacy of interceptive treatment for posterior crossbite during the primary and early mixed dentition. In their study, 86 four-year-old children with posterior crossbite were selected from a total of 1046 children, representing a prevalence of 9.6%. The treatment outcomes were compared to those of a non-treatment group.

Kutin and Hawes (Kutin & Hawes, 1969) found a rate of 7.7% in 515 patients aged 3-9 years, whereas Tausche et al. (Tausche et al., 2004) reported a rate of 8.2% in 1975 patients aged 6-8 years.

Lindner and Modeer (Lindner & Modeer, 1989) reported that 23% of the children showed a cusp-to-cusp relationship between one pair of teeth, which were always situated anterior to the teeth affected by the crossbite.

The Third National Health and Nutrition Examination Survey (NHANES III) reported a prevalence of 7,1% in U.S. children aged 8 to 11 years in 1992, and the incidence does not seem to have changed significantly since then (Brunelle et al., 1996).

Helm (Helm, 1968) reported a prevalence of 9,4% for posterior crossbite in males and 14,1% in females among 1700 Danish children with permanent dentition.

Sandikcioglu and Hazar (Sandikçioğlu & Hazar, 1997) conducted a study on a Turkish population of 958 children and reported a prevalence of 2.7% for posterior crossbite. Another study conducted in Turkish population by Gungor et al. (Gungor et al., 2016) evaluated a prevalence of 15,6% for posterior crossbite. It was reported that 9,4% of the subjects had unilateral posterior crossbite (with

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5,9% on the right side and 3,6% on the left side), whereas 6,2% had bilateral posterior crossbite.

Aetiology

Anomalies in the transverse dimension can manifest as narrowing of the maxilla and/or upper dental arch, widening of the mandible and/or lower dental arch, or a combination of both. The presence of posterior crossbite is indicated when the maxillary posterior teeth are positioned lingually relative to the mandibular teeth. The majority of transverse anomalies are thought to be maxilla-originated (Proffit WR et al., 2019).

The development of posterior crossbite may be originated from various factors, including the neuromuscular system, soft tissue, and skeletal or dentoalveolar structures (Moyers RE, 1988).

In summary, transverse maxillary deficiency can have a genetic and/or environmental origin, or a combination of both (Bishara & Staley, 1987; Malandris & Mahoney, 2004).

Genetic factors

Genetic factors play a significant role in the development of transverse maxillary deficiency. These factors can affect transverse dimension directly through osteogenesis or indirectly through alterations in muscle morphology. In addition, certain hereditary disorders can result in the development of transverse deficiency (Moyers RE, 1988).

Apert and Crouzon syndromes are known to cause maxillary hypoplasia and transverse deficiencies, leading to posterior crossbite (Kreiborg & Cohen, 1992).Similarly, Muenke and Saethre-Chotzen syndromes are also associated with craniofacial anomalies, including maxillary hypoplasia and dental malocclusions such as posterior crossbite (Allen et al., 2003; Choi et al., 2019; Kimonis et al., 2007).

Patients with cleft lip and palate may develop maxillary constriction due to scar tissue formation resulting from surgical repair of the cleft, which can limit the width of the upper jaw and cause insufficient occlusion, leading to compromised masticatory function. As a result, maxillary collapse can occur, leading to transverse maxillary deficiency. The presence of transverse maxillary deficiency can further exacerbate the functional and aesthetic problems associated with cleft

lip and palate, highlighting the importance of timely intervention and comprehensive treatment planning in these patients (Bishara & Staley, 1987; Moss, 1968; Proffit WR et al., 2019).

Down Syndrome is a genetic disorder that can affect the growth and development of the midface, resulting in a range of craniofacial abnormalities. One of the most common findings in individuals with Down Syndrome is the presence of a pseudoprognathic mandible and posterior crossbite due to midfacial hypoplasia. This can lead to functional limitations such as difficulties with chewing and speech, as well as aesthetic concerns. Hemifacial microsomia is a congenital condition characterized by underdevelopment of one side of the face. This can result in asymmetric transverse deficiency, where one side of the maxilla is narrower than the other. The severity and presentation of hemifacial microsomia can vary widely, and it may be associated with other craniofacial anomalies such as mandibular hypoplasia, ear anomalies, and soft tissue deficiencies. In both Down Syndrome and hemifacial microsomia, early diagnosis and intervention by a skilled orthodontist is important to manage the associated orthodontic and functional problems (Cassi et al., 2017; Moss, 1968).

In a study investigating the influence of genetics on dental arch form, conducted by Cassidy et al. (Cassidy et al., 1998) found that transverse arch widths had the highest heritability estimates among all dental arch dimensions, averaging about 60%.

Corruccini and Potter (Corruccini & Yap Potter, 1980) investigated the heritability of occlusal variation in a sample of 32 monozygotic (MZ) and 28 dizygotic (DZ) twin pairs. They found that tooth displacement and crossbite were the most significantly heritable criteria of occlusion accounting for an average of 36% of the total variance. This study highlights the importance of genetic factors in the development of malocclusion and provides insight into the relative contributions of genetics and environment to occlusal variation.

Environmental Factors

Development of the maxilla is influenced not only by genetics but also by environmental factors such as soft tissue and certain habits. During the growth process, the position and size of the tongue, mouth breathing, prolonged pacifier use, and parafunctional habits such as tongue thrust and thumb-sucking can lead to the development of posterior crossbite. Additionally, dental crowding, persistent primary teeth, early loss of primary teeth, disproportionate tooth size, as well

as discrepancies between the size of the dental arch and the size of the teeth can also play a role in the development of crossbite (Behlfelt et al., 1989; Corruccini et al., 1985; Dean JA, 2021; Graber LW et al., 2022; Harvold et al., 1972; Kutin & Hawes, 1969; Lindner & Modeer, 1989; Melsen et al., 1979; Ninou & Stephens, 1994; Proffit WR et al., 2019; Thilander et al., 1984).

During parafunctional habits such as mouth breathing, thumb sucking or pacifier use, the tongue is positioned at the floor of the mouth and the upper posterior teeth are not palatally supported, resulting in an imbalance of forces. This can lead to transverse discrepancies in the upper and lower jaws and an increased tendency for posterior crossbite (Larsson, 2001; Ogaard et al., 1994; Subtelny, 1980; Warren et al., 2001).

Mouth breathing due to nasal inflammation, enlarged tonsils or chronic nasal obstructions can cause mandibular descent with tongue positioning in the mandible (Behlfelt et al., 1989; Linder-Aronson & Lindgren, 1979; Proffit WR et al., 2019).

Diagnosis

Early diagnosis is crucial in the effective treatment of transverse maxillary deficiency. Left untreated, this condition can lead to aesthetic discrepancies, nasal breathing difficulties, sleep apnea syndrome, crossbite, and even facial asymmetries (Manzella et al., 2018; Nowak et al., 2015).

Unilateral crossbite may be caused by a bilateral narrowing of the maxillary arch with a shift to the affected side. In this case, treatment should focus on expanding the maxillary arch to correct the crossbite. However, if the crossbite is caused by a true unilateral problem, such as a skeletal discrepancy or a tooth size discrepancy, the treatment plan should address the underlying issue, which may involve orthognathic surgery or tooth movement. Therefore, a thorough clinical examination, including radiographic and diagnostic records, is necessary to accurately diagnose and plan the appropriate treatment for a patient with a unilateral crossbite (Proffit WR et al., 2019).

To diagnose and treat transverse maxillary deficiency, accurately, methods such as clinical evaluation, model analysis, and radiographic assessment are utilized (Vanarsdall, 1999).

During clinical evaluation, the form and symmetry of the maxillary arch, the shape of the palate, the width of the buccal corridors during smiling, breathing

pattern, facial asymmetry, and occlusal balance are assessed to diagnose maxillary transverse deficiency. A narrow maxillary arch shape, resembling an hourglass, a deep and narrow palatal vault, severe crowding, excessive width of the buccal corridors, and a narrow nasal base are significant indicators of maxillary transverse deficiency (Bishara & Staley, 1987; Dawson, 1995; McNamara, 2000). This evaluation is crucial for determining the appropriate treatment plan and achieving long-term stability. Therefore, it is essential for orthodontists to carefully examine these factors to accurately diagnose and treat maxillary transverse deficiency (Vanarsdall, 1999).

Assessment of chin asymmetry and jaw shifting is also necessary. The existence of chin asymmetry and unilateral crossbite may indicate the presence of a genuine unilateral skeletal asymmetry, even without a lateral shift. These observations serve as crucial clinical signs in the diagnosis and treatment planning of patients with skeletal asymmetries (Marshall et al., 2005).

The use of cast analysis or study model analysis is an important technique in orthodontics to evaluate the occlusal relationship and obtain essential information about the upper and lower dental arches in three dimensions. It enables the assessment of the correlation between the total tooth material, arch length, and basal arch width, which is crucial for determining the most appropriate treatment approach for a patient (Proffit WR et al., 2019).

Howes Analysis, proposed by Ashley Howe, is one of the most frequently used methods in cast analysis. This analysis examines the relationships between teeth and the apical base of the alveolar bone in the transverse direction (Eunike, 2017).

The model analysis proposed by Staley et al. (Staley et al., 1985) is a valuable tool in orthodontics for assessing dental arch widths. It involves measuring the inter-molar width between the mesiobuccal cusp tips of maxillary molars and the distance between the closest or middle points of the mandibular molar's median sulcus and the gingiva. This analysis provides important information for evaluating the total tooth material, arch length, and basal arch width, which is crucial for determining the most appropriate treatment approach for a patient.

Orthodontic plaster models are employed to differentiate between relative and absolute transverse discrepancies. Relative transverse discrepancy is observed when the buccal-lingual cusp-fossa relationship of posterior teeth is not ideal in centric occlusion, but a Class I molar relationship can be achieved on the models, indicating that the discrepancy is not due to a skeletal issue. On the other hand,

absolute transverse discrepancy occurs when transverse discrepancy is not corrected even when the teeth are brought into Class I relationship on the models (Marshall et al., 2005). In addition, the lingual crown torque of lower posterior teeth and buccal crown torque of upper posterior teeth should be examined in dental models. The buccally inclined crowns of upper molars indicate that conventional expansion is contraindicated, while the lingually inclined crowns of lower molars suggest that the need for expanding the upper arch is greater than what is initially perceived (Bishara & Staley, 1987).

In assessing the effects of rapid maxillary expansion on transverse dimension, postero-anterior and occlusal radiographs are utilized. Postero-anterior radiographs are necessary for radiographic evaluation of asymmetries, determination of whether crossbite is skeletal or dental, and identification of any transverse discrepancy between the maxilla and mandible (Cureton & Cuenin, 1999; Lagravere et al., 2005; Marshall et al., 2005).

Maxillary occlusal radiographs are an essential tool for evaluating mid-palatal suture opening and ossification. However, it has been noted that their use is limited in the posterior region due to the overlapping of cranial base structures, which can result in an unclear image. This limitation may pose a challenge in accurately assessing the degree of mid-palatal suture opening and subsequent bone formation in the posterior region. Therefore, other imaging modalities such as cone-beam computed tomography (CBCT) may be necessary to supplement occlusal radiographs for a comprehensive evaluation of the mid-palatal suture. Despite this limitation, occlusal radiographs remain a valuable tool for assessing mid-palatal suture opening in the anterior region, where overlapping structures are less of a concern (Lehman et al., 1984; Loddi et al., 2008; Marshall et al., 2005; Suri & Taneja, 2008).

Frontal analysis is emphasized comparing the widths of dental arches, alveolar arches and skeletal structures. Additionally, a cephalometric analysis is performed to analyze the transverse discrepancy between the maxilla and mandible using specific radiographic landmarks and measurements (Ricketts, 1981).

Due to the limitations of traditional 2-dimensional (2D) imaging methods, such as panoramic and cephalometric radiographs, craniofacial abnormalities may not always be accurately diagnosed. 2-D images may be limited in identifying specific anatomical features due to the possibility of superimposing structures. With the advancements in technology, 3-dimensional (3D) imaging methods such as cone beam computed tomography (CBCT) has become increasingly popular in orthodontic diagnosis and treatment planning. In addition, 3D imaging

methods offer the ability to combine information from cephalometric, posteroanterior radiographs, and dental models, onto a single image (Jacobson & Jacobson, 2006; Lagravere et al., 2005; McNamara et al., 2003).

Clinical Management

For more than a century, maxillary expansion treatments have been used to correct maxillary transverse deficiency. The first documented report of rapid maxillary expansion (RME) was conducted by Angell and published in 1860 (Angell EH, 1860). Although RME was discredited initially, it is now commonly recognized as a simple and effective orthodontic treatment. Addressing transverse deficiencies usually requires orthopedic and orthodontic tooth movements to expand the palate.

When planning a treatment for expanding dental arches, it is important to consider several factors to decide whether to use conventional expansion methods or RME. To determine whether rapid maxillary expansion (RME) is necessary, two factors must be taken into account. Firstly, the extent of the difference in width between the maxillary and mandibular first molars and premolars needs to be considered. If the difference is 4 millimeters or more, RME should be considered. Secondly, the severity of the crossbite is a crucial factor to consider. The crossbite can involve single or multiple teeth, which will affect the treatment choice. Finally, the initial angulation of the posterior teeth (premolars and molars) is also crucial to consider. If the maxillary molars are already inclined towards the cheeks, traditional expansion methods may exacerbate this, pushing them further towards the buccal musculature. Similarly, if the mandibular molars are already inclined lingually, then expanding them towards the buccal side will increase the need for upper arch widening. Overall, it is important to carefully assess these factors during treatment planning to determine the most appropriate method for expanding dental arches (Bishara & Staley, 1987).

Clinical indications for RME include transverse maxillary deficiency, posterior crossbite, correction of axial inclinations of posterior teeth, increase in arch length, anteroposterior discrepancies, mobilization of circummaxillary sutures, skeletal class II malocclusion, skeletal class III malocclusion, cleft lip and palate patients with collapsed maxilla, reduction of nasal resistance, preparations for functional jaw orthopedics or orthognathic treatment, broadening of the smile and reduction of buccal corridors (Bell, 1982; Bishara & Staley, 1987; da Silva Filho et al., 1991; Graber LW et al., 2022; Haas AJ, 1970; McNamara, 2000; Proffit WR et al., 2019; Wertz, 1970).

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Contraindications for RME include patients who are uncooperative with the clinician, those with a single tooth in crossbite, anterior open bites, steep mandibular planes, and convex profiles. Patients with skeletal asymmetry of the maxilla or mandible, and adults with severe anteroposterior and vertical skeletal discrepancies are also not ideal candidates for RME. However, patients with significant dental issues may still be qualified for RME if orthognathic surgery is planned (Bell, 1982; Bishara & Staley, 1987; Graber LW et al., 2022; Wertz, 1970).

During the active treatment period of rapid maxillary expansion, which typically lasts 1-3 weeks, the expansion rate is generally 0.2-0.5 mm per day (Bell, 1982; Haas, 1980; Haas AJ, 1965, 1970; Wertz, 1970; Zimring & Isaacson, 1965). The individual activation schedule is adjusted empirically based on the desired amount of expansion and patient tolerance (Bell, 1982).

Clinicians commonly recommend activating the rapid maxillary expansion device twice a day, once in the morning and once in the evening. Typically, the device is turned a total of two-quarter turns per day (Bell, 1982; Biederman, 1973; Lima et al., 2004; Oliveira et al., 2004; Timms DJ, 1981; Velázquez et al., 1996; Wertz, 1970). Zimring and Isaacson (Zimring & Isaacson, 1965) suggested that in growing patients, the screw should be turned twice a day by one quarter-turn for the first 4-5 days, and then once a day by one-quarter turn for the following days. The researchers have also suggested that in adults, due to increased skeletal resistance, the screw should be turned twice a day by one-quarter turn on the first two days, followed by once a day by one-quarter turn until the fifth or seventh day until the sutural opening occurs. After sutural opening, the screw should be turned once every two days by one-quarter turn. In the finite element analysis study conducted by Iseri et al. (Işeri et al., 1998), it was highlighted that RME can cause significant deformation as well as stress accumulation in the facial bones potentially leading to long-term relapse. Therefore, the researchers recommend RME until the separation of the midpalatal suture, followed by slow maxillary expansion.

The appliances used for rapid maxillary expansion can be classified as follows:

1) Banded RME
a) Tooth-borne Appliance
i) Hyrax expander
ii) Minne expander
b) Tooth-tissue-borne Appliance

i) Haas expander
ii) Derichsweiler expander
2) Bonded RME

Banded RME appliances come in two types, tooth-borne and tooth-tissue-borne, and are attached to the maxillary first molar and first premolars using bands.

Tooth-borne appliances consist of bands and wires without any acrylic covering part. An example of a tooth-borne appliance is the HYRAX expander, invented by William Biederman in 1968 (Biederman, 1968). This appliance consists of a non-spring loaded jackscrew with an all-wire frame and heavy gauge wire extensions that follow the palatal contours and are soldered to bands on posterior teeth such as premolars and molars. Unlike other expanders, HYRAX does not irritate the palatal mucosa and is easy to keep clean. The screw is activated from front to back, providing approximately 0.2 mm of lateral expansion with each activation.

Minne expander is a tooth-borne appliance, that applies continuous force using a spring-loaded screw, which is directly attached to the bands on the first premolars and molars. The expander was developed by the dental school at the University of Minnesota and is also known as the "Minne expander." The powerful screw is positioned between the bands on the first molars, enabling it to provide continuous force (Zimring & Isaacson, 1965).

Tooth-tissue-borne RME appliances consist of an expansion screw with acrylic abutting on alveolar ridges. These appliances offer numerous benefits, such as more parallel expansion, less relapse, greater gain in nasal cavity and apical base, and more favorable denture base relationships (Haas AJ, 1965, 1970). However, these appliances also have the disadvantage of causing higher soft tissue irritation. There are two main types of tooth-tissue-borne RME appliances: Haas and Derichsweiler expander.

Haas expander is a tooth-tissue-borne appliance invented by Haas (Haas AJ, 1961) in 1961 and produces immediate midpalatal suture separation by disruption of the sutural connective tissue. The expander is designed for maximum dental anchorage, using a jackscrew to produce expansion in 10 to 14 days (Haas AJ, 1961, 1965).

Derichsweiler expander is a tooth-tissue-born appliance similar to the Haas design but does not have the buccal connector. The appliance involves banded

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first premolars and molars with wire tags soldered to these bands and then inserted into split palatal acrylic containing the screw (Almuzian et al., 2016).

Bonded RME appliance was conducted by Cohen and Silverman (Cohen & Silverman, 1973) in 1973, to treat patients with an excessive inclination of the mandibular plane by intruding the posterior mandibular teeth. It is similar to the banded version, except for its method of attachment to the teeth. The appliance is attached to the teeth with a full acrylic surface coverage that encloses all occlusal surfaces using a dental adhesive, rather than being secured with metal bands around the teeth. Bonded RME appliances are tooth-tissue-borne appliance and can consist of cobalt chrome occlusal capping linked to the expansion screw via an acrylic connector or the occlusal capping constructed from acrylic (Işeri & Ozsoy, 2004; McNamara JA Jr & Brudon WL, 2001; Memikoğlu & Iseri, 1997; Sarver & Johnston, 1989).

Retention and Stability

Following rapid maxillary expansion, it is crucial to allow for a retention period of 3-6 months to facilitate bony infill in the space between palatal shelves and for the residual load of the screw/spring to dissipate (Haas AJ, 1961; Sarver & Johnston, 1989; Wertz, 1970).

The degree of relapse following RME expansion can be influenced by several factors, including age and gender, with greater relapse observed in adult patients compared to adolescent patients (Wertz, 1970). Achieving good buccal segment intercuspation and eliminating causative habits are associated with high stability of maxillary expansion. These findings underscore the importance of proper patient selection, diligent retention, and the use of appropriate orthodontic mechanics to achieve optimal treatment outcomes (Lagravere et al., 2005).

The tendency of relaps can be attributed to several factors, including the accumulation of residual forces in certain areas, strong muscle structures surrounding the maxilla, the resistance of the zygomatic bone and surrounding sutures, as well as insufficient bone formation due to occlusal forces during the retention period (Bishara & Staley, 1987; Cameron et al., 2002; Wertz, 1970; Zimring & Isaacson, 1965).

Side Effects

During the active phase of rapid maxillary expansion (RME), patients commonly experience pain and soreness. Studies have reported that around 98% of cases experience pain during the first six turns of expansion, which tends to diminish over time. Pain is more likely to occur when the rate of expansion exceeds one turn per day (Needleman et al., 2000). Other potential side effects of RME include temporary damage to the dental pulp and periodontal tissues, minimal loss of support in the alveolar bone, irritation of the gingival tissue, inflammation, bone dehiscence, and root resorption of the anchor teeth due to the orthodontic forces applied (Barber & Sims, 1981; Greenbaum & Zachrisson, 1982; Odenrick et al., 1991; Sardessai & Fernandesh, 2004). While rare, more serious complications such as dizziness, nosebleeds, temporary double vision, or compression of the oculomotor nerve, especially in cases of surgically assisted RME, have been reported in the literature (Lanigan & Mintz, 2002).

Conclusion

Rapid maxillary expansion is an effective treatment for transverse maxillary deficiency, leading to improvements in dental and skeletal relationships, reduced need for extractions, and improved breathing function. While RME is generally safe and effective, there are potential complications and limitations that should be considered, such as temporary discomfort or pain during the expansion process and risk of relapse if proper retention is not maintained after treatment. Understanding these factors and their potential impact on post-treatment stability is crucial for successful orthodontic treatment outcomes.

Keywords: Transverse maxillary deficiency, narrow maxilla, rapid maxillary expansion, crossbite.

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